RESCUE: A Randomized, Blinded, Placebo-controlled, Parallel Group Design to Determine the Safety of RNS60 in Large Vessel Occlusion Stroke Patients Undergoing Endovascular Thrombectomy

PROTOCOL 06.5.1.H1

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Coordinating Center
Rhode Island Hospital
593 Eddy Street
Providence, Rhode Island 02903

Sponsor
Revalesio Corporation
1202 East D Street
Tacoma, WA 98421

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Signatures of Approval

Protocol No: 06.5.1.H1

Study Title: RESCUE: A Randomized, Blinded, Placebo-controlled, Parallel Group Design to Determine the Safety of RNS60 in Large Vessel Occlusion Stroke Patients Undergoing Endovascular Thrombectomy (RNS60 Stroke Trial)

My signature below confirms that I have read and approved this protocol and assures that this clinical study will be conducted according to all requirements of this protocol, the Declaration of Helsinki, and the International Conference on Harmonization Guideline for Good Clinical Practice (ICH-GCP), where applicable.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Title	RESCUE: A Randomized, Blinded, Placebo-controlled, Parallel Group Design to Determine the Safety of RNS60 in Large Vessel Occlusion Stroke Patients Undergoing Endovascular Thrombectomy.
Protocol Number	06.5.1.H1
Trial Design	This study is a Phase 2, randomized, blinded assessor, placebo-controlled, parallel group, and two-dose design. Patients with a large vessel occlusion and acute ischemic stroke (AIS) who meet the criteria for endovascular revascularization will be given a 48-h infusion of either 0.5 mL/kg/h RNS60 (up to a maximum of 65 mL/h), 1 mL/kg/h RNS60 (up to a maximum of 130 mL/h), or 1 mL/kg/h (up to a maximum of 130 mL/h) placebo (normal saline) starting within 30 minutes of randomization (but prior to arterial access closure) with the exact time to start dosing being determined by the timing of the informed consent. Randomization will be done with block urn randomization to balance age, National Institutes of Health Stroke Scale (NIHSS), and Alberta stroke programme early CT score (ASPECTS). Outcomes will be evaluated throughout a 90-day observation period. Block urn randomization provides consistent imbalance control but provides greater allocation randomness compared with permuted block design and can be used for more than three arms (see Section 6.3.1). Block urn designs have been used in other stroke trials.
Trial Objectives	The primary objective is to determine the safety of the neuroprotectant RNS60 in patients with large vessel occlusion (LVO) AIS receiving a 48-h infusion of either 0.5 mL/kg/h RNS60 (up to a maximum of 65 mL/h) or 1 mL/kg/h RNS60 (up to a maximum of 130 mL/h). The secondary objectives are to evaluate the efficacy of RNS60 in: 1) Reducing global disability 2) Reducing mortality rate 3) Improving neurological outcome 4) Reducing worsening of stroke* 5) Reducing functional dependence * Worsening of stroke is defined as progression, or hemorrhagic transformation of the index stroke, as documented by brain imaging, and that is (a) life-threatening requiring intervention and/or (b) results in increased disability as gauged by a ≥ 4-point increase from lowest NIHSS pre decline and/or (c) results in death.

	The tertiary objectives are to evaluate the efficacy of RNS60 in: • Decreasing infarct volume • Improving health related quality of life
Safety Outcomes	Safety outcomes include: • Serious adverse events (SAEs) to Day 90 • 90-day mortality Additional Safety outcomes include: • Adverse events (AEs) to Day 90 • Drug administration discontinuations due to AEs • Baseline and 48-h vital signs • Baseline and 48-h electrocardiogram • Baseline and 48-h chest X-ray (CXR)
Efficacy Outcomes	The efficacy outcomes (secondary) are: 1) Mean modified Rankin Scale (mRS) at Day 90 2) 90-day mortality 3) Mean NIHSS at 24h and Day 90 4) Proportion of patients exhibiting a worsening of their index stroke.* 5) Mean Barthel Index (BI) at Day 90 relative to pre-stroke BI. *Worsening of stroke is defined as progression, or hemorrhagic transformation of the index stroke, as documented by brain imaging, and that is (a) life-threatening requiring intervention and/or (b) results in increased disability as gauged by a ≥ 4-point increase from lowest NIHSS score pre decline and/or (c) results in death. Tertiary/exploratory outcomes include: 1) Infarct progression/regression as measured by MRI brain imaging. 2) Health-related quality of life, as measured by the 5-level EuroQoL 5D index (EQ-5D-5L) at Day 90.

Number of Participants	An initial target of 100 male and female participants with LVO AIS and who are selected for endovascular revascularization will be enrolled. Attrition factors include death from stroke but not treatment (10%), symptoms of fluid overload (20%) and early discharge (5%).
Inclusion/ Exclusion Criteria	Inclusion Criteria 1) AIS patients selected for emergency endovascular treatment. 2) Age 18 years or older. 3) Stroke symptom onset or, if not known, last known well time to randomization within 24 hours. 4) Disabling stroke defined as a baseline NIHSS score: a. NIHSS score NIHSS > 5 for internal carotid artery (ICA) and M1-middle cerebral artery (MCA) occlusion or b. NIHSS > 10 for M2-MCA occlusion. 5) Confirmed symptomatic intracranial occlusion at one or more of the following locations: Intracranial carotid I/T/L, M1 or M2 segment MCA. Tandem extracranial carotid and intracranial occlusions are permitted. 6) Pre-stroke (24 hours prior to stroke onset) historical modified Rankin Scale (mRS) ≤ 2. Patient must be living independently without requiring nursing care. 7) Qualifying imaging performed less than 2 hours prior to randomization. 8) Consent process completed as per applicable laws and regulation and the IRB requirements. Exclusion Criteria 1) Evidence of a large core of established infarction defined as ASPECTS 0-4. 2) Evidence of absence of collateral circulation on qualifying imaging (Collateral score of 0 or 1 if mCTA is used, or absence of adequate ischemic penumbra in the judgment of the Investigator if CTP is used). 3) Any evidence of intracranial hemorrhage or mass lesion on the qualifying imaging. 4) Planned use of an endovascular device not having approval or clearance or has been recalled by the relevant regulatory authority.

	5) Endovascular thrombectomy procedure is completed as defined by the presence of arterial access closure. 6) Clinical history, past imaging or clinical judgment suggesting that the intracranial occlusion is chronic or there is suspected intracranial dissection such that there is a predicted lack of success with endovascular intervention. 7) Estimated or known weight > 130 kg (287 lbs). 8) Known pregnant/lactating female. 9) Myocardial infarction within 6 months prior to Screening including non-Q wave MI; Diagnosis of congestive heart failure (CHF) with either: a) current clinical signs and symptoms of ventricular dysfunction (e.g., edema, shortness of breath), b) CHF medication adjustment within the prior 30 days or c) ejection fraction (if report available) of 30% or less measured in the 6 months prior to Screening; as either medically documented or reported by patient or another person considered by the Investigator to be reasonably reliable. 10) Known renal impairment defined as requiring renal replacement therapy (hemo- or peritoneal dialysis) 11) Inability to have MRI imaging (Non- MR compatible implants or any other foreseeable reason (including claustrophobia) 12) Severe or fatal comorbid illness that will prevent improvement or follow up. 13) Inability to complete follow-up treatment to Day 90. 14) Participation in another clinical trial investigating a drug, medical device, or a medical procedure in the 30 days preceding trial inclusion and throughout the duration of the trial. 15) Reported known seizure at time of stroke onset. 16) Ischemic stroke within previous 30 days. 17) Patients in normal sinus rhythm with a known QTcF > 460 ms at Screening. 18) Any other symptom that in the investigator's opinion may complicate or preclude the subject from participating in this trial.
Treatment	RNS60 0.5 mL/kg/h (up to a maximum of 65 mL/h) or RNS60 1 mL/kg/h RNS60 (up to a maximum of 130 mL/h) intravenous infusion.

Consent	**Initial Informed Consent** Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of applicable laws and regulation and Internal Review Boards (IRBs). **Regained Capacity Consent** If the original consent process involved anyone other than the participant, and if required by local standards, consent will be sought for the remaining procedures from the participant once they are deemed to have regained capacity. Note: Electronic consent tools may be used for initial and regained capacity consent, as permitted under applicable laws and regulations and the applicable IRB Committee.
Randomization Method	Treatment will be assigned using 1:1:1 randomization of RNS60 0.5 mL/kg/h: RNS60 1 mL/kg/h: placebo (normal saline) with block urn randomization by age, NIHSS score, and ASPECTS score (8 urns).
Duration of Treatment	Participants will receive a 48-h infusion of study drug or placebo. Each participant will be followed for 90 days. At Day 30 and Day 90 it is preferred that participants will return to clinic. If an in-clinic visit is not possible, the participant (or LAR) will be contacted by telemedicine (preferred) or by telephone (last option).
Laboratory Tests	If the participant is female and is of childbearing potential, a pregnancy test (urine or serum point-of-care pregnancy test) must be completed. In order to support the assessment of safety, pre-dose (baseline) and post-dose (48-h) complete blood count, electrolytes including magnesium, liver function test panel (LFT), blood urea nitrogen (BUN), creatinine, chest Xray (CXR) and cardiac electrocardiogram (at baseline, 24-h and 48-h) results will be reported and analysed.
Assessment of Efficacy	As the primary purpose of this trial is the assessment of safety, there is no power analysis for efficacy. However, the design and analyses of this trial will provide estimates for the powering of a subsequent trial for efficacy. The primary efficacy metric for assessment of efficacy is a lower mean mRS at 90 days.
Statistical Assumptions	Analyses will be examined on the intent-to-treat (ITT) sample, defined as all randomized participants, regardless of treatment actually received. The per protocol sample will also be examined separately. Patients who receive treatment but do not get full 48 hours of treatment due to fluid overload or early discharge will be included in the ITT analysis. Patients who complete the full 48 hours will be included in both per protocol and ITT analysis.

	All analyses will be accomplished using SAS Software 9.4 (SAS Inc. Cary, NC). Primary: The frequency of SAEs, SAEs resulting in death, AEs, and discontinuations due to AEs will be summarized as counts and percentages between the three arms. Comparisons will be conducted using Fisher's Exact tests. Secondary: Comparisons between conditions for mRS will be evaluated using generalized mixed modeling assuming a binomial distribution (0-6) with sandwich estimation nested by site and patient, when applicable. Pairwise comparisons of mRS will be conducted at Day 90 using a Dunnett correction. In addition, simple and interaction effects between pre-stroke, discharge, 30-day and 90-day mRS by condition will be examined. Both NIHSS and BI at Day 90 will be examined in a similar fashion assuming a binomial distribution (0-42 & 0-100) with sandwich estimation. Pairwise comparisons between conditions will be conducted at Day 90 using a Dunnett correction. In addition, simple and interaction effects between pre-treatment, discharge, 30-day and 90-day NIHSS and BI by condition will be examined. Mortality will be examined using Kaplan-Meier estimation with pairwise comparisons with a Dunnett correction. DWI volume post treatment and at 48 hours, and 90-day T2 will be modeled between conditions using generalized linear modeling assuming a normal or lognormal distribution (where appropriate), where simple and interaction effects will be examined. Because superiority over placebo and lower dose is hypothesized, testing will reflect this superiority framework. Because the main aim of this trial is to examine safety, efficacy analysis results are intended to yield estimates to inform powering for a future efficacy trial. Alpha is established at the 0.05 level and all interval estimates will be calculated for 95% confidence.
Data Safety Monitoring Board	A Data Safety Monitoring Board (DSMB) will monitor patient safety and scientific integrity during the trial.

Table 1-1: Schedule of Activities for Randomized Participants

Visit/Contact	V1	V2	V3	V4	V5	V6/ End of Trial
Day	**Day 0 Baseline**	**Day 1 Post-EVT**	**Day 2/or early discharge**	**Day 6[1] or discharge**	**Day 30[2]**	**Day 90[2]**
Window		**(24 h+/-4h)**	**(48 h±4h)**		**(±5 d)**	**(-21 to +7d)**
Informed consent	X					
Regained capacity informed consent[3]			X	X	X	X
History and physical examination[4]	X	X	X			
Weight[5]	X		X			
Vital Signs (BP, HR, Temperature) [6]	X	X	X			
Chest radiograph	X[12]	X	X			
Electrocardiogram[7]	X[12]	X	X			
Randomization/ Study drug administration	X	X	X			
Continuous telemetry[7]	X	X	X			
Mortality		X	X	X	X	X
NIHSS[13]	X	X	X	X	X	X
mRS	X			X	X	X
Barthel Index	X				X	X
EQ-5D-5L						X
Imaging (NCCT & mCTA)	X					
Endovascular Procedure	X					
MRI head[8]		X	X			X
Laboratory Assessments	X[9]		X			
Pregnancy test[10]	X					
Blood collection for RNA analysis[11]		X	X			X
Blood collection for Plasma Biomarker		X	X			X
AE	Collected to Day 90					
SAE	Collected to Day 90					
Prior medications	X					
Concomitant medications	Collected to Day 90					

1. Visit will occur at Day 6 or hospital discharge if prior to Day 6.
2. At Day 30 and Day 90 it is preferred that participants will return to clinic. If an in-clinic visit is not possible the participant can be contacted by telemedicine (preferred) or by telephone (last option).
3. If the original process involved anyone other than the participant (and if required), site staff will make ongoing efforts until: (1) regained capacity consent is obtained from participant, (2) death, or (3) completion of the Day 90 assessment.
4. Physical exam every 8-12 hours during Day 1 and Day 2.
5. At baseline estimated or actual weight will be collected. If an estimated weight was collected at baseline, actual weight should be collected as soon as feasible and prior to discharge.
6. Vital signs (BP, HR only) will be recorded immediately before and after completion of the study drug infusion, and every 8-12 hours during Day 1 and Day 2, temperature will be collected at baseline only if standard of care.
7. Abnormal electrocardiogram or continuous telemetry result that suggests clinical instability will prompt a formal cardiology consult.
8. MRI head with perfusion imaging within approximately 2h post-EVT on Day 1 and at 48h +/- 4h. MRI head only at 90d.
9. Blood should be drawn at baseline, but results are not required prior to randomization. Results from primary hospital (within 8 hours) are accepted.
10. If the participant is female and is of childbearing potential a pregnancy test (urine or serum point-of-care pregnancy test) must be collected at baseline, but result is not required prior to randomization.
11. Day 1 collection 12-24 h (+/-4 hours) after additional consent is obtained for optional collection.
12. Results from the baseline ECG and CXR are not required prior to randomization.
13. NIHSS score is obtainable in-person or via telemedicine visit only (not over the phone).

d = days; h = hours

1.2 Coordinating Center and Sponsor

Coordinating Center	Redacted
Overall Coordinating Investigator:	Redacted Redacted Phone: Redacted Email: Redacted
Co-Coordinating Investigator	Redacted Phone: Redacted E-mail: Redacted
Co-Coordinating Investigator	Redacted Phone: Redacted E-mail: Redacted
Sponsor Study Manager:	Redacted Redacted Phone: Redacted
Sponsor Drug Safety Manager:	Redacted Redacted Phone: Redacted
Sponsor Medical Oversight:	Redacted Redacted Phone: Redacted

Imaging Core Laboratory:	Redacted Redacted Phone: Redacted
Clinical Research Organization	Redacted Redacted Redacted Phone: Redacted
Medical Monitor	Redacted Redacted Redacted Redacted Phone: Redacted

2 INTRODUCTION

2.1 Background

Stroke is a leading cause of mortality and neurological disability worldwide[1, 2]. When blood flow to the brain is interrupted during a stroke, some brain cells die immediately, while others remain at risk for death. These damaged cells make up the ischemic penumbra and can linger in a compromised state for periods varying from minutes to several hours[3, 4].

Given that there is a critical time, a "therapeutic window", which may vary from minutes to a few hours in which cerebral ischemia can be reversed or mitigated[3, 4], stroke should be treated as a medical emergency. Brain tissue is rapidly and irretrievably lost with delays in care and as the stroke progresses and early intervention is critical to improve stroke outcome[5, 6]. Alteplase, recombinant tissue plasminogen activator, is the only approved pharmacological treatment for acute ischemic stroke (AIS) and must be administered within 3-4.5 hours of symptom onset, and only in those patients for which the possibility of hemorrhagic stroke was excluded. According to the 2017 claims data only 10% of all ischemic strokes in the USA are treated with alteplase.

Endovascular thrombectomy (EVT) is being used to retrieve blood clots in AIS caused by large vessel occlusion (LVO)[7]. Even with EVT, only about 10% patients return to normal after their AIS[7], and only approximately half reach functional independence[8]. Therefore, although reperfusion therapies improve stroke prognosis, there remains a significant unmet medical need. Such a need would be fulfilled by a neuroprotective therapy – one that enhances the brain's resilience to ischemia. However, at present, no approved neuroprotective pharmacotherapy exists. RNS60 is a first in class neuroprotectant that is designed to address the major unmet medical need for treatments that reduce the functional disability produced by acute stroke and the disability resulting from delays in care relating to time until the vessel is reopened. RNS60 is intended, alone or in combination with available therapies, to treat acute ischemic stroke, a serious and life-threatening disease.

For this reason, RNS60 is being developed as an emergency drug aimed at reducing global disability in patients with AIS. RNS60 may provide significant benefit for the treatment of acute cerebral ischemia if administered to stroke patients who present to medical attention before infarction is complete. The rapid progression of irreversible brain injury in most acute strokes implies a short window of clinical efficacy of any treatment, including RNS60. The ability to timely identify patients with salvageable brain using the criteria used in the ESCAPE trial[9] and the ESCAPE-NA1 trial[10] provides an opportunity to target patients who may have the greatest benefit from neuroprotection, and to enhance further the impact of existing reperfusion therapies.
A detailed description of the chemistry, pharmacology, preclinical efficacy, and safety of RNS60 is provided in the Investigator's Brochure.

2.1.1 RNS60: An Introduction

RNS60 is Redacted

Redacted

RNS60 has demonstrated exceptional safety in rodent and non-human primate toxicity studies. Additionally, RNS60 has demonstrated significant efficacy in a non-human primate model of acute ischemic stroke without any indications of adverse effects. In all clinical studies to date, RNS60 has been well tolerated. More information is provided in the Investigator's Brochure.

2.1.2 Thrombectomy as a Stroke Treatment

Medical devices may be used with or without alteplase to retrieve blood clots in large cerebral arteries that cause severe brain ischemia ("endovascular thrombectomy")[7]. The evidence that EVT is effective in improving neurological outcome is strongest in patients who have the combination of an LVO as well as direct or indirect imaging evidence of salvageable brain (an ischemic penumbra) at the time of treatment initiation. Current generation devices are intended for patients whose AIS is caused by an LVO; they produce higher rates of reperfusion than alteplase in such appropriately selected patients. However, even with EVT, only about 10% patients return to normal as defined by an mRS score of 0 after their AIS[7], and only approximately half become functionally independent[8]. In other words, about half of patients who receive EVT still remain functionally dependent or die from their stroke.

Although reperfusion therapies such as alteplase and/or EVT improve stroke prognosis, a significant need remains to reduce the overall number of LVO AIS patients who have poor outcomes. As such, stroke remains a serious condition, with an unmet medical need.

2.1.3 Treatment of Stroke with RNS60 in Mice

In order to test the therapeutic efficacy of RNS60 in an animal model of AIS, 4-month-old male C57BL/6J mice were subjected to a temporary occlusion of the MCA for 60 minutes following a method described by Laing et al., 2020[11], Mice were treated with 200 µL of RNS60 or a control fluid (normal saline or oxygenated saline control) via intraperitoneal injection daily for 13 days, starting with the first dose an hour after reperfusion. The experiment demonstrated a clear and significant therapeutic effect of RNS60 in reducing stroke size 2 weeks after occlusion. Moreover, RNS60 treated mice performed better overall in cognitive tests such as novel object recognition and active place avoidance tests compared to the control treated mice. The work is still ongoing, but preliminary results indicated that RNS60 treated mice regained an almost healthy control level of microvascular perfusion 14 days after surgery. Work is in progress to identify the underlying mechanism of RNS60's effects by immunohistochemistry for markers of cell survival and inflammation.

2.1.4 Treatment of Stroke with RNS60 in Non-Human Primates

In a preclinical efficacy study in cynomolgus macaques, RNS60 was dosed at 5 mL/kg/h for the first hour followed by 2.5 mL/kg/h for a total of 48 hours (equivalent to a human dose of 0.8mL/kg/h following the dose conversion factor of 0.324 for a 3 kg monkey[12]). The treatment

was followed by neurobehavioral tests for 30 days. RNS60 achieved a significant reduction of infarct size and significant improvements in the neurobehavioral assessment without any notable signs of adverse effects. The two proposed doses for this clinical trial (0.5 and 1 mL/kg/h) are comparable to the dose used in monkeys. This model has previously been successfully used to test another drug for clinical translation in stroke[13].

More detailed information on these and other non-human primate pharmacology and toxicology studies is provided in the Investigator's Brochure.

2.1.5 Previous Clinical Trials

To assess clinical safety, RNS60 was administered intravenously to healthy volunteers at three escalating dose levels of 100 mL/h (1.2 mL/kg/h) for the first 48 hours, 150 mL/h (1.8 mL/kg/h) for the following 48 hours, and 200 mL/h (2.4 mL/kg/h) for the final 48 hours, for a total infusion volume of 21,600 mL (259 mL/kg) over 144 hours (6 days) total in a Phase I safety trial (ClinicalTrials.gov Identifier: NCT01264783). There were no reported SAEs related to RNS60. AEs that were reported as possibly treatment related were headache and musculoskeletal pain, all of which were mild except for one instance of moderate abdominal pain.

RNS60 has been tested in three clinical trials in disease populations: a completed clinical pilot study in 16 amyotrophic lateral sclerosis (ALS) patients (Clinicaltrials.gov ID #NCT02525471)[14], an ongoing 148-patient ALS Phase II trial (Clinicaltrials.gov ID #NCT03456882), and a completed Phase IIa trial in 10 multiple sclerosis patients (EudraCT #2014-000221-20). In each of these trials, RNS60 was well tolerated. Only a single SAE was reported by investigators as possibly related to treatment, although it presented as an isolated, non-sustained event that did not result in any clinical symptoms or sequelae and did not repeat after the subject continued treatment (negative re-challenge)[*].

More detailed information on RNS60 and its previous clinical and nonclinical use is provided in the Investigator's Brochure.

2.2 Study Rationale

RNS60 has shown a significant neuroprotective effect in preclinical models of stroke as well as in other models of chronic neurodegenerative diseases. There is a compelling need to develop neuroprotectants in order to increase the proportion of patients who may benefit from EVT and do not suffer from delays in care. Effective neuroprotectants could improve the outcomes of patients and bridge patients with AIS into candidates for endovascular or pharmacological recanalization treatment. The rapid progression of irreversible brain injury in most acute strokes implies a short window of clinical efficacy for any treatment, including RNS60.

[*] A single SAE of elevated systolic and diastolic arterial blood pressure (~200/100 mmHg) was reported by the investigators of the 148-patient ALS Phase II trial as possibly related to treatment.

2.3 Benefit/Risk Assessment

More detailed information about the chemistry, pharmacology, safety, efficacy, and expected benefits and risks of RNS60 is provided in the Investigator's Brochure.

2.3.1 Risk Assessment

Based on the clinical data available for RNS60 to date, the major possible risk for the proposed use is:

- Circulatory volume expansion/fluid volume overload

2.3.2 Benefit Assessment

The following is a list of possible benefits to the trial participants receiving RNS60:

- Improved functional outcome (lower mean mRS)
- Reduced stroke mortality
- Improved good neurologic outcome (lower mean NIHSS score)
- Reduced chance of stroke worsening
- Improved functional independence (higher mean BI)

2.3.3 Overall Benefit: Risk Conclusion

The potential risks identified in association with RNS60 are justified by the anticipated benefits that may be afforded to participants.

The maximal dose of RNS60 administered over 48 hours to the subjects in this proposed trial equals approximately 55% of the average dose administered over 48 hours to healthy human subjects in the Phase I study (Protocol 11.1.1.H1, NCT01264783), and approximately 18.5% of the total volume administered (average dose of 1.8 mL/kg/h over 144 hours. Based on the nonclinical and clinical safety profile of RNS60, we submit that the proposed dose is safe for patients with AIS. Additionally, participants will be monitored for fluid overload by our DSMB.

3 TRIAL OBJECTIVES

3.1 Objectives

Table 3-1: Objectives and Outcomes

Objectives	Outcomes
Primary – Safety	
To determine the safety based on SAEs	Proportion of participants with SAEs to Day 90
90-day mortality	Proportion of participants alive at Day 90
Secondary – Efficacy	
Reducing global disability in participants with AIS	Mean mRS score
Reducing mortality rate	Median or proportion of death on survival curve
Improving neurological outcome	Mean NIHSS score at discharge
Reducing worsening of stroke	See 3.1.2
Reducing functional dependence	Mean BI at Day 90
Tertiary/Exploratory	
Decreasing infarct volume	Volume of stroke as measured by MRI brain imaging
Improving health related quality of life	EQ-5D-5L at Day 90

3.1.1 Primary Objective

The primary objective is to determine the safety of the neuroprotectant RNS60 in patients with LVO AIS. Patients must have sudden onset of focal neurological symptoms or, if not known, last known well time within 24 hours consistent with an ischemic stroke. Symptoms must be persistent and present at the time of enrollment.

The safety objectives are to determine the safety in participants with AIS of the 48-h infusion of either 0.5 mL/kg/h RNS60 (up to a maximum of 65 mL/h) or 1 mL/kg/h RNS60 (up to a maximum of 130 mL/h), based on serious SAEs and 90-day mortality.

3.1.2 Secondary Objectives

The secondary objectives are to evaluate the efficacy of RNS60 in:

1) Reducing global disability
2) Reducing mortality rate
3) Improving neurological outcome
4) Reducing worsening of stroke*
5) Reducing functional dependence

* Worsening of stroke is defined as progression, or hemorrhagic transformation, of the index stroke as documented by medical imaging and that is (a) life-threatening requiring intervention and/or (b) results in increased disability as gauged by a ≥ 4-point increase from lowest NIHSS pre decline and/or (c) results in death.

3.1.3 Tertiary/Exploratory Objectives

The tertiary objectives are to evaluate the efficacy of RNS60 in:

1) Decreasing infarct volume
2) Improving health related quality of life

3.2 Outcomes

3.2.1 Primary Safety Outcomes

1) The safety outcomes are the frequencies and severities of SAEs and 90-day mortality

3.2.2 Secondary Efficacy Outcomes

Secondary outcomes include:

1) The mean mRS score at Day 90, where a lower score is better.
2) A reduction in mortality rate, as defined by a lower event rate on a Kaplan Meier survival curve
3) The mean NIHSS score post randomization, where a lower score is better
4) The proportion of patients with worsening of stroke over the 90-day study period
5) The mean BI at Day 90

3.2.3 Tertiary/Exploratory Outcomes

The following tertiary outcomes will be assessed descriptively:

1) The volume of stroke as measured by MRI brain imaging
2) Health-related quality of life, as measured by the EQ-5D-5L at Day 90

4 TRIAL DESIGN

4.1 Overall Design

This trial is a block urn randomized (by age: <80 vs. ≥80, NIHSS score: 6-10 vs. >10, and ASPECTS: 5-7 vs. 8-10, for a total of 8 urns), blinded assessor, placebo-controlled, parallel group, two-dose (full and half), longitudinal (pre-stroke, post-treatment, 48-hour, discharge, 30-day, and 90-day) study with equal arm sample sizes (1:1:1). Although the trial's main purpose is to demonstrate safety, superiority is hypothesized over placebo and lower dose for secondary and tertiary aims.

AIS large vessel occlusion participants who are selected for EVT will be given a 48-h infusion of either 0.5 mL/kg/h RNS60 (up to a maximum of 65 mL/h), 1 mL/kg/h RNS60 (up to a maximum of 130 mL/h) or 1 mL/kg/h RNS60 (up to a maximum of 130 mL/h) of saline.

The end of the trial is defined as the date that the last enrolled participant has completed their Day 90 visit/contact.

A target of 100 male and female participants aged 18 years and older with AIS and who are selected for EVT will be enrolled.

All participants in the trial will be followed for 90 days (or until death if prior to 90 days). At Day 30 and Day 90 participants will return to clinic. If an in-clinic visit is not possible the participant, or if participant cannot be contacted or cannot communicate well, a legally authorized representative can be contacted by telemedicine (preferred) or by telephone (last option).

4.2 Scientific Rationale for Study Design

The RNS60 trial design rationale is based on the promising design of the recently completed ESCAPE-NA1 trial[10]. There is a compelling need to develop neuroprotectants in order to increase the proportion of patients who may benefit from EVT and do not suffer from delays in care. Effective neuroprotectants could improve the outcomes of patients and bridge patients with AIS into candidates for endovascular or pharmacological recanalization treatment. The rapid progression of irreversible brain injury in most acute strokes implies a short window of clinical efficacy for any treatment, including RNS60.

The current trial is intended to demonstrate safety of RNS60 and, as a secondary aim, to provide first data on whether RNS60 may improve functional independence, reduce mortality, and reduce infarction volumes. As such, this trial is a block urn randomized (by age: <80 vs. ≥80, NIHSS score: <10 vs. ≥10, and ASPECTS: 5-7 vs. 8-10 for a total of 8 urns), blinded assessor, placebo-controlled, parallel group, two-dose (full and half), longitudinal (pre-stroke, post-treatment, 48-hour, discharge, 30-day, and 90-day) study with equal arm sample sizes (1:1:1). Although the trial's main purpose is to demonstrate safety, superiority of the higher dose is hypothesized over placebo and the lower dose (secondary and tertiary objectives).

Randomized LVO stroke patients will be given a 48-h infusion of either 0.5 mL/kg/h RNS60 (up to a maximum of 65 mL/h), 1 mL/kg/h RNS60 (up to a maximum of 130mL/h), or 1 mL/kg/h (up to a maximum of 130 mL/h) placebo (normal saline) within 30 minutes of randomization but prior to arterial access closure (the exact time to start dosing will be determined by the timing of the informed consent).

4.3 Justification for the Target Study Population

RNS60 is being developed as an emergency drug aimed at reducing global disability in patients with AIS. RNS60 is intended to enhance the outcome of patients who may benefit from EVT and add to the existing standard of care stroke treatments including thrombolysis.

4.4 Justification for Dose

RNS60 was selected to be infused at either a 0.5 mL/kg/h (up to a maximum of 65 mL/h) or 1 mL/kg/h (up to a maximum of 130 mL/h) because of:

1) The safety profile observed in the nonclinical toxicology studies and in Phase 1 clinical trials
2) The efficacy of a similar dose of RNS60 to reduce stroke tissue damage and to improve neurological function in mice and non-human primates.

4.5 End of Study Definition

A participant is considered to have completed the study if he/she has completed to Day 90 or has died prior to Day 90. The end of the study is defined as the date of the last visit of the last participant in the trial.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. The study population includes adults 18 years and older with AIS who are selected for EVT. Subjects must have sudden onset of focal neurological symptoms, or if not known, last known well time within 24 hours consistent with an ischemic stroke. Symptoms must be persistent and present at the time of enrollment.

5.1 Inclusion Criteria

1) AIS selected for emergency endovascular treatment.
2) Age 18 years or older.
3) Stroke symptom onset or, if not known, last known well time to randomization within 24 hours.
4) Disabling stroke defined as a baseline NIHSS score:
   a. NIHSS > 5 for internal carotid artery (ICA) and M1-middle cerebral artery (MCA) occlusion; or
   b. NIHSS > 10 for M2-MCA occlusion.
5) Confirmed symptomatic intracranial occlusion at one or more of the following locations: Intracranial carotid I/T/L, M1 or M2 segment MCA. Tandem extracranial carotid and intracranial occlusions are permitted.
6) Pre-stroke (24 hours prior to stroke onset) historical modified Rankin Scale (mRS) ≤ 2. Patient must be living independently without requiring nursing care.
7) Qualifying imaging performed less than 2 hours prior to randomization.
8) Consent process completed as per applicable laws and regulation and the IRB requirements.

5.2 Exclusion Criteria

1) Evidence of a large core of established infarction defined as ASPECTS 0-4.
2) Evidence of absence of collateral circulation on qualifying imaging (collateral score of 0 or 1 if mCTA is used or absence of adequate ischemic penumbra in the judgment of the Investigator if CTP is used).
3) Any evidence of intracranial hemorrhage or mass lesion on the qualifying imaging.
4) Planned use of an endovascular device not having approval or clearance or has been recalled by the relevant regulatory authority.
5) Endovascular thrombectomy procedure is completed as defined by the presence of arterial access closure.

6) Clinical history, past imaging or clinical judgment suggesting that the intracranial occlusion is chronic or there is suspected intracranial dissection such that there is a predicted lack of success with endovascular intervention.
7) Estimated or known weight >130 kg (287 lbs).
8) Known pregnant/lactating female.
9) Myocardial infarction within 6 months prior to Screening including non-Q wave MI; Diagnosis of congestive heart failure (CHF) with either:

   a) current clinical signs and symptoms of ventricular dysfunction (e.g., edema, shortness of breath),

   b) CHF medication adjustment within the prior 30 days or

   c) ejection fraction (if report available) of 30% or less measured in the 6 months prior to Screening;

   as either medically documented or reported by patient or another person considered by the Investigator to be reasonably reliable.
10) Known renal impairment defined as requiring renal replacement therapy (hemo- or peritoneal dialysis).
11) Inability to have MRI imaging (non-MR compatible implants or any other foreseeable reason including claustrophobia)
12) Severe or fatal comorbid illness that will prevent improvement or follow up.
13) Inability to complete follow-up treatment to Day 90.
14) Participation in another clinical trial investigating a drug, medical device, or a medical procedure in the 30 days preceding trial inclusion and throughout the duration of the trial.
15) Reported known seizure at time of stroke onset.
16) Ischemic stroke within previous 30 days.
17) Patients in normal sinus rhythm with a known QTcF > 460 ms at Screening.
18) Any other symptom that in the investigator's opinion may complicate or preclude the subject from participating in this trial.

5.3 Lifestyle Considerations

No restrictions are required.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently randomized to be a trial participant. The informed consent form will be maintained at the study site, but these participants will not be entered in the CRF.

5.5 Study Enrollment Process

In this AIS trial, patients should be randomized into the trial and receive study drug as soon as possible (within 30 minutes of randomization and before completion of EVT procedure as defined by completion of arterial access closure), following review of trial eligibility and the local informed consent process. Participants will be identified using usual standard of care screening methods at the acute stroke hospital. All participants will undergo an acute clinical assessment, blood laboratory assessment, baseline electrocardiogram, baseline chest radiograph, and baseline brain imaging. Due to the short time-period from arrival at the hospital to the EVT, the results of the baseline blood work and the results from the initial ECG and CXR are not required prior to randomization or start of infusion.

If the participant remains eligible after completion of routine stroke screening, the patient will be consented (as required) and enrolled into the trial. A participant is considered randomized the moment the randomization process is completed on-line. Participants who are randomized but do not receive study drug will still be followed through the 90-day study period.

5.5.1 Imaging

All sites will perform an NCCT brain and CTA (CTP is allowed but not preferred) to determine patient eligibility. The NCCT head will be assessed using ASPECTS prior to randomization. Instructions for the determination of the ASPECT score and evidence of absence of collateral circulation are provided at www.aspectsinstroke.com. The CTA will be assessed for collateral status using a collateral scoring system if multiphase CTA is used. If CTP is used, evidence of adequate penumbra must be confirmed. Confirmed symptomatic intracranial occlusion will be based on multiphase (preferably) CTA. Sites will only be selected to participate in the trial if they have established mechanisms for screening this population of participant. This includes standard of care use of NCCT and CTA.

5.5.2 Consent Process

After completing a formal screening process to determine eligibility, Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of applicable laws and regulation and the ethics committee.

The investigator or his/her representative will explain the nature of the trial to the participant or his/her legally authorized representative and answer all questions regarding the trial.
The medical record must include a statement describing under which process consent was obtained, and the timing of the consent and regained capacity consent. The authorized person obtaining the informed consent must also sign the informed consent form (ICF).

An electronic consent process is permitted for consent of subjects or their surrogate if all the requirements for electronic records/electronic signatures, informed consent, and IRBs as set forth in 21 CFR parts 11, 50, and 56 are followed.

5.5.3 Regained Capacity Consent

If the original process involved anyone other than the participant, and if required by local standards, consent will be sought for the remaining procedures from the participant once they are deemed to have regained capacity. Site staff will make ongoing efforts until: (1) regained capacity consent is obtained from participant, (2) death, or (3) completion of the Day 90 assessment.

5.5.4 Amendment of the ICF

In the event that new information is available and the ICF is amended, and if required by local IRBs, participants must be re-consented to the most current version of the ICF(s) during their participation in the trial. A copy of each ICF must be provided to the participant or the participant's legally authorized representative.

Note: Electronic consent tools may be used for initial and regained capacity consent, as permitted under applicable laws and regulations and the IRBs.

5.5.5 Physical Examinations

To support the assessment of inclusion and exclusion criteria and medical history, a stroke focused physical examination at baseline will include, at a minimum, assessments of the Neurological, Cardiovascular, Respiratory, Genitourinary, and Gastrointestinal systems. Investigators should pay special attention to clinical signs related to previous strokes. Additionally, physical examinations will be conducted every 8-12 hours during the treatment phase to assess any signs of fluid overload or worsening of any clinical symptoms. Results taken from standard of care assessment/timepoints may be used.

6 STUDY INTERVENTIONS and CONCOMITANT THERAPY

6.1 Study Intervention Administration

RNS60 is produced using 0.9% sodium chloride for injection and medical grade oxygen. It is supplied in single-use IV bags and contains no preservatives. RNS60 has been extensively tested in preclinical toxicological studies and has shown little attributable side effects to date. In addition, RNS60 was well tolerated in three Phase I human safety studies, one after IV administration and two after inhalation, and in other Phase I and Phase II studies, including one in multiple sclerosis and one in ALS patients[14]. More information can be found in the Investigator's Brochure.

RNS60 IV bags are to remain Redacted RNS60 Redacted

Table 6-1: Study Interventions

	RNS60	**Placebo**
Test Product Name	RNS60	Placebo
Type	Drug	Drug
Dose Formulation	Sterile fluid for IV infusion	Sterile fluid for IV infusion
Dosage Level(s)	0.5 mL/kg/h and 1 mL/kg/h	1 mL/kg/h
Route of Administration	IV Infusion	IV Infusion
Use	Investigational	Placebo
Sourcing	Provided by the sponsor	Provided by the sponsor
Packaging and Labeling	Study drug will be provided in 375-mL IV bags	Study drug will be provided in 375-mL IV bags Redacted .

6.2 Preparation / Handling / Storage / Accountability

Only participants enrolled in the trial may receive study drug and only authorized site staff may supply or administer study drug. Study drug dosing will be carried out by, or under the supervision of, the investigator who is supervising the care of the participant for the planned or ongoing endovascular reperfusion procedure.

As soon as the participant is deemed eligible for the trial, the investigator (or delegate) will log into the central randomization website to receive the assigned bag number.

Dose timing starts at the time of infusion onset. Study drug is intended to be administered as soon as possible after randomization (i.e., <30 minutes) and must be started prior to arterial access closure.

Study drug will be provided in a Redacted will contain 375 mL of study drug for single use only.

Redacted Redacted

Research site staff will inform the Investigational Pharmacy about local inventory so that the pharmacy can prepare and have correct bags (RNS60 or placebo) on time to study staff.

6.2.1 Storage and Accountability

Study drug must be stored in a secure, temperature controlled (2 to 8°C), and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. Temperatures will be monitored using a device that can continuously monitor and record temperature readings.

The drug supply will have access limited to the investigational pharmacy staff and those directly involved in the study.

The investigator and investigational pharmacist are responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Any expired, lost, damaged or out-of-specification study drug must be properly documented and reported to the sponsor.

6.2.2 Disposition of Study Drug Supplies

Following IV administration, any remaining fluid may be disposed of in any normal drain. Empty bags will not be retained. Used bags will be disposed of on site. Drug accountability will be captured by study staff and pharmacy staff using Drug Accountability Logs and the CRO's investigational product management system to record bags used (using Bag IDs). Any unused IV bags will be destroyed/disposed of or returned to sponsor at the conclusion of the study.

6.3 Measures to Minimize Imbalance: Block Urn Randomization and Blinding

All patients will be centrally assigned to a randomized study intervention (i.e. RNS60 0.5 mL/kg/h, RNS60 1mL/kg/h, or placebo 1 mL/kg/h) using block urn randomization tables (8 urns). The randomization table will be set for up to 100 people per urn to ensure no urn can be filled prior to enrollment completion. Each site will have their own randomization table.

Treatment allocation will be assigned using 1:1:1 randomization (RNS60 0.5 mL/kg/h, RNS60 1 mL/kg/h, or placebo 1 mL/kg/h). Randomized allocation will be fully concealed by having allocations based upon random assignment and blinded by the use of visually identical appearing RNS60 and placebo infusion bags. All infusion bags will have a unique number.

The purpose of using block urn randomization is to minimize the possibility of imbalance of treatment assignment by age, NIHSS score, and ASPECTS due to the small sample size.

All participants, investigators, their clinical staff, local and central laboratories, the clinical coordinating center, the data management group, and the sponsor staff and delegates will be blinded to the randomization codes.

6.3.1 Appendix 1 Block Urn Randomization

Because of the small sample size distributed among three arms, imbalance of treatment assignment across important baseline factors should be minimized. Block urn randomization provides consistent imbalance control but provides greater allocation randomness compared with permuted block design[15]. Block urn designs use blocking of balls with an active urn and inactive urn. A ball is randomly selected from the active urn (treatment allocation) and then placed in the inactive urn; this process is repeated until a minimum balance is achieved in the inactive urn at which point these balls are replaced in the active urn while the other balls are left in the inactive urn. This process is repeated until the last patient is randomized. Block urn randomization has been used in other stroke trials[16-18].

6.3.2 Procedure for Breaking the Randomization Code

In case of an emergency, the investigator has the sole responsibility for determining whether the unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind[†]. The date and the reason why the blind was broken must be recorded in the source documentation as applicable.

To maintain the overall quality and legitimacy of the clinical trial, code breaks should occur only in exceptional circumstances when knowledge of the actual treatment is absolutely essential for further management of the patient to ensure their safety and well-being.

In case of an emergency, a rapid unblinding procedure is available to investigators. The investigator will contact the randomization provider to request unblinding of the specific participant. The randomization provider will respond in writing to the investigator only with the unblinded participant treatment allocation.

Only the investigator requesting the unblinding will receive the unblinding information. The investigator is requested to maintain the blind as far as possible. The actual treatment allocation should not be disclosed to the participant and/or other site personnel unless, in the judgment of the

[†] In cases where a participant was unblinded on a Friday, where possible the investigator will aim to send the notification prior to the weekend. If not possible, or if the unblinding occurs on a weekend or a holiday, notification will be sent on the first business day after the event.

investigator, this information is required for the participant's safety. The actual treatment allocation must not be disclosed to study personnel on site not involved in the participant's medical care, to monitors or the sponsor.

In order to fulfill expedited regulatory reporting requirements, the sponsor may be required to unblind the participant if the SAE meets the criteria for reporting to health authorities. The sponsor's independent third party (CRO) will initiate the request that the participant's treatment group be unblinded. In this case, the code will be broken only for the participant(s) in question. The information resulting from code-breaking (i.e., the participant's treatment allocation) will not be communicated to either the investigator or the sponsor, except as needed for determination of causality of a reportable SAE.

Otherwise, randomization data will be kept strictly confidential, accessible only to authorized persons, until the time of unblinding after database lock at the time of interim analysis and at end of the study (Day 90).

6.4 Study Drug Compliance

Study drug will be dispensed under the instructions of the investigator or designee and under medical supervision. The date and time of dose administered will be recorded in the source documents and in the CRF. The dose of study drug and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug. The investigator may terminate study drug administration at his/her discretion.

6.5 Continued Access to Study Drug after the End of the Study

Not applicable in this trial.

6.6 Participant Infusion Stopping Criteria

Because RNS60 chemically contains only sodium chloride and oxygen, and based on the nonclinical and clinical safety information, the sponsor does not recommend specific treatment for an overdose. However, because a saline infusion of up to 130 mL/h for 48h could present a volume challenge the investigator should:

1) Contact the PI and sponsor in case of any signs of possible fluid overload, including worsening dyspnea, hypoxia, or cardiac function which do not resolve with treatment.
2) Closely monitor the participant for any AEs/SAEs and electrocardiogram (ECG), CXR, laboratory abnormalities for at least 1 day. (See Section 8.1.2 Clinical Safety Laboratory Assessments for additional infusion stopping criteria related to ECG values).
3) Document the quantity (infusion duration) in the CRF.

6.7 Concomitant Therapy

There are no restricted medications in this trial.

Any medication or vaccines (including over the counter or prescription medicines) that the participant is receiving at the time of enrollment or receives up to Day 90 must be recorded along with:

- Dates of administration including start and end dates, medications that were ongoing at the last contact will be updated with a stop date or confirmed as ongoing,
- Indication for use.

6.8 Rescue Medicine/Treatment

6.8.1 Early Study Drug Cessation

The intervention is 0.5 mL/kg/h RNS60 (up to a maximum of 65 mL/h) and 1 mL/kg/h RNS60 (up to a maximum of 130 mL/h) intravenous infusion using an infusion pump, starting after randomization to a participant undergoing endovascular mechanical thrombolysis/thrombectomy. It is expected that infusion will begin prior to the completion of the procedure (defined as the time of arterial access closure) and complete 48h after the infusion is initiated.

The infusion may be stopped if the treating investigator believes the volume of infusion can no longer be tolerated due to volume overload (worsening dyspnea, hypoxia, or cardiac function). As such, the investigator may terminate drug administration at his/her discretion.

6.9 Endovascular Intervention and Stroke Care

EVT should be conducted as per the local protocol and in compliance with the current treatment guidelines such as those published by the American Heart Association (AHA)[19-21]. All participants are expected to be admitted to the hospital as part of routine standard of care. All participants are expected to receive expert stroke unit care and then rehabilitation according to their clinical need throughout the full 90 days.

7 DISCONTINUATION of STUDY DRUG and PARTICIPANT DISCONTINUATION / WITHDRAWAL

7.1 Discontinuation of Study Drug

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study drug. If study drug administration is discontinued, the participant will remain in the trial and be evaluated to Day 90.

7.2 Participant Discontinuation/Withdrawal from the Trial

Participation in this clinical trial may be discontinued for any of the following reasons:

- Administrative reasons (uncooperative, noncompliant, etc.)
- Participant's decision not to participate any further
- If it is in the participant's best interest, per the qualified/principal or sub-investigator

If the participant or legally authorized representative (LAR) withdraws consent, participant data will be included in the analysis up to the date of the consent withdrawal and this withdrawal of consent will be documented in the CRF.

If the LAR has originally provided consent and the participant subsequently declines consent, this will be deemed to be a withdrawal of consent. The investigator and sponsor would continue to have access to data that have already been collected.

A participant may not withdraw use of his or her data that have already been collected. This is in alignment with the FDA guidance document "Data Retention When Participants Withdraw from FDA-Regulated Clinical Trials", which is based on the importance of avoiding selection biases that could compromise the analysis of the overall trial.

Otherwise, all randomized participants will continue to be followed according to protocol requirements and follow-up data will be included in the analysis. Criteria for removal of participants will be recorded and reported.

7.3 Lost to Follow up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits/contacts and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic or if they cannot be contacted by phone for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit/contact as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the trial.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (at a minimum 3 telephone calls/contacts). These contact attempts should be documented in the participant's study record.
- Should the participant and/or LAR continue to be unreachable, he/she will be considered to have withdrawn from the trial. Every effort will be made to collect functional assessment and/or mortality data or any other data from the LAR if the participant is unreachable.
- Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS and PROCEDURES

Study procedures and their timing are summarized in Table 1-1: Schedule of Activities. Adherence to the trial design requirements is essential and required for study conduct.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in Table 1-1: Schedule of Activities.

8.1 Safety and Efficacy Assessments

Planned time points for all safety and efficacy assessments are provided in Table 1-1: Schedule of Activities. Further definition/description of those assessments are provided here:

8.1.1 Vital Signs

Blood pressure and heart rate will be taken at baseline (pre-dose) and per routine (every 8-12 hours) until completion of the infusion at 48h. Results taken from standard of care assessment/timepoints may be used. Temperature will be taken at baseline (if available per standard of care). Clinically significant findings post-dose will be reported as AEs.

8.1.2 Clinical Safety Laboratory Assessments

Blood work will be done at baseline (within 4 hours of admission) and at Day 2 (48h +/- 4 hours), and include: complete blood count (hemoglobin, platelets and hematocrit), full metabolic profile including magnesium and other electrolytes (sodium, potassium, chloride, bicarbonate and magnesium), serum creatinine and serum glucose, coagulation panel: prothrombin time test (PTT) and international normalized ratio (INR), BUN, LFT panel: alanine transaminase (ALT), aspartate aminotransferase (AST) and bilirubin. All blood assessments will be done by the local laboratory. Results from local standard of care procedures and testing may be used. A central lab will not be used. Due to the short time-period from arrival at the hospital to the EVT, the results of the baseline blood work and the results from the initial ECG and CXR are not required prior to randomization or start of infusion. Baseline results from the primary hospital (within 8 hours) are accepted, if written documentation is available. Clinically significant laboratory findings that follow the initiation of the infusion (post dose) will be reported as AEs.

A baseline ECG and CXR will be obtained within 4 hours of admission and will represent the baseline measure of cardiopulmonary function. A repeat ECG and CXR will be obtained at 24h (+/- 4 hours), 48h (+/- 4 hours) and any new abnormality will be reported as an AE.

For elevated QTcF values, the patient is not to be automatically withdrawn from the study and the infusion will not be automatically stopped. Determination of continuation in the study will be at the clinical judgment of the investigator and/or the medical monitor as detailed in the instructions

on repeating ECGs below. Cardiologist consultation should be used to correct and/or overread an ECG with elevated QTcF values.

For Day 1 or Day 2 ECG:
If a subject has a QTcF > 500 ms with at least an increase from baseline > 40 ms, or an isolated increase from baseline > 70 ms, then the ECG must be repeated in approximately one hour and the ECGs must be over-read by a cardiologist. If a QTcF > 500 ms or an increase > 70 ms is confirmed and not due to a new bundle branch block (QRS > 110 ms), then the medical monitor must be contacted, and the following steps must be completed:

1) Study drug dosing must be stopped while serum electrolytes are evaluated, and it is determined if new medications that prolong the QTc interval were inadvertently initiated.
2) If no significant hypokalemia or hypomagnesemia are identified and no new medications that prolong the QTc interval were initiated, study drug must be discontinued, not to be restarted.
3) If significant hypokalemia or hypomagnesemia are identified, these must be corrected and if a new QT-prolonging medication was initiated, then the study drug must be stopped.
    - Study drug can be restarted after the QTcF is < 480 ms and the increase from baseline < 60 ms. ECGs must be repeated at approximately 2 hours and 6 hours post resumption of the dose and on the succeeding days of dosing.
4) If a repeat on-drug ECG's absolute QTcF > 500 ms or an increase from baseline > 70 ms is confirmed, study drug must be discontinued, not to be restarted.

If the initial increased QTcF occurs in the setting of a new bundle branch block, calculate the "adjusted QTcF" (See Appendix 7: Adjusted QTcF Calculation) and contact the Medical Monitor to discuss the management plan. If the Adjusted QTcF is < 500 ms and the increase from baseline is < 70 ms, drug infusion need not be stopped while contacting the Medical Monitor. Note: The adjusted QTcF calculation should be done by someone qualified and experienced in making this calculation.

8.1.3 Pregnancy Testing

If the participant is female and is of childbearing potential, a pregnancy test (urine or serum point-of-care pregnancy test) must be collected at baseline.

8.1.4 Blood Collection for RNA Analysis

Subjects will be asked to consent for the optional collection of blood samples for RNA biomarker analysis at Day 1, Day 2 and Day 90. Obtaining consent for this blood collection may occur at any time after randomization and is not required at the same time as the main consent for study participation. Subjects have the option of declining participation in this blood collection at any time by withdrawing their consent to have their sample used. However, it will not be possible to destroy samples that may have already been collected and analyzed. These samples will be used

for biomarker research and labeled with a deidentified subject number. Samples will be stored for research until they are used, damaged, decayed or otherwise unfit for analysis. All samples will be sent to a Revalesio-contracted lab for analysis. Sample processing and handling instructions for sites are provided separately.

8.1.5 Blood Collection for Plasma Biomarker

Additional blood collection (10mL EDTA tube) for plasma biomarker will occur at Day 1, Day 2 and Day 90. All sample processing and handling instructions for sites are provided separately. Sites capable of collecting, processing and shipping of the biomarker samples will be confirmed by the Sponsor.

8.1.6 The Modified Rankin Scale

The main efficacy endpoint used in this trial will be global disability, as measured by the mRS, at Day 90. The mRS is a valid and reliable clinician-reported measure of global disability that has been widely applied for evaluating recovery from stroke. It is a scale used to measure functional recovery (the degree of disability or dependence in daily activities) of people who have suffered a stroke[22, 23]. The mRS scores range from 0 to 6, with 0 indicating no residual symptoms; 5 indicating bedbound, requiring constant care; and 6 indicating death.

The baseline mRS score will be used for study eligibility. The post dose mRS score will be obtained at Day 6 (or discharge), Day 30 and Day 90. The mRS will only be scored by those trained and certified in the use of this scale.

8.1.7 Mortality Rate

Mortality status will be obtained at all visits during the 90-day study period

8.1.8 The National Institutes of Health Stroke Scale

The NIHSS is a standardized neurological examination scale that is a valid and reliable measure of disability and recovery after acute stroke[24]. Scores range from 0 to 42, with higher scores indicating increasing severity. The scale includes measures of level of consciousness, extra ocular movements, motor and sensory tests, coordination, language and speech evaluations. The NIHSS will be administered at baseline, post-EVT (2h), 24h, 48h, Day 6 (or discharge), Day 30 and Day 90. The NIHSS will only be scored by those trained in the use of this scale.

8.1.9 Worsening of Stroke

Worsening of stroke is defined as progression, or hemorrhagic transformation, of the index stroke as documented by medical imaging that is (a) life-threatening requiring intervention and/or (b)

results in increased disability as gauged by a ≥4-point increase from lowest NIHSS score during hospitalization and/or (c) results in death.

8.1.10 Volume of Strokes

Prior to database lock at the end of the study, the total volume of infarct growth as measured by MRI brain images in RNS60 versus placebo control participants will be calculated from the Day 2 (48h) imaging and compared to the immediate post-thrombectomy scan.

In addition, the volume of injured tissue on FLAIR and T2 weighted images will be compared between the 90-day and post-thrombectomy time points for the RNS60 groups and placebo group, respectively.

The plan for MRI data will be detailed in the Imaging Charter.

8.1.11 Barthel Index

The BI is an index of functional independence[25] that is a valid measure of activities of daily living when employed in stroke trials[26]. Modified BI scores range from 0 to 100, with higher scores indicating greater independence in activities of daily living and mobility. The BI will be scored at baseline (pre-morbid), Day 30 and Day 90, by those trained in the use of this scale. Note that the original BI was a scale from 0-20. The modified BI simply multiplies the original scale by 5 to provide a 100-point score.

8.1.12 EQ-5D-5L

The EQ-5D-5L is a generic instrument for describing and valuing health. It is based on a descriptive system that defines health in terms of five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression[27]. Each dimension has five response categories corresponding to: no problems, slight, moderate, severe and extreme problems[28]. The version of the instrument selected for the trial is interviewer administered either in-person, or by telemedicine or by telephone. The respondents will also rate their overall health on the day of the interview on a 0–100 visual analogue scale (EQ-VAS). The EQ-5D-5L will be administered at Day 90.

8.2 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of an AE or SAE can be found in Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

AEs will be reported by the participant (or, when appropriate, by a healthcare provider, caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious,

considered related to the study intervention or study procedures, or that caused the participant to discontinue the trial.

The method of recording, evaluating, and assessing causality of AEs and SAEs, and the procedures for completing and transmitting SAE reports are provided in Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.2.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the start of study drug administration until Day 90, in addition SAE assessed as related to study drug or that have a fatal outcome will be collected to Day 90, see Table 1-1: Schedule of Activities.

All AEs will be collected from the start of study drug administration through Day 90 at the time points specified in Table 1-1: Schedule of Activities.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded in the Past Medical and Surgical History section of the electronic case report form (CRF), not in the AE section.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours of knowledge of the event, as indicated in Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.2.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences. A consistent methodology of eliciting AEs at all participant evaluation timepoints will be used. Non-directive questions include:

- How have you felt since your last clinical visit/hospital discharge?
- Have you had any new or changed health problems since you were last here?
- Have you had any unusual or unexpected worsening of your underlying medical condition or overall health?
- Have there been any changes in the medicines you take since your last clinical visit/hospital discharge?

AE identification while the participant is admitted to the acute stroke hospital will be collected via acute stroke hospital patient records and verbal histories from the participant or LAR. For follow up visits after discharge from the acute stroke hospital the participant (or LAR if the participant is not able to respond to the questions) will be asked about the occurrence of AEs since the last contact, and if available, from records at the acute stroke hospital.

Diagnosis versus signs and symptoms for the purpose of AE reporting: if known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only pneumonia rather than pyrexia, coughing, shortness of breath). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis it is acceptable to report the information that is ultimately available.

8.2.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

AEs that were ongoing at the last contact will be updated with a stop date or confirmed as ongoing. AE collection will continue until Day 90, and SAE to Day 90 or the final contact. Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.2.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety evaluation of the study drug under clinical investigation are met.

The sponsor has a legal responsibility to notify the FDA about the safety of a study intervention under clinical investigation. The sponsor will comply with regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and investigators.

- ***Initial reporting:*** IND application sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected.

  Suspected unexpected serious adverse reactions (SUSARs) and observations from animal studies suggesting significant risk to human subjects must be reported to FDA as soon as possible but no later than within **15 calendar days** following the sponsor's initial receipt of the information.

  Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than **7 calendar days** following the sponsor's initial receipt of the information.

- ***Follow-up reporting:*** Any relevant additional information obtained by the sponsor that pertains to a previously submitted IND safety report must be submitted as a Follow-up IND Safety Report. Such report should be submitted without delay, as soon as the information is available but no later than 15 calendar days after the sponsor receives the information

Investigator safety reports must be prepared by the sponsor for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
The Sponsor will notify the Investigators in writing of the occurrence of any reportable SAEs. The Investigators will be responsible for informing their local IRBs of any reportable SAEs as per their local requirements.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

8.2.5 Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until Day 90.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4 (Appendix 5: Collection of Pregnancy Information). Should the participant be pregnant, the infusion will be stopped immediately but the participant will still be monitored for safety up to 90 days.

Pregnancy itself is not considered an AE, but any complications during pregnancy are to be considered as AEs, and in some cases, could be considered SAEs. Spontaneous abortions, fetal death, stillbirth, and congenital anomalies reported in the baby are always considered as SAEs, and the information should be provided to the sponsor regardless of when the SAE occurs (e.g., even after the end of the trial).

9 STATISTICS

9.1 Sample Size Determination

As the primary aim of this study is to demonstrate safety, there was no power analysis conducted. Attrition factors include death from stroke but not treatment (10%), fluid overload (20%) and early discharge (5%).

9.2 Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Intent to Treat (ITT)	All participants randomized into the trial with grouping by randomized treatment, regardless of whether any treatment was actually received. Participant grouped according to the randomized (intended) treatment. (Participant who receive treatment but do not get the full 48 hours of treatment due to fluid overload, early discharge, or death will be included in the ITT analysis.)
Per Protocol	All participants randomized and treated, with no major protocol deviations including: did not meet inclusion/exclusion criteria, did not receive planned dose volume, incorrect study drug, consent not obtained (Participant who completes the full 48 hours will be included in both per protocol and ITT analysis.)
Full Analysis Set / Safety	All participants randomly assigned to study intervention and who receive any volume of study drug. Participants will be analyzed according to the intervention they actually received.

The primary efficacy analysis will be conducted in the ITT population. The primary analysis will be repeated on the per protocol population. An ITT analysis will also be conducted for the secondary endpoints, with participant grouped according to the randomized (intended) treatment.

9.3 Statistical Analysis

9.3.1 General Considerations

Mortality will be estimated using Kaplan-Meier estimation censoring on last known follow up. For participants missing observations, mRS, NIHSS and BI will have the last recorded value carried forward, when possible. Categorical data will be summarized using counts and percentages. Continuous data will be summarized using median and interquartile range.

9.3.2 Analyses of Safety

All safety analyses will be performed on the Safety Population. The main analyses will be frequency of SAEs and 90-day mortality.

Endpoint	Analysis Methods
SAEs	The frequency of SAEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0.
SAEs leading to death	The frequency of fatal SAEs will be summarized using the MedDRA Version 24.0.
AEs	The frequency of AEs will be summarized using the MedDRA Version 24.0.
Vital Signs	Absolute values and changes for vital signs from pre-dose to Day 2 will be documented. The maximum deviation of BP from baseline between drug and placebo control groups (systolic and diastolic) to Day 2 will be analyzed.
Laboratory Safety	Absolute values for laboratory results will be summarized descriptively.

Prior and Concomitant Medications	Prior and concomitant medications will be summarized using the WHO Drug Dictionary.

9.3.3 Analyses of Safety and Efficacy

All efficacy results will be examined using both ITT and per protocol populations. Although the trial's main purpose is to demonstrate safety, several measures of efficacy will be examined in order to provide effect size estimates for a appropriately powered future trial demonstrating efficacy. As such, both pairwise comparisons at various timepoints and longitudinal data will be examined.

1) Primary efficacy outcome
2) Secondary efficacy outcomes, as specified in the order presented below

Outcome	Statistical Analysis Methods
Primary	All analyses will be accomplished using SAS Software 9.4 (SAS Inc. Cary, NC). Primary: The frequency of SAEs, SAEs resulting in death, AEs, and discontinuations due to AEs will be summarized as counts and percentages between conditions. Comparisons will be conducted using Fisher's Exact tests.
Secondary	Secondary: Comparisons between conditions for mRS will be evaluated using generalized mixed modeling assuming a binomial distribