1 FINAL CLINICAL STUDY PROTOCOL

Lumosa Therapeutics Co., Ltd.

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 Number: LT3001-205

[redacted]

Name of Investigational Product:	LT3001 drug product
Phase of Development:	II
Indication:	Acute Ischemic Stroke (AIS)
Sponsor:	Lumosa Therapeutics 4th Floor, No. 3-2, Park Street, Nangang District, Taipei, 11503, Taiwan Tel: +886-2-26557918 Fax: +886-2-26557919
Protocol Version:	8.1
Protocol Date:	23 Apr 2025

PROTOCOL APPROVAL SIGNATURES

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 Number: LT3001-205

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP), and applicable regulatory requirements.

[redacted]

INVESTIGATOR SIGNATURE PAGE

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Protocol Number: LT3001-205

Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement

- I, the undersigned, have reviewed this protocol (and amendments, as applicable), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant International Council for Harmonisation (ICH) guidelines.
- I am thoroughly familiar with the appropriate use of the investigational product, as described in this protocol and any other information provided by Lumosa Therapeutics Co., Ltd including, but not limited to, the current investigator's brochure.
- Once the protocol has been approved by the independent ethics committee (IEC)/institutional review board (IRB), I will not modify this protocol without obtaining prior approval of Lumosa Therapeutics Co., Ltd and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Lumosa Therapeutics Co., Ltd and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about Lumosa Therapeutics Co., Ltd's investigational product and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.
- Information developed in this clinical study may be disclosed by Lumosa Therapeutics Co., Ltd to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

INVESTIGATOR'S AGREEMENT

I have read the LT3001-205 Protocol Version 8.1 dated 23 Apr 2025 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

[redacted]

2 SYNOPSIS

Title of Study:	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 Number:	LT3001-205
Investigators/Study Sites:	The study is planned to take place [redacted]
Phase of Development:	Phase II
Objectives:	Primary Objective To determine the safety of multiple doses of LT3001 drug product in subjects with AIS. Secondary Objective To determine the efficacy of multiple doses of LT3001 drug product in subjects with AIS.
Study Endpoints:	**Primary Endpoint** The proportion of subjects with Adverse Events (AEs), judged to be probably or definitely related to the investigational product (IP) within 90 days after the 1st IP administration. **Secondary Endpoints** **Clinical efficacy outcomes** 1. Functional outcome a. The proportion of subjects achieve [redacted] Modified Rankin Scale (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] after the 1st IP 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 at 24 hours after the 1st IP by MRI/CTP adjusted [redacted]. **Safety outcomes** 1. The occurrence of symptomatic intracranial hemorrhage (sICH) [redacted] after the 1st IP; clinical deterioration defined as an increase in the National Institute of Health Stroke Scale (NIHSS) of 4 points or more AND confirmed by magnetic resonance (MR)/computed tomography (CT) 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.
Study Design:	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. 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 [redacted], baseline NIHSS [redacted], and time of AIS symptoms onset to the planned 1st IP [redacted]. The stratified randomization is to ensure similar risk distributions with regards to efficacy measures at baseline in the treatment groups. [redacted] Each eligible subject will [redacted] The first dose of LT3001 drug product or placebo (1st IP) will be administered within 24 hours after stroke symptoms onset. [redacted] LT3001 drug product or placebo will be administered [redacted]. 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.
Selection of Subjects:	**Inclusion Criteria:** 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] 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.

Exclusion Criteria:

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/mm^3 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.
Planned Sample Size:	Approximately 200 eligible subjects will be randomized 1:1 to LT3001 drug product or placebo. [redacted]
Investigational Therapy:	LT3001 drug product [redacted]
Reference Therapy:	Placebo [redacted]
Treatment Duration:	All subjects will receive the first dose of IP within 24 hours after stroke symptoms on Day 0 and will be hospitalized for the care of AIS according to each study site's current standard of care. Each subject will receive [redacted] LT3001 drug product or placebo via a 30-minutute intravenous infusion twice within every approximately 24 hours, total 6 doses of IP within approximately 72 hours. The participation for each subject is approximately 92 days from the Screening (Visit 1) to the last visit.

Efficacy:	Efficacy will be evaluated by assessing the functional outcomes measured by mRS, neurological outcome assessed by NIHSS, the occurrence of recurrent stroke, and cognition assessed by the MoCA; and imaging outcomes measured by change in infarct volume and hypoperfusion lesion.
Safety:	Safety assessments include the occurrence of sICH, aICH, mortality, and AEs.
Statistical Methods and Planned Analyses:	Study populations • Enrolled Population: all individuals who sign the informed consent form. The Enrolled Population will be used for all subject disposition analyses. • 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]. • 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]. • 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]. • 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. **Primary endpoint analysis** *Proportion of subjects with AEs, judged to be probably or definitely related to the IP within 90 days after the 1st IP administration:* 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. The difference of the proportions between the treatment groups with the corresponding exact 95% Clopper Pearson confidence intervals (CIs) will be presented. [redacted] **Secondary endpoint analyses** The analyses of all efficacy and imaging endpoints will be performed on the ITT population as the main analysis and will be repeated on the PP and Completers populations as supportive analysis. Efficacy endpoints will be summarized and statistically compared between the treatment groups in the subgroups of the variables used for randomization stratification, also. [redacted] *Proportion of subjects with independent functional outcome and excellent functional outcome [redacted] after the 1st IP:* The number and percentage of subjects who achieve a score of 0 to 2 on the mRS [redacted] will be presented by treatment group. The number and percentage of subjects

achieve [redacted] mRS 0-1 [redacted] and the number and percentage of subjects achieve [redacted] mRS 0-2 [redacted]. The difference of the proportions between the treatment groups with the corresponding 95% CIs will be presented for each defined timepoint. [redacted] The same analysis will also be presented for subjects who achieve a score of ≤1 on the mRS. [redacted]

Shift of proportion of subjects with each grade on mRS [redacted] *after the 1st IP from Baseline:*
The number and percentage of subjects in each score category of mRS will be presented for baseline and for the post-baseline timepoints [redacted] by treatment group. A shift table will be presented by treatment with shifts from baseline to each defined post-baseline timepoint by providing the number and percentage of subjects [redacted]

The NIHSS [redacted] *after the 1st IP* [redacted]:
A comparison between the treatment groups using the analysis of covariance (ANCOVA) will be applied, with the NIHSS at 24 hours, 48 hours, 7 days and 30 days as the dependent variable while adjusting for Baseline NIHSS as a covariate. [redacted]

Proportion of subjects with neurological outcome improvement [redacted] *from Baseline:*
The number and percentage of subjects with neurological outcome improvement, defined as a decrease in NIHSS ≥4 points, will be summarized at each defined timepoint by treatment group and overall. The difference of the proportions between the treatment groups with the corresponding 95% CIs will be presented for each defined timepoint. [redacted] The same analysis will also be presented for subjects with decrease in NIHSS ≥4 points or NIHSS of 0 to 1 point. Additionally, a RMLR model considering all assessments until Day 30 will be applied for [redacted]

[redacted]

Proportion of subjects with NIHSS ≤2 [redacted] *after the 1st IP:*
The number and percentage of subjects with NIHSS of 0 to 2 points will be presented by treatment group at each defined timepoints, and the difference of the proportions between the treatment groups with the corresponding 95% CIs will be presented. [redacted] The same analysis will also be presented for subjects with NIHSS of 0 to 1 point. [redacted]

Change in NIHSS [redacted] *from Baseline:*
The total score and change from baseline in NIHSS will be summarized at each defined timepoint by treatment group and overall. A figure will be presented with the percentage of subjects with a decrease of ≥4 points compared to baseline, a decrease of 1 to 3 points, no change (0 points), increase of 1 to 3 points, and increase of ≥4 points for each scheduled visit by treatment group – with change presented on the x-scale and visit presented on the y-scale. [redacted]

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. The difference of proportions between the treatment groups with the corresponding 95% CI will be presented. [redacted]

Change of cognition assessment by MoCA:
The total score and change from baseline will be summarized [redacted]

[redacted]

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]

The infarct volume [redacted] *after the 1st IP by MRI/CTP* [redacted]*:*
A comparison between the treatment group [redacted]

Change of hypoperfusion lesion [redacted] *from Baseline:*
The absolute and percentage changes from baseline in hypoperfusion lesion in perfusion-weight imaging MRI/CTP will be summarized [redacted]

Proportion of subjects with 90% reduction in hypoperfusion lesion [redacted]*:*
The number and percentage of subjects showing 90% reduction in hypoperfusion lesion [redacted]

Occurrence of sICH [redacted] *after the 1st IP:*
The number and percentage of subjects with sICH (clinical deterioration defined as an increase in the NIHSS score of 4 points or more AND confirmed by MR/CT imaging - documentation) [redacted]

	[redacted] *Occurrence of aICH* [redacted] *after the 1st IP:* The number and percentage of subjects with aICH [redacted] *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. [redacted] *Other safety analyses:* AE data, clinical laboratory assessments, vital signs, and 12-lead electrocardiogram will be summarized descriptively.
Ethical Considerations	This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; Regulation (EU) No. 536/2014; and in compliance with GCP guidelines. IECs/IRBs will review and approve this protocol and the ICF. All subjects are required to give written informed consent before participation in the study. Lumosa Therapeutics Co., Ltd. has begun the LT3001-205 (BRIGHT) trial as a possible treatment of LT3001 Drug Product for AIS patients, who are not eligible to be treated with EVT and or rtPA. The trial with placebo-controlled design is ethically acceptable to evaluate the safety and efficacy results of LT3001 Drug Product objectively because there is no approved treatment for AIS patients, who are not eligible to be treated with EVT and or rtPA in the acute stage. According to the protocol, subjects who participate in the trial should be treated with standard of care of AIS therapies when appropriate. The use of placebo. The design is support by the Declaration of Helsinki and current AIS treatment guidelines. Meanwhile, the use of placebo serves to both provide the understanding of the safety findings of LT3001 Drug Product and to ensure that efficacy results can be clearly interpreted. Please refer to the protocol section 5.3 "Clinical Risks/Benefit of LT3001", 5.4 "Study Rationale" and 10.1 "Informed Consent" for more details.

3 TABLE OF CONTENTS

3.1 List of In-text Tables

3.2 List of In-text Figures

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
aICH	asymptomatic intracranial hemorrhage
AIS	acute ischemic stroke
[redacted]	[redacted]
aPTT	activated partial thromboplastin time
[redacted]	[redacted]
CFR	Code of Federal Regulations
CI	confidence interval
CS	clinically significant
CT	computed tomography
CTP	computed tomography perfusion
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
EVT	endovascular thrombectomy
FDA	Food and Drug Administration
GCP	good clinical practice
GLP	Good Laboratory Practice
GMR	geometric mean ratio
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	International Normalized Ratio
IP	investigational product
IRB	institutional review board
ITT	Intent-to-Treat
IV	intravenous/intravenously
LAR	legally acceptable representative
LDR	legally designated representative
[redacted]	[redacted]
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
mRS	Modified Rankin Scale
MTD	maximum tolerated dose
NCS	not clinically significant
NIHSS	National Institute of Health Stroke Scale
[redacted]	[redacted]
PD	pharmacodynamic(s)

Abbreviation	Definition
PK	pharmacokinetic(s)
PP	Per-Protocol
PT	prothrombin time
rtPA	recombinant tissue-type plasminogen activator
[redacted]	[redacted]
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
sICH	symptomatic intracranial hemorrhage
SoC	standard of care
SUSAR	suspected unexpected serious adverse reactions
WOCBP	women of childbearing potential
US	United States

5 INTRODUCTION

5.1 General Information on Acute Ischemic Stroke

Stroke is classically characterized as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause.[1] Ischemic strokes account for about 87% of all strokes; 10% are intracerebral hemorrhage strokes, whereas 3% are subarachnoid haemorrhage strokes.[2] Annually, 15 million people worldwide suffer a stroke; in the United States (US), on average, someone experiences stroke every 40 seconds.[2,3] Globally, stroke is the second leading cause of death in individuals above the age of 60 years and is the leading cause of disability.[3,4]

The ultimate result of ischemic cascade initiated by acute stroke is neuronal death along with an irreversible loss of neuronal function via direct starvation from lack of glucose, failure of adenosine triphosphate production, membrane depolarization, rise in intracellular calcium, and free radical production.[4,5] Furthermore, free radicals directly damage cells and also initiate other reactions that lead to cerebral edema.[6] Based on the pathogenesis of ischemic stroke, the 2 main aims of the treatment strategies in ischemic stroke are restoration of cerebral blood flow and reduction of the harmful effects of ischemia on neurons.[4]

Alteplase (Activase®), a recombinant tissue-type plasminogen activator (rtPA), was the first medication approved for the treatment of ischemic stroke by the US Food and Drug Administration (FDA) in 1996 (BLA 103172/S-1055). Although alteplase has been shown to improve the outcome of subjects with acute ischemic stroke (AIS), its use has been limited because of the low eligibility rate for this medication. The most common exclusion for alteplase is the delay in seeking medical attention; only 22% to 31% of patients with ischemic stroke present to an emergency department within the time window approved for rtPA administration, which is 3 or 4.5 hours after symptom onset.[7] In addition, symptomatic intracerebral hemorrhage is the most feared complication after intravenous (IV) alteplase; with nearly 5-fold risk even when alteplase was given within 3 hours, as shown in a recent meta-analysis of 1779 subjects.[7] The time window allowed for rtPA treatment varies among countries; for example, the US FDA did not approve the change from 3 hours to 4.5 hours after their review of the trial results and unpublished data from alteplase manufacturer.[7] Administration later than 4.5 hours is associated with an increased risk of mortality, and the risk-benefit ratio has not been established (SIGN 2008).[8]

Restoration of the blood supply is essential to minimize the damage caused by the ischemic condition, but reperfusion by thrombolytic drugs such as alteplase and angioplasty techniques often lead to an increase in the extent of brain injury. This reperfusion injury is thought to be caused by the activity of free radicals.[9] Although the benefit of alteplase is well established, its adverse effects remain the major concerns for the use of the thrombolytic agent. Additionally, rtPA also has potential for direct neurotoxicity that is not related to its thrombolytic activity.[10]

Due to the abovementioned reasons, the usage rate of alteplase is low, with only approximately 5% of stroke patients being administered alteplase.[11] As such, there is a need to develop

treatments that can offer similar efficacy to alteplase but with a lower increase of bleeding and/or longer therapeutic window.

5.2 Background on LT3001

LT3001 [redacted] is a novel small molecule designed to have both thrombolytic and free radical scavenging activities, which were characterized in various *in vitro* and *in vivo* models. *In vitro* studies have shown that LT3001 exhibits substantial anti-oxidation activity. In animal studies, LT3001 can restore blood flow, reduce cerebral infarct volume, and improve neurological outcome in rodent and non-human primate stroke models, with an apparent wider therapeutic time window and a better safety profile than those reported for rtPA. Effect of LT3001 on the bleeding time was evaluated in male Institute of Cancer Research mice using an amputation tail model. The tail bleeding time of mice treated with [redacted] LT3001 was comparable to animals that received vehicle control and significantly shorter than those treated with rtPA (10 mg/kg).

LT3001 appears to have both thrombolytic and free radical scavenging effects with minimal risk of bleeding and potentially extended treatment time window. Therefore, LT3001 is being developed for the treatment of AIS.

5.2.1 Nonclinical Studies

The nonclinical program for LT3001 included the following:

- *In vitro* pharmacology studies to evaluate antioxidant activity, anti-platelet activity, [redacted] induced leukocyte migration, interaction with Aspirin, and binding to receptors and critical enzymes;
- *In vivo* pharmacology studies to evaluate efficacy in mouse, rat, and monkey models of stroke;
- *In vivo* pharmacology study to evaluate the interaction with Aspirin, Clopidogrel, Apixaban, or Dabigatran in a rat model;
- Good Laboratory Practice (GLP) safety pharmacology studies, involving neurological and respiratory in rats, cardiovascular in dogs and mini-pigs, an *in vitro* human Ether-a-go-go Related Gene assay, and a non-GLP cardiovascular study in monkeys;
- *In vivo* pharmacokinetic (PK)/toxicokinetic evaluations in rats, dogs, and mini-pigs;
- *In vitro* absorption, distribution, and metabolism studies using mouse, rat, dog, monkey, mini-pig, and human hepatocytes;
- Acute toxicity studies in rats, dogs, monkeys, and mini-pigs;
- 14-day repeat-dose GLP toxicity studies in rats and dogs;
- 6-day repeat-dose GLP toxicity study in mini-pigs;
- *In vitro* genotoxicity studies and *in vivo* genotoxicity evaluation in rats; and
- *In vitro* phototoxicity study.

A summary of noteworthy findings from these nonclinical studies is listed below:

- Effect of LT3001 [redacted] on the bleeding time was evaluated in male Institute of Cancer Research mice and was comparable to animals that received vehicle control and significantly shorter than those treated with rtPA (10 mg/kg).
- LT3001 showed superior total antioxidant capacity than the known antioxidant control substances (Trolox®, L-ascorbic acid, and Edaravone) in CUPric Ion Reducing Antioxidant Capacity assay *in vitro*.
- LT3001 significantly inhibits [redacted] polymorphonuclear leukocytes migration and [redacted] platelet aggregation.
- LT3001, administered [redacted] at 3 and 6 hours post stroke, was considered efficacious in the preclinical rat embolic stroke model.
- Repeat administration of LT3001 once- or thrice-daily for 6 consecutive days was considered efficacious in a preclinical rat embolic stroke model. In addition, twice-daily administration of LT3001 also showed a significant smaller infarct size than vehicle control and rtPA-treated stroke rat model.
- In a dose range finding and blood flow monitoring study, LT3001 [redacted] increased the blood flow compared to those of vehicle control in embolic stroke rat model. There was a dose-dependent effect, higher dose LT3001 had a better therapeutic effect of restoring blood flow.
- In macaque monkey of embolic stroke model, LT3001 [redacted] improved neurological deficit score measured at 24, 48, and 72 hours after ischemia, which was induced by injection of pooled clots into the internal carotid artery, when compared to that improved by rtPA.
- The interaction of LT3001 and Aspirin was assessed by optical microplate-based assay and in male Wistar rats. LT3001 [redacted] showed no effect on Aspirin's anti-platelet aggregation activity *in vitro*. LT3001 [redacted] has no impact on Aspirin induced bleeding time elongation or gastric mucosal injury *in vivo*.
- The interaction of LT3001 and Dabigatran, Clopidogrel, or Apixaban was assessed in male Sprague-Dawley rats. Dabigatran, Clopidogrel, and Apixaban prolonged the prothrombin time (PT), activated partial thromboplastin time (aPTT), and/or thrombin time in the rat clotting time assay. LT3001 [redacted] in combination with Dabigatran, Clopidogrel, or Apixaban did not elicit synergistic effects in clotting time assay *in vivo*.
- In secondary pharmacodynamics (PD) studies, LT3001 [redacted] had no effect on any of the receptors or critical enzymes evaluated.
- In GLP safety pharmacology studies *in vivo*, LT3001 [redacted] showed no biologically significant effect in either the central nervous system Irwin test or respiratory physiological parameters in rats.

- In a GLP assay *in vitro*, [redacted] inhibition of mean human Ether-a-go-go Related Gene-mediated potassium currents was observed at the highest concentration tested (10 mM). No inhibition was observed at [redacted] LT3001.
- In 2 GLP cardiovascular studies in dogs, a decrease in blood pressure and an increase in heart rate (with concomitant decreases in RR interval, PR interval, and uncorrected QT intervals) were observed at LT3001 [redacted].
- In a GLP cardiovascular study in mini-pigs, a decrease in blood pressure and increase in heart rate were noted at LT3001 [redacted]. There was no effect of LT3001 on qualitative electrocardiogram (ECG) parameters.
- In a non-GLP cardiovascular study in monkeys, a decrease in blood pressure and an increase in heart rate (a compensatory response to decreased blood pressure) were observed [redacted]. The effects on cardiovascular parameters were all transient and recovered to normal range within a few hours.
- PK studies of LT3001 in rats, dogs, and mini-pigs indicated that LT3001 plasma levels increased roughly in proportion to the IV dose [redacted] with no signs of accumulation after repeated doses.
- *In vitro* protein binding studies showed that LT3001 does not bind significantly to human serum albumin or serum acid alpha-1-glycoprotein, which are considered the most relevant drug carriers in human plasma. [redacted]
- *In vitro* metabolite identification studies with LT3001 were conducted using plasma and following *in vitro* incubation with hepatocytes from mice, rats, dogs, monkeys, mini-pigs, and humans. [redacted] *In vitro* studies of LT3001 [redacted], no inhibitory effect on the activity of CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A or P-glycoprotein, nor induction effect on the activity of CYP1A2, CYP2B6 or CYP3A4 were observed. Therefore, LT3001 is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes.
- LT3001 was not phototoxic and showed no genotoxic activity in either the Ames test or the chromosomal aberration assay with Chinese Hamster Ovary cells. LT3001 did not induce micronuclei in rat bone marrow cells.
- Acute toxicity studies with LT3001 were conducted in rats, dogs, monkeys, and mini-pigs, respectively. [redacted]

- The repeat-dose toxicity of LT3001 was evaluated in a 5-day non-GLP study in dogs [redacted] 14-day GLP repeat-dose (once daily) IV toxicity studies in rats and in dogs [redacted] and a GLP repeat-dose study in Bama mini-pigs [redacted]. Notable LT3001-related findings included swelling and discoloration at the injection site on the tail and mild vocalization during dosing in rats; and prolonged capillary refill time, weak pulse, rapid respiration, recumbency, decreased activity, and skin redness in dogs. These clinical signs subsided or became absent with subsequent dosing. There was no mortality reported in either of the 14-day studies or during the dosing period in the 6-day mini-pig study [redacted] prior to scheduled Day 14 sacrifice, because of a moribund condition). The no observed adverse effect levels were determined [redacted]

5.2.2 Clinical Studies

[redacted], 4 clinical studies of LT3001 have been completed:

- LT3001-101, a first-in-human Phase I, single-ascending dose study conducted at 1 clinical site in the US, evaluating LT3001 [redacted]. The objectives of the study were to evaluate the safety, tolerability, and PK of single ascending doses [redacted] LT3001 drug product in healthy subjects. The results of this study were used to determine the doses to be assessed for a Phase I multiple-ascending dose study in healthy subjects, and to determine the Recommended Phase II Dose of LT3001 drug product to be tested in future studies in AIS patients, including this study.
- LT3001-103, a randomized, double-blind, placebo-controlled, parallel-group study in healthy Chinese subjects to determine the safety, tolerability, and PK of multiple doses of LT3001 drug product [redacted]

[redacted]. This study also determined the effect of multiple doses of LT3001 drug product on blood pressure and coagulation function.

- LT3001-105 was a two-part Phase I study of multiple doses of LT3001 drug product [redacted] in healthy adult subjects in the US. Part A was randomized, double-blind, placebo-controlled design to evaluate the safety, tolerability, and PK of multiple doses of LT3001 drug product. Part B was open-label without placebo-controlled design to assess the drug-drug interaction of LT3001 drug product when co-administered with aspirin, clopidogrel, apixaban or dabigatran.
- LT3001-201, a Phase IIa, double-blind, single-dose, randomized, placebo-controlled study to evaluate the safety, tolerability, and potential efficacy of LT3001 drug product [redacted] in subjects with AIS.

In addition, 3 studies on LT3001 are planned/ongoing (enrollment stage):

- LT3001-202: Randomized, double-blind, placebo-controlled, parallel-group study to determine the safety and efficacy of multiple doses of LT3001 drug product [redacted] in patients with AIS.
- LT3001-203: Randomized, double-blinded, placebo-controlled Phase II study to evaluate the safety and efficacy of LT3001 drug product [redacted] in subjects with AIS undergoing endovascular thrombectomy.
- LT3001-205: current study described in this protocol.

5.3 Clinical Risks/Benefits of LT3001

In the first-in-human LT3001-101 study for single dose of LT3001 drug product [redacted] (Cohort 0) and [redacted] (Cohort 1) [redacted] healthy human volunteers, the LT3001 drug product was safe and well tolerated in both dosing cohorts. There were no severe adverse events (AEs) or serious adverse events (SAEs) reported in either cohort.

There were no AEs reported in Cohort 0. In Cohort 1, 1 subject presented with an allergy to medical tape, 1 subject developed a hematoma that was acquired during IV needle removal, and 1 subject receiving [redacted] LT3001 drug product developed a headache. All AEs occurred post dosing, were classified as mild in severity, and were resolved. The AE of headache was considered by the Investigator to be mild in intensity and possibly related to the investigational product (IP); the other AEs were considered unrelated.

Safety data collected in this study also included vital signs (pulse rate, blood pressure, respiratory rate, and body temperature), ECGs, clinical biochemistry, hematology, and coagulation/clotting parameters. There were no clinically significant findings in any of the safety parameters measured.

In the LT3001-103 study, the multiple doses [redacted] of LT3001 drug product [redacted] was generally safe and well tolerated in healthy Chinese adult subjects. No SAEs were reported. 14 AEs were reported in 9 subjects: 3 subjects (30%) with 4 AEs in the [redacted] LT3001 drug product group, 6 subjects (54.5%) with 10 AEs in the [redacted] LT3001 drug product group and no AEs in the placebo group. No statistical significance (P> 0.05) was observed among 3 groups on AEs frequency. All AEs were classified as mild and considered unrelated or unlikely related to the IP. No significant difference was observed among 3 groups on each safety assessment, including vital signs, ECGs, hematology, urinalysis, and coagulation parameters.

The pharmacodynamic effects of multiple doses of LT3001 drug product on coagulation function (PT and aPTT) and blood pressure were also evaluated. There was no significant trend of changes of blood pressure in the two LT3001 drug product groups compared with placebo group. Compared with the baseline, there was no clinically significant abnormal shift in PT and aPTT after dosing in each treatment group. Overall, no significant effect on blood pressure and coagulation function was observed in [redacted] LT3001 drug product groups after dosing.

The average of C_{max} values were approximately [redacted] The maximum of C_{max} was [redacted].

In Part A of the LT3001-105 study, the multiple doses of LT3001 drug product [redacted] was generally safe and well tolerated when administered alone and in combination with the concomitant medications. All of the reported AEs were mild in severity and non-serious. No clinically relevant abnormal vital signs, ECG, oxygen saturation, hematology, chemistry, urinalysis, coagulation, platelet aggregation tests were found during the study period. LT3001 has limited effect on coagulation when co-administrated with apixaban and dabigatran, and limited effect on collagen/ADP and collagen/epinephrine when co-administrated with aspirin and clopidogrel.

The [redacted] LT3001 resulted in no to limited accumulation in subjects, and the plasma concentration profile of LT3001 was comparable for Parts A and B of the study.

The effect of aspirin on LT3001 was limited [redacted].

[redacted]

[redacted] The effect of LT3001 on clopidogrel [redacted] was limited [redacted].

The effect of apixaban on LT3001 was limited [redacted].

The effect of dabigatran on LT3001 was limited [redacted]

In the Phase IIa LT3001-201 study in subjects with AIS, a single dose of LT3001 drug product [redacted] was generally safe and well tolerated. No subject was reported with symptomatic intracranial hemorrhage (sICH) during the study or within 7 days of receiving IP. Asymptomatic ICH (aICH) was reported in 2 subjects, 1 subject in each treatment arm within 24 hours of receiving IP. Within 7 days of receiving IP, there was a higher proportion of subjects with aICH in the LT3001 drug product group (3 subjects, 18.8%) compared with the placebo group (1 subject, 12.5%), with relative risk (95% confidence interval [CI]) of 1.5 (0.2 to 12.2). No subject died because of intracerebral or other major bleeding complications within 90 days. Eleven SAEs were reported in 6 subjects: 4 subjects (25.0%) in the LT3001 drug product group and 2 subjects (25.0%) in the placebo group, all of which were considered as unrelated or unlikely related to IP. Among these 6 subjects, 2 subjects died because of SAEs. One subject died because of an SAE of pneumonia of severe intensity in the LT3001 drug product group (6.3%) and the other subject died because of an SAE of respiratory arrest of severe intensity in placebo group (12.5%). Among the 11 SAEs, 7 SAEs of severe intensity were reported for 3 subjects (18.8%) in the LT3001 drug product group (pneumonia aspiration for 1 subject, cerebral infarction in a second subject, and pneumonia and bronchial neoplasm in the third subject) and for 1 subject (12.5%) in the placebo group (pneumonia, COVID 19, and respiratory arrest). No subject discontinued the IP because of treatment-emergent AEs. No clinically significant trend was observed for laboratory parameters, vital signs, ECGs, or neurological examinations.

Regarding the efficacy data, the decrease in National Institute of Health Stroke Scale (NIHSS) of ≥4 points at Visit 5 (Day 30) showed promise: a higher proportion of subjects in the LT3001 drug product group (46.67%) showed decrease in NIHSS of ≥4 compared with the placebo group (14.29%).

Based on the outcomes of the clinical and nonclinical studies, the safety monitoring plan for this study and future LT3001 clinical studies will include the following:

1. Physical examination.
2. Assessment of vital signs.

3. Clinical laboratory tests including hematology and clinical biochemistry.
4. Coagulation/clotting parameters, including PT, and aPTT.
5. Monitoring of AEs.

Overdose

The dose level of LT3001 drug product will be calculated by the Investigator or a qualified designee [redacted]. Because drug accumulation is not anticipated [redacted], and subjects will only receive LT3001 drug product administered by an Investigator or a qualified designee and under close monitoring, it is anticipated that the risk of overdose or medication error will be low.

Any overdose, with or without associated AEs, should be promptly reported by the Investigator or designee [redacted] Pharmacovigilance (see contact details in Section 12.7.3). Overdoses and medication errors will be documented as protocol deviations and communicated to the Study Monitor.

No specific therapy for overdose of LT3001 drug product exists. In the event of overdose or medication error, appropriate standard of care (SoC) therapy for the subject's symptoms and clinical status will be provided.

Details regarding known or anticipated benefits and risks, as well as reasonably anticipated AEs for LT3001 may be found in the investigator's brochure.

5.4 Study Rationale

Tissue plasminogen activator (alteplase) is the only approved drug treatment for stroke in the US and Taiwan. Per the labeling, it must be administered within 3 hours of stroke symptom onset. The approved window of administration in some other countries is 4.5 hours of stroke symptom onset.

LT3001 is a novel chemical entity designed to have both thrombolytic and free radical scavenging activities, which were characterized in various *in vitro* and *in vivo* models. Its advantages over IV rtPA include: shorter infusion time, within 24 hours of stroke onset (as opposed to 3 to 4.5 hours), better recanalization rate, prevention of reperfusion injury by scavenging free radicals, no effect on bleeding time, no evidence of increase in intracranial hemorrhage (as seen with IV rtPA), and ease of use.

This Phase II, double-blind, randomized, placebo-controlled study is to evaluate the efficacy and safety of multiple doses of LT3001 drug product in subjects with AIS.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

The primary objective is to determine the safety of multiple doses of LT3001 drug product in subjects with AIS.

6.1.2 Secondary Objective

The secondary objective is to determine the efficacy of multiple doses of LT3001 drug product in subjects with AIS.

6.2 Study Endpoints

6.2.1 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.

6.2.2 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 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 sICH [redacted] after the 1st IP; clinical deterioration defined as an increase in the NIHSS of 4 points or more AND confirmed by magnetic resonance (MR)/computed tomography (CT–) imaging - documentation.
2. The occurrence of 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.

7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

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 [redacted] Subjects who participate in this trial should be treated with SoC 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 [redacted], baseline NIHSS [redacted], and time of AIS symptoms onset to the planned 1st IP [redacted]. The stratified randomization is to ensure similar risk distributions with regards to efficacy measures at baseline in the treatment groups.

[redacted]

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

LT3001 drug product or placebo will be administered [redacted].

A Data Safety Monitoring Board (DSMB) will be formed to assess all data (including imaging data) of LT3001 drug product or placebo treatment. [redacted] 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. [redacted]

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

Figure 1 presents the study design. The Schedule of Assessments is provided in Section 10.

Figure 1. Study Design

7.2 Discussion of Study Design

Because there is no approved drug treatment for AIS for administration beyond 3 hours of stroke onset in the US and in Taiwan and 4.5 hours in some countries, a placebo-controlled study will be ethically acceptable to evaluate the drug effect objectively.

Efficacy will be evaluated by assessing the functional outcomes measured by mRS, neurological outcome assessed by NIHSS, the occurrence of recurrent stroke, and cognition assessed by the MoCA; and imaging outcomes measured by change in infarct volume and hypoperfusion lesion.

Safety assessments include occurrence of sICH, aICH, and mortality, and AEs. Besides, vital signs, physical examinations, 12-lead ECGs recordings, laboratory results (hematology, clinical biochemistry, and coagulation) will also be assessed.

The dose and regimen chosen are based on results from the nonclinical studies, the completed clinical studies, and US FDA recommendations. Based on the NOEL of the more sensitive species and the safety factor of 10 recommended by the "Guidance for Industry - Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, CDER, July 2005," the proposed human doses for the Phase I single-ascending-dose first-in-human study, LT3001-101, was determined . The has an excellent safety profile, with even the highest dose at producing only 1 mild AE (headache) and no clinically significant findings in any of the safety parameters measured (AEs, vital signs, electrocardiograms, clinical chemistry, urinalysis, hematology, or coagulation parameters).

The dose for the phase II single-dose study in patients with acute ischemic stroke, LT3001-201, is , based on the "no adverse event observed" dose tested in the Phase I single-dose study. No subject was reported with sICH during the study or within 7 days of receiving IP. Eleven serious TEAEs were reported by 4 subjects (25%) in the LT3001 drug product group and by 2 subjects (25%) in the placebo group, all of which were considered as unrelated or unlikely related to IP. The single-dose regimen was generally safe and well tolerated in AIS patients.

The doses for the phase I multiple-dose studies in healthy subjects, LT3001-103 and LT3001-105 are [redacted] These multiple-dose regimens were generally safe and well tolerated. All AEs were classified as mild and considered unrelated or unlikely related to the IP. No significant difference was observed between LT3001 drug product and placebo treatment groups on each safety assessment, including vital signs, ECGs, hematology, urinalysis, and coagulation parameters.

According to the safety conclusion from LT3001-103 and LT3001-105 studies, the proposed dose for this Phase II multiple-dose study, LT3001-205[redacted].

COVID-19 related measures

Considerations related to COVID-19 and related measures will be documented in a separate risk assessment and mitigation plan. Details relating to statistical analyses, handling of protocol deviations, handling of missing data, and any other considerations related to COVID-19 and related measures will be detailed in the Statistical Analysis Plan (SAP).

7.3 End of Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed all study periods, including the last scheduled follow-up visit as indicated in the Schedule of Assessments (Table 1).

The end of the study will be the last subject's last visit.

8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding number of subjects planned to be randomized.

8.1 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 (LAR)/ legally designated representative (LDR) consents to participation by signing the informed consent form (ICF) 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 (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 the last dosing of IP administration. A woman is considered to be a WOCBP after menarche and until she is in a postmenopausal state for 12 months or otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). For the definition and list of highly effective methods of contraception, see Appendix 1.

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.

8.2 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 IV thrombolytic (e.g., rtPA) 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 (INR) >1.7 or aPTT >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/mm^3 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.

8.3 Study Withdrawal, Removal, and Replacement of Subjects

If a subject discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the Medical Monitor (see contact details in Section 12.7.3). The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF). Subjects who discontinue early from the study will be asked to complete all assessments listed at Visit 6 as indicated in the Schedule of Assessments (Table 1).

In the event that a subject discontinues prematurely from the study because of a AE or serious AE, the AE or serious AE will be followed up until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the Investigator to no longer be clinically significant.

Once a subject is withdrawn from the study, the subject may not reenter the study.

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- unacceptable toxicity or AE

- subject withdrawal of consent: at any time,' a subject's participation in the study may be terminated at his/her request or on the basis of the Investigator's clinical judgment. The reason for subject withdrawal will be noted on the eCRF.
- intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the subject's termination from the study
- general or specific changes in the subject's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria
- subject fails to adhere to the protocol requirements (e.g., drug noncompliance, failure to make the return visits in the Follow-Up Period)
- lost to follow-up: the subject stopped coming for visits, and study personnel were unable to contact the subject 3 times
- pregnancy, as indicated in Section 12.7.5.

Additionally, the Sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with good clinical practice (GCP). This study may be terminated at the discretion of the Sponsor or any regulatory agency. An Investigator may elect to discontinue or stop the study at his or her study site for any reason, including safety or low enrollment.

Randomized but not treated subjects will not be replaced.

8.3.1 Study and Site Closure

The Sponsor reserves the right to close the study sites or terminate the study at any time for any reason at its sole discretion. All study sites will be closed after the study is completed or following the decision to close or terminate the study. A study site is considered closed when all subjects have completed study procedures [redacted] all protocol-required data have been collected and entered into the electronic data capture (EDC) system, all required documents have been collected and reconciled, and the study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a study site by Sponsor or the Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC/IRB or health authorities, Sponsor's procedures, or ICH-GCP guidelines.
- Difficulties in the recruitment of planned number of subjects in the indicated time with insufficient recruitment rate.
- Discontinuation of further LT3001 development.

Sponsor or health authorities may terminate the study for reasonable cause. Conditions that may warrant termination of the study include, but are not limited to:

- Negative risks/benefits assessment.
- New scientific evidence of any unexpected, serious, or unacceptable risks of LT3001 that could impact the subjects' enrolled or continuing in the study.
- Sponsor decision to suspend or discontinue testing, evaluation, or development of LT3001.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, IECs/IRBs, regulatory authorities, and any contracted vendors used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subjects and ensure appropriate therapy and/or follow-up.

9 TREATMENTS

9.1 Details of Study Treatments

Each eligible subjects will be randomized centrally in a ratio of 1:1 to LT3001 drug product or placebo.

LT3001 drug product will be provided [redacted] in glass vials with butyl rubber stoppers and flip-off aluminum crimp seals. Each vial will contain LT3001 drug substance [redacted]

All drug supplies will be provided by the Sponsor.

9.2 Dosage Schedule

Subjects randomized to the study [redacted].
The 1st IP will be administered within 24 hours after stroke symptoms onset. [redacted]

9.3 Measures to Minimize Bias: Study 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 IP, and site staff conducting study assessments will not know which treatment a subject receives to allow assessment of the study objectives without bias.

9.3.1 Method of Study Treatment Assignment

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 planned 1st IP [redacted]. The stratified randomization is to ensure similar risk distributions [redacted].

[redacted]

At Screening (Visit 1), [redacted] EDC system will assign a unique subject identification number to the subject known as the Subject Number. This number will be associated with the subject throughout the study. Every subject who signs an ICF (or has a LAR/, LDR or impartial witness sign the ICF on their behalf) must be entered into [redacted] EDC system regardless of eligibility in order to obtain a Subject Number. [redacted] The unblinded statistician will produce a Master Randomization list for the random assignment of subjects to each treatment [redacted] and a Kit Randomization list for the random assignment of kit numbers for labelling to each treatment. [redacted] Randomization Manager will receive the Master randomization list and the Kit randomization list [redacted].

The subjects will be centrally randomized at a study level.

9.3.2 Blinding

According to the randomization schedule as indicated in the Schedule of Assessments (Table 1) and in accordance with the Pharmacy Manual, the Investigator or designee will obtain the

Randomization Number and the Kit Number from [redacted] EDC system for each randomized subject. [redacted] Study site personnel, subjects, Sponsor personnel, or Sponsor designees will be blinded 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.

Subject unblinding will only occur if details of the treatment assigned to the subject are necessarily required to determine the care needed to manage an AE or other serious safety situation. The Investigator and at least one designee will have the access to the unblinding module [redacted] and will be able to perform subject unblinding in an emergency. [redacted] Investigator must make every effort to contact the Medical Monitor before unblinding a subject (contact details are provided in Section 12.7.3). 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. [redacted] The unblinding and its cause will also be documented in the eCRF [redacted].

9.4 Treatment Accountability and Compliance

The pharmacist or designee will maintain records of IP delivered to the study site, the inventory at the study site, the distribution to and use by each subject, and the return of materials to the Sponsor for storage or disposal. These records should include dates, quantities, batch/serial numbers, retest dates, in-clinic temperature log, and unique code numbers assigned to the product and study subjects.

Investigators will maintain records that adequately document that the subjects were administered the correct study treatment and reconcile the products received from the drug dispensing center. IP will not be returned to the Sponsor until accountability has been fully monitored.

Administration of IP will be supervised by study site personnel to ensure compliance.

9.5 Prior and Concomitant Therapy

9.5.1 Prior and Concomitant Medications

Restricted prior therapies are provided in Section 8.2. Low dose subcutaneous conventional heparin or low molecular weight heparin at a preventive dose are allowed.

All medications and other treatments taken by the subject during the course of the study, including those treatments initiated before Screening (Visit 1), must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

After the subject has been administered the IP, medication to treat minor treatment-emergent illness(es) will generally be permitted. The SoC of AIS therapies will be permitted when appropriate.

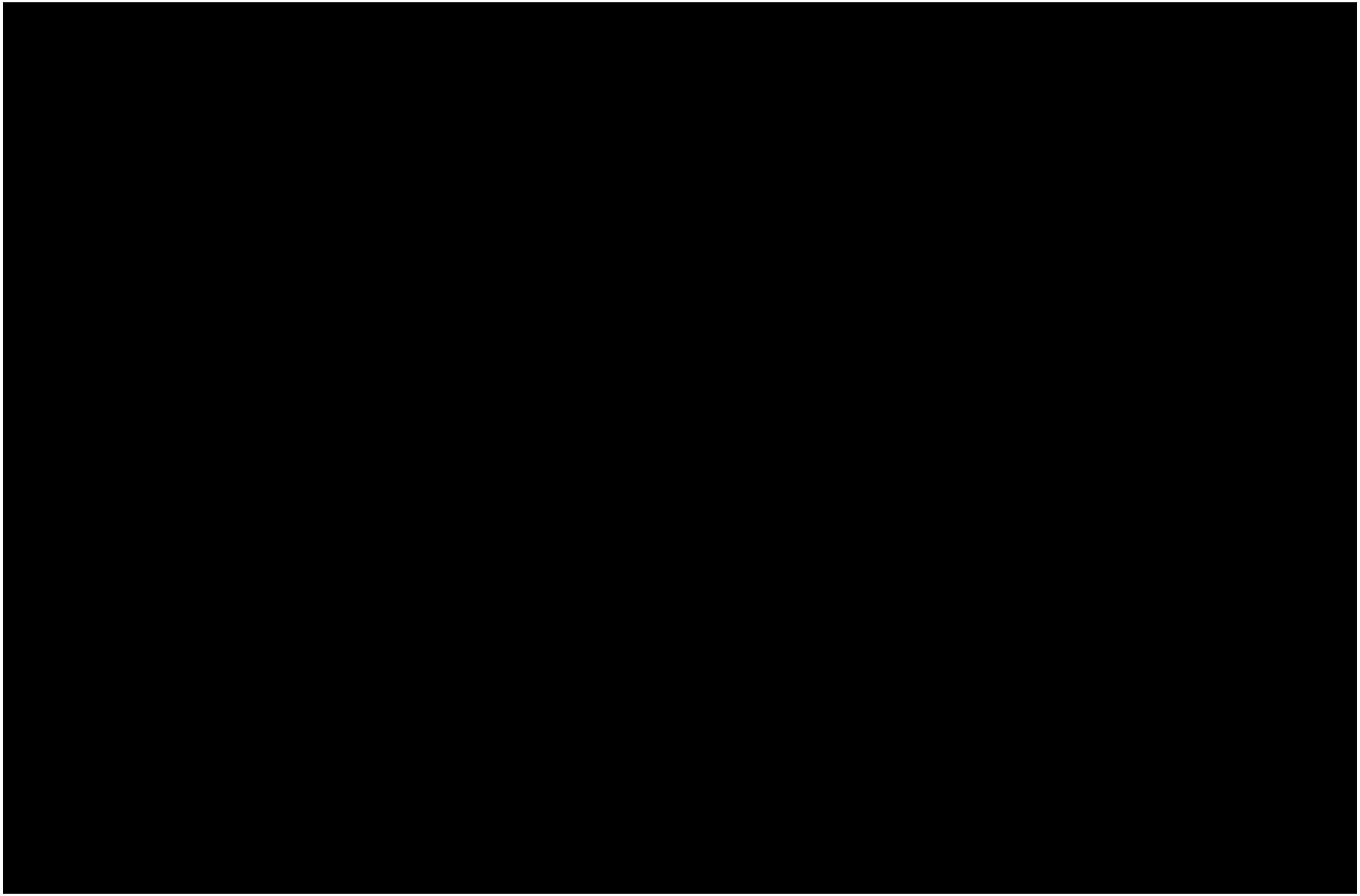
9.6 Post-Trial Treatments

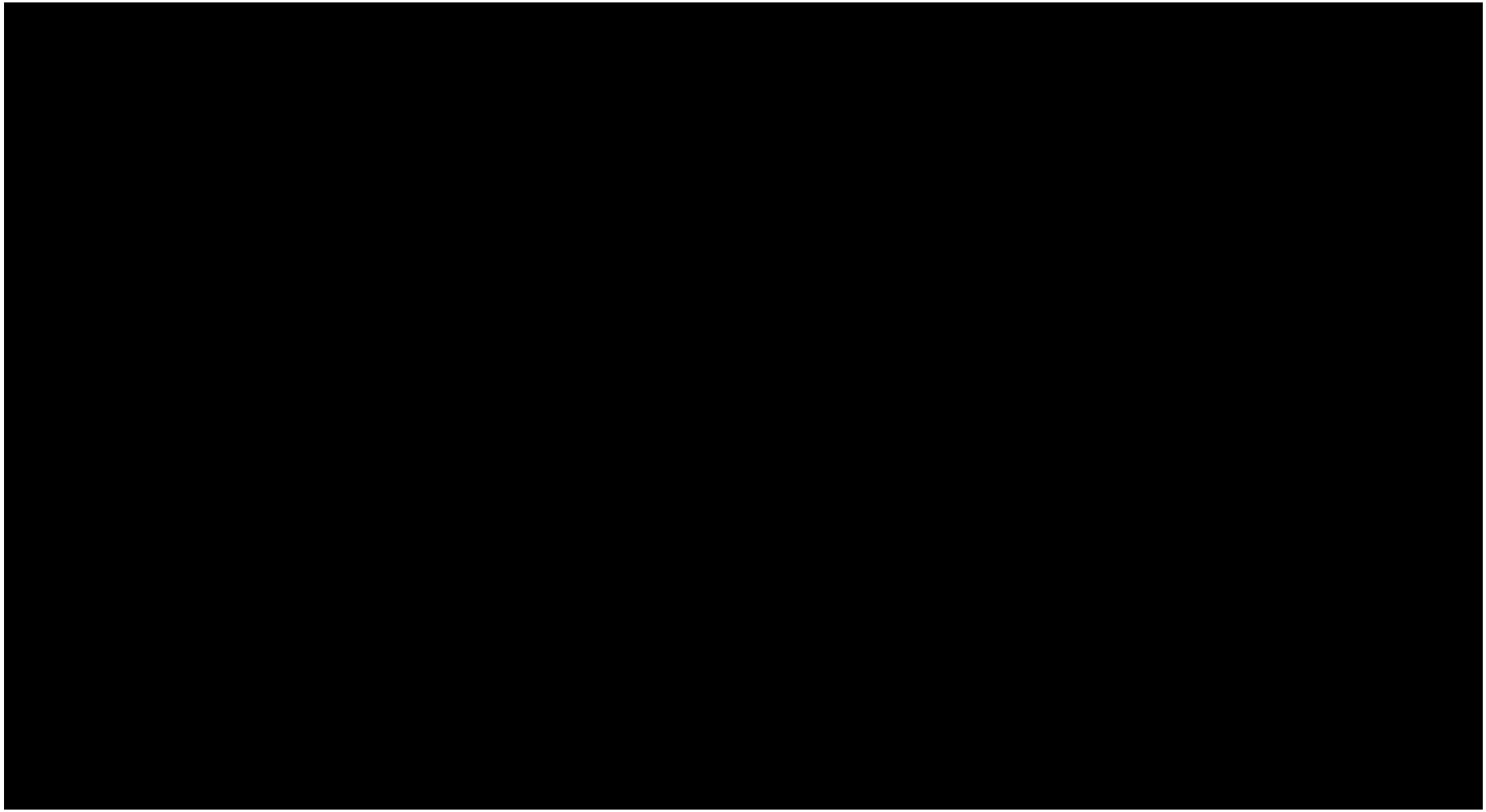
Sponsor does not intend to provide any investigational or non-investigational products (specified in this protocol), or any other interventions to subjects who have completed the study or who are withdrawn earlier. When subjects leave the study, they will be under the care of their regular health care provider who will decide the best way to follow up with the AIS condition, including taking anti-platelet or anti-coagulant drugs to prevent secondary ischemic stroke, and receiving rehabilitation to improve physical functions.

10 STUDY PROCEDURES

Table 1 outlines the timing of procedures and assessments to be performed throughout the study. Section 12.6 specifies laboratory assessment samples to be obtained. See Section 11 and Section 12 for additional details regarding efficacy assessments and safety assessments, respectively.

Table 1. Schedule of Assessments





10.1 Informed Consent

Before performing any study-related procedures except the SoC assessments of AIS therapies, the Investigator or designee will obtain the signed ICF from the subject or if applicable the subject's LAR/LDR, impartial witness or decision of independent physician who is not from the clinical study team. Country-specific considerations are provided in Appendix 4.

In acute phase of AIS, patients may suffer from dizziness, loss of balance, trouble walking, weakness on one side of the body, trouble speaking or understanding speech, or trouble seeing with different severity. The AIS patients may be affected by the stroke symptoms and influenced in his/her decision.

The following points should be considered while obtaining the signed ICF:

- If the subject is unconscious, incapacitated and/or incapable, the Investigator or designee must obtain the signed ICF from the subject's LAR/LDR.
- If the subject has a known history or ongoing condition of anosognosia, the Investigator or designee must obtain the signed ICF from the subject's LAR/LDR.
- Where the subject is conscious but is unable to read and/or write or the subject's LAR/LDR is unable to read and/or write, consent may be given and recorded through appropriate alternative means in the presence of at least one independent impartial witness.

The impartial witness must not be a member of the clinical study team. In that case, the impartial witness shall sign and date the ICF. By signing the ICF, the impartial witness attests that

- the information in the ICF and any other written information was accurately explained to, and apparently understood by, the subject or the subject's LAR/LDR;
- adequate time was given for the subject or the subject's LAR/LDR to consider the decision to participate in the study and
- that informed consent was freely given by the subject or the subject's LAR/LDR.

The informed consent shall be documented. The subject or, where the subject is not able to give informed consent, the subject's LAR/LDR shall be provided with a copy of the document (or the record) by which informed consent has been given. Subjects and/or subject's LAR/LDR will not be given any incentives or financial inducements, except for the compensation for expenses directly related to the participation in this trial.

In all these situations, the subject must be informed about the study in a way that is adequate in view of their capacity to understand it. The subject shall as far as possibly take part in the informed consent procedure. The informed consent of the subject and subject's LAR/LDR must be obtained as soon as possible to continue or withdraw from the trial.

In any country where national rules prohibiting the conduct of clinical trials on incapacitated subjects, ICF should not contain signature line for the incapacitated subject's LAR/LDR and incapacitated subjects must not be enrolled in the study.

The study will comply with ICH-GCP guidelines, Regulation (EU) No. 536/2014 and applicable regulatory requirements of each country.

10.2 Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 1). The SoC assessments of AIS patients may be used to evaluate the eligibility of subjects, including but not limited to laboratory and MRI/CTP assessments. The SoC assessments will not need to be repeated at Screening (Visit 1). Section 12.6 specifies laboratory assessment samples to be obtained.

Assessments and procedures scheduled at a visit where IP is administered should be performed before administration of treatment unless otherwise indicated in the Schedule of Assessments (Table 1).

Efficacy assessments are described in Section 11. Efficacy will be evaluated by assessing the functional outcomes measured by mRS, neurological outcome assessed by NIHSS, occurrence of recurrent stroke, and cognition as assessed by the MoCA; and imaging outcomes measured by change in infarct volume and hypoperfusion lesion.

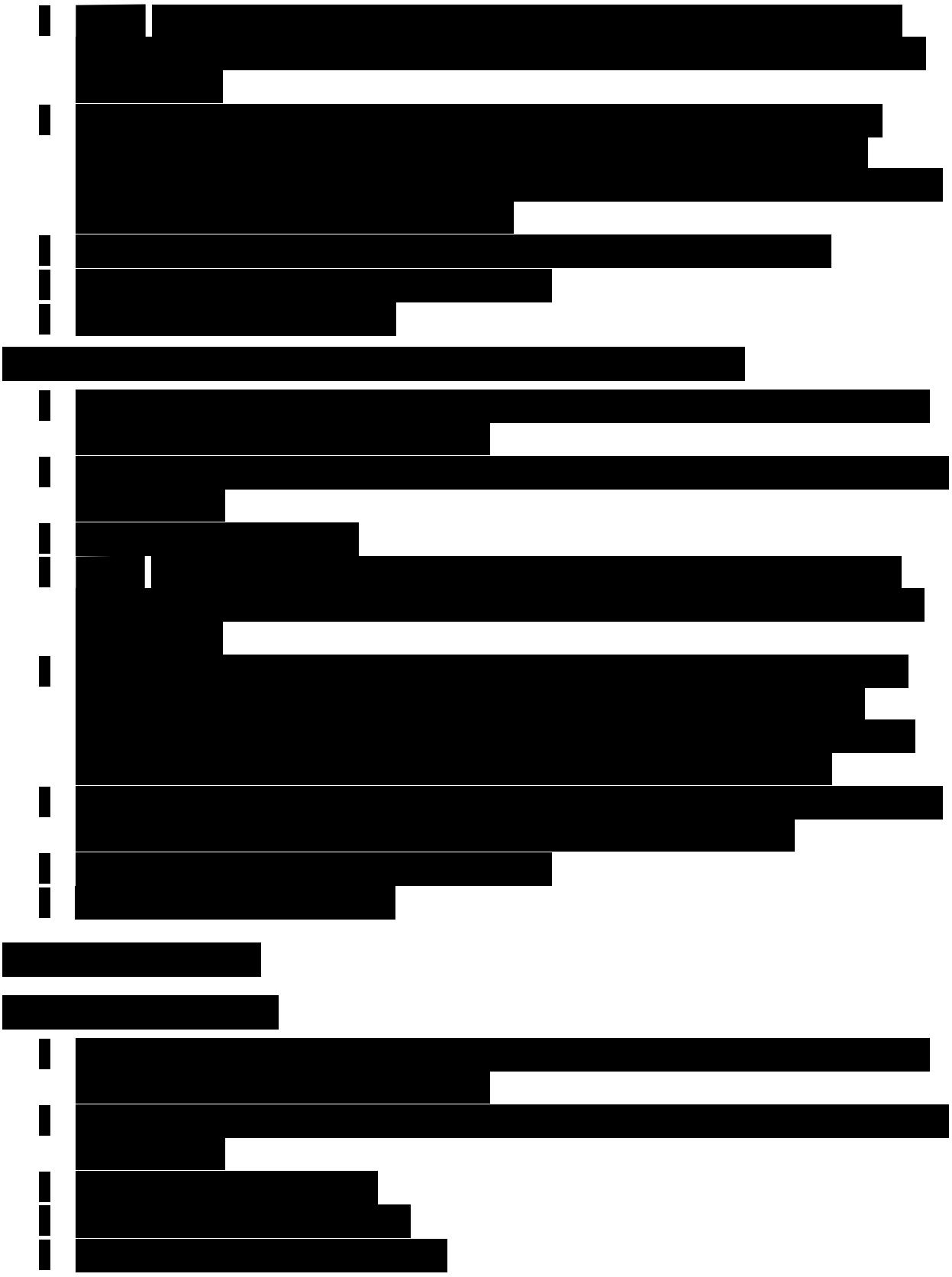
Safety assessments are described in Section 12 and include the occurrence of sICH, aICH, mortality, and AEs. Besides, vital signs, physical examinations, 12-lead ECG recordings, clinical laboratory results (hematology, clinical biochemistry, and coagulation) will also be assessed.

The Investigator may, at his/her discretion, arrange for a subject to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the Investigator to be possibly related to the use of IP. The unscheduled visit page in the eCRF must be completed.

Study discontinuation procedures are described in Section 8.3.

Assessments will be done at each visit as detailed in the subsections below. Assessments at individual visit could occur over multiple days as long as assessments are still within the visit window as specified.

[redacted]



11 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 1) outlines the efficacy assessments to be performed throughout the study and their timing. Efficacy will be evaluated by assessing the functional outcomes measured by mRS, neurological outcome assessed by NIHSS, the occurrence of recurrent stroke, and cognition as assessed by the MoCA; and imaging outcomes measured by change in infarct volume and hypoperfusion lesion.

11.1 Modified Rankin Scale

The mRS measures the degree of disability or dependence in the daily activities of patients who have suffered a stroke. The scale runs from 0 (perfect health without symptoms) to 6 (dead).

[redacted] The score and corresponding description for the mRS is provided in Appendix 2.

11.2 National Institute of Health and Stroke Scale

The NIHSS is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. It consists of 11 items, each with a score range of 0 to 2 or 4, with higher scores indicating more deficit/impairment in that specific ability. The total score ranges from 0 (no deficit) to 42 (dead). The score and corresponding description for the NIHSS is provided in Appendix 3.

[redacted]

11.3 Montreal Cognitive Assessment

The MoCA is a 30-question test for assessment of cognitive impairment and takes approximately 10 minutes to administer. It screens 8 domains: visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation. The score ranges between 0 and 30. A score of 26 to 30 is normal, a score of 18 to <26 is considered as mild cognitive impairment, a score of 10 to 17 is considered as moderate cognitive impairment, and a score of <10 is considered as severe cognitive impairment. [redacted]

11.4 Magnetic Resonance Imaging or Computed Tomography Perfusion

Magnetic resonance imaging, including perfusion, is a widely used imaging technique and plays an important role in the evaluation of patients with AIS. [redacted]

12 SAFETY ASSESSMENTS

Safety assessments (vital signs, physical examinations, 12-lead ECG recordings, AEs, clinical laboratory results [hematology, clinical biochemistry, and coagulation]) are to be performed at protocol -specified visits, as specified in the Schedule of Assessments (Table 1).

12.1 Bleeding Assessment

Bleeding assessment will be done by the Investigator or designee and categorized as sICH and aICH. The occurrence of sICH and aICH [redacted] after the 1st IP will be assessed.

- Symptomatic ICH: clinical deterioration is defined as an increase in the NIHSS of 4 points or more AND confirmed by MR/CT imaging-documentation.
- Asymptomatic ICH is defined per the Heidelberg Bleeding Classification: new hemorrhage that has no implications for prognosis or change in management, and there is no substantive change in the subject's neurological status.

12.2 Medical History/Concomitant Illness

Medical history, including AIS (the primary disease), will be recorded before the 1st IP administration [redacted]. Investigators should document the occurrence, signs, and symptoms of the subject's preexisting conditions, including all prior significant illnesses, up to and including 1 year before Screening (Visit 1). Additional preexisting conditions present at the time when informed consent is given and up to the time of the initiation of the 1st IP administration [redacted] are to be regarded as concomitant illnesses. Medical history will include alcohol consumption and smoking history, if applicable.

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 12.7. All changes not present at Baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

Additionally, demographic data will be collected for all subjects and include date of birth or age according to applicable regulations, gender, and race.

12.3 Vital Signs

Vital signs (body temperature, pulse rate, respiration rate, and systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the Schedule of Assessments (Table 1). All vital signs will be measured after the subject has been resting in a supine position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure, respiration rate, or pulse rate measurements will be repeated at the Investigator's or designee's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

Body weight (without shoes) will be recorded at Screening (Visit 1) only. For subjects who cannot stand on a scale, bed weight measurement is allowed at the Investigator's or designee's discretion.

12.4 Complete/Limited Physical Examination

A complete physical examination (head, eyes, ears, nose, and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; and musculoskeletal systems) including neurological examination (mental status, cranial nerve functions, motor and sensory function, cerebellar function, speech, gait) will be performed at Screening (Visit 1). The complete physical examinations will be performed by a physician.

[redacted]

12.5 Electrocardiograms

A 12-lead, resting ECG will be obtained at the visits indicated in the Schedule of Assessments (Table 1).

At Screening (Visit 1), the Investigator will examine the ECG traces for signs of cardiac disease that could exclude the subject from the study. An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented on the eCRF. ECGs will be repeated if clinically significant abnormalities are observed or artifacts are present at the Investigator's or designee's discretion.

[redacted]

12.6 Laboratory Assessments

Laboratory assessment samples (Table 2) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 1).

Table 2. Laboratory Assessments

[redacted]

Blood and urine samples will be analyzed at each study site and used only for the tests in the above-mentioned table for this study. Blood and urine samples will be tested and destroyed according to the standard procedures of the study site laboratory. All laboratory reports must be reviewed, signed, and dated by the Investigator. A legible copy of all reports must be filed with both the subject's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the Investigator or designee to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

12.7 Adverse Events

12.7.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study if present on or after the 1st IP administration [redacted], worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions present [redacted] before the subject receives the 1st IP administration will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the subject enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the subject's medical history.

Subjects will be instructed to report AEs during the study. All AEs are to be followed up until resolution or a stable clinical endpoint is reached.

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to IP, action taken with IP, treatment of event, and outcome. Furthermore,

each AE is to be classified as being serious or nonserious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the subject receives the 1st IP [redacted] until the last follow-up visit. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists, until the event resolves or stabilizes at a level acceptable to the Investigator.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Specific guidelines for classifying AEs by intensity and relationship to IP are given in Table 3. and Table 4.

Table 3. Classification of Adverse Events by Intensity

MILD: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An event that prevents normal everyday activities.

Table 4. Classification of Adverse Events by Relationship to Investigational Product

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the IP but for which no extraneous cause may be found. An AE may be considered unlikely to be related to IP if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the IP ; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the IP; or (4) it does not reappear or worsen when the IP is readministered.
POSSIBLY: This category applies to those AEs for which a connection with the IP administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the IP; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the IP.
PROBABLY: This category applies to those AEs that the investigator feels with a high degree of certainty are related to the IP. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the IP; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the IP, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the IP.

DEFINITELY: This category applies to those AEs that the investigator feels are incontrovertibly related to IP. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the IP; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with reexposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the IP.

Abbreviation: AE, adverse event; IP, investigational product.

12.7.2 Serious Adverse Events

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. SAEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the Investigator's and the Sponsor's assessment. If either the Sponsor or the Investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

12.7.3 Serious Adverse Event Reporting

An SAE occurring from the subject receives the 1st IP [redacted], during the study, or within 3 months of stopping the treatment must be reported to [redacted] Pharmacovigilance group and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the IP, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event. Notification can be made using the dedicated fax line or email [redacted]

The Medical Monitor should be contacted in the event of medical emergencies.

If the Investigator contacts [redacted] Pharmacovigilance group by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the Investigator considers the event to be related to the investigational product.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The Investigator must report all additional follow-up evaluations to [redacted] Pharmacovigilance group within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the Investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the IP or procedures.

12.7.4 Suspected Unexpected Serious Adverse Reactions

AEs that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (i.e., the event is not consistent with the safety information in the investigator's brochure)
- there is at least a reasonable possibility that there is a causal relationship between the event and the IP

The Investigator will assess whether an event is causally related to IP. The Sponsor [redacted] will consider the Investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the independent ethics committee (IEC)/institutional review boards (IRBs) (where required) within 7 days after the Sponsor [redacted] has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the Sponsor [redacted] first has knowledge of them.

The Sponsor [redacted] is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IEC/IRBs of reportable events within the applicable timeframes.

12.7.5 Pregnancy

All female subjects of childbearing potential must have a negative pregnancy test at Screening (Visit 1). Following administration of IP, any known cases of pregnancy in female subjects or in male subjects whose sexual partners are WOCBP will be reported until 3 months after the last dose of study treatment. The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the Investigator will follow up with the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The Investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up pregnancy report. If the outcome of the pregnancy involved spontaneous or therapeutic abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly, the Investigator will report the event by faxing/emailing a completed pregnancy report form to the Sponsor (or designee) within 24 hours of knowledge of the event.

If the Investigator becomes aware of a pregnancy occurring in the female partner of a male subject participating in the study, the pregnancy should be reported to the Sponsor (or designee) within 24 hours of knowledge of the event. Information regarding the pregnancy must only be submitted after obtaining written consent from the pregnant partner. The Investigator will arrange counseling for the pregnant partner by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Upon discontinuation from the study, only those procedures that would not expose the subject to undue risk will be performed. The Investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

12.7.6 Overdose

See Section 5.3.

13 STATISTICAL ANALYSIS

A SAP will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

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 (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. [redacted]

Further details of statistical analyses including relevant SAS code will be presented in the SAP.

13.1 Determination of Sample Size

[redacted]

[redacted]

13.2 Analysis Populations

All data analyses will be performed using at least one of the following analysis sets.

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

13.3 Efficacy Analysis

13.3.1 Analysis of Secondary Efficacy Endpoints

Analyses of all secondary efficacy and imaging endpoints will be performed on the ITT population as the main analysis and will be repeated on the PP and Completers populations as supportive analysis.

Efficacy endpoints will be summarized and statistically compared between the treatment groups and in the subgroups of the variables used for randomization stratification, also. [redacted]

Proportion of subjects with independent functional outcome and excellent functional outcome [redacted] after the 1st IP administration

The number and percentage of subjects who achieve a score of 0 to 2 on the mRS [redacted] will be presented by treatment group. The number and percentage of subjects achieve mRS 0-1 [redacted], and the number and percentage of subjects achieve [redacted] mRS 0-2 [redacted]. The difference of the proportions between the treatment groups with the corresponding 95% confidence intervals (CIs) will be presented for the defined timepoints. [redacted] The same analysis will also be presented for subjects who achieve a score of ≤1 on the mRS. [redacted]

[redacted]

[redacted]

Shift of proportion of subjects with each grade on mRS [redacted] from Baseline

The number and percentage of subjects in each score category of mRS will be presented for baseline and for the post-baseline timepoints [redacted] by treatment group. A shift table will be presented by treatment with shifts from baseline to each defined post-baseline timepoint by providing the number and percentage of subjects [redacted].

[redacted]

The NIHSS [redacted] after the 1st IP [redacted]

A comparison between the treatment groups [redacted].

Proportion of subjects with neurological outcome improvement [redacted] from Baseline

The number and percentage of subjects with neurological outcome improvement from baseline (defined as a decrease in NIHSS ≥4 points) will be summarized at each defined timepoint by treatment group and overall. The difference of the proportions between the treatment groups with the corresponding 95% CIs will be presented for each defined timepoint. [redacted]

[redacted] The same analysis will also be presented for the proportion of subjects with decrease in NIHSS ≥4 points or NIHSS of 0 to 1 point.

[redacted]

Proportion of subjects with NIHSS ≤2 [redacted] after the 1st IP

The number and percentage of subjects with NIHSS of 0 to 2 points will be presented by treatment group at each defined timepoint, and the difference of the proportions between the treatment groups with the corresponding 95% CIs will be presented. [redacted] The same analysis will also be presented for subjects with NIHSS of 0 to 1 point. [redacted]

[redacted]

Change in NIHSS [redacted] from Baseline

The total score and change from baseline in NIHSS will be summarized at each defined timepoint by treatment group and overall. A figure will be presented with the percentage of subjects with a decrease of ≥4 points compared to baseline, a decrease of 1 to 3 points, no change (0 points), increase of 1 to 3 points, and increase of ≥4 points for each defined timepoint by treatment group – with change presented on the x-scale and timepoint/visit presented on the y-scale.

[redacted]

[redacted]

[redacted]

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. The difference of the proportions between the treatment groups with the corresponding 95% CI will be presented. [redacted]

Change of cognition assessment by MoCA

The MoCA total score and change from baseline will be summarized [redacted]

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]

[redacted]

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

A comparison between the treatment group [redacted].

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]

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]

[redacted]

13.4 Safety Analysis

All safety analyses will be performed using the Safety population. No imputation of missing safety data will be applied.

13.4.1 Analysis of 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. The difference of the proportions between the treatment groups with the corresponding exact 95% Clopper Pearson CIs will be presented. [redacted]

13.4.2 Analysis of Secondary Safety Endpoint

Occurrence of sICH [redacted] after the 1st IP

The number and percentage of subjects with sICH (clinical deterioration defined as an increase in the NIHSS score of 4 points or more AND confirmed by MR/CT imaging - documentation) [redacted]

[redacted]

Occurrence of aICH [redacted] after the 1st IP

The number and percentage of subjects with aICH [redacted].

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. [redacted]

Other safety analyses

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities in place at the time of analysis. An overall summary of AEs will be presented including categories of serious AEs, related AEs, AEs leading to IP discontinuation and AEs with fatal outcome. The incidence of AEs will be summarized by System Organ Class and Preferred Term. Summary of AEs by maximum severity and AEs leading to permanent discontinuation of IP will be included. The summary tables will include the number of subjects and the number of events. Percentages will be based on the number of subjects in the Safety population. Events with missing onset dates will be included as AEs. If a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the IP will be used in the summary tables. All AEs will be listed by subject, along with information regarding onset, duration, severity and relationship to IP, action taken with IP, treatment of event, and outcome.

Local laboratory data will be summarized in shift tables presenting the number and percentage of subjects with values below / within / above reference range in each post-baseline visit compared to baseline. Abnormal laboratory results will be flagged in the data listings. [redacted]

Vital signs and 12-lead ECG parameters will be summarized using descriptive statistics, including mean values and mean change from baseline values. [redacted]

[redacted]

For laboratory tests, vital signs and 12-lead ECG overall evaluation, abnormal values (NCS or CS) will be flagged in the data listings.

Summary tables will be provided for concomitant medications initiated during the study period.

13.5 Interim Analysis

No interim analysis is planned.

14 STUDY MANAGEMENT

14.1 Approval and Consent

14.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the US Code of Federal Regulations (CFR); Regulation (EU) No. 536/2014; and in compliance with International Council for Harmonisation (ICH) and GCP guidelines, and according to the appropriate regulatory requirements in the countries where the study was conducted.

14.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC/IRB. Approval is required for the study protocol, protocol amendments (if applicable), investigator's brochure, ICFs, recruitment material and subject information sheets, and other subject-facing material.

14.1.3 Informed Consent

For each study subject, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the Investigator or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The subject should be informed that he/she may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and guidelines for the ICH. The Investigator will provide the subject or its representative with a copy of the IEC-/IRB-approved ICF before the start of the study.

14.2 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 14.3.

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. Only the Investigator and authorized personnel will be able to connect the codes to subject names. The primary method of

data transmittal is via the secure, internet-based EDC system [redacted]. Access to the EDC system is available to only authorized users via the study's internet web site, where a user unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of the EDC system. Electronic CRFs will be considered complete when all missing and/or incorrect data have been resolved.

14.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The Investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The Investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

14.4 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 Privacy Regulation), and the EU 2016/679 General Data Protection Regulation (GDPR). The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with Health Insurance Portability Accountability Act of 1996 Privacy Regulation, the EU GDPR, and in a form satisfactory to the Sponsor.

In case of a suspected personal data breach related to the processing of subject health information, Sponsor and the Investigator will jointly decide on the basis of all available information and applicable laws if the incident will be considered personal data breach and arrange for prompt notification to data subjects, government authorities, and other third parties if required by applicable laws, in order to mitigate the possible adverse effects.

14.5 Monitoring

The study will be monitored according to the study monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits (on-site and remote [telephone] or a combination of both) and contacts will be made at appropriate times during the study. The Principal Investigator will assure he/she and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The Investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the Investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

14.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

The Sponsor will be responsible for audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites to assure that safety and efficacy data are adequate and well documented.

14.7 Protocol Amendment and Protocol Deviation

14.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC/IRB for information. Submission to regulatory authorities only required according to local regulations. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at study sites until such approvals are received other than in the case of an urgent safety measure.

14.7.2 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 IRB/IEC and in accordance with applicable regulatory authority.

[redacted]

14.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; Regulation (EU) No. 536/2014; and in compliance with GCP guidelines.

IECs/IRBs will review and approve this protocol and the ICF. All subjects are required to give written informed consent before participation in the study.

14.9 Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor (or its designee).

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

14.10 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

Sponsor will submit a summary of trial results within the periods specified in all EEA MSC or globally, in accordance with applicable regulatory authority, except for if the submission of trial

results at a given time would hinder Sponsor's development of LT3001 drug product, or when it is not possible to submit the final trial results within the established timeframes due to a delay in data analysis and report writing.

15 REFERENCES

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16 APPENDICES

Appendix 1 Contraception Guidelines

Appendix 2 Modified Rankin Scale (Sample)

Appendix 3 National Institute of Health Stroke Scale (Sample)

Appendix 4 Country-Specific Requirements for Informed Consent Forms

Appendix 1: Contraception Guidelines

Women of childbearing potential (WOCBP) and men whose sexual partners are WOCBP must use at least 1 highly effective method of contraception during the study and for 3 months after the last dose of study treatment.

A woman is considered to be a WOCBP (fertile) after menarche and until becoming postmenopausal, unless she is permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Highly effective methods of contraception are those which have a failure rate of <1%

All subjects will be strongly advised that they (or the female partners of male subjects) should not become pregnant while on study treatment or for 3 months after the last dose. A female subject will be advised that she must report immediately to the study site for pregnancy testing and appropriate management in the event that she may be pregnant.

Reference

1. [HMA] Heads of Medicines Agencies. Clinical Trial Facilitation Group page. Recommendations related to contraception and pregnancy testing in clinical trials. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. September 15, 2014. Accessed 22 Aug 2023.

Appendix 2: Modified Rankin Scale (Sample)

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

Appendix 3. National Institute of Health and Stroke Scale (Sample)

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

Time: ___ ___:___ ___ [ ]am [ ]pm

Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____

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NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	_____ _____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	_____

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NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	____

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NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	_____

_____

_____

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Appendix 4. Country-Specific Requirements for Informed Consent Forms

The following points should be considered in different countries while obtaining the signed ICF from the subject or if applicable the subject's LAR/LDR, impartial witness or decision of independent physician who is not from the clinical study team.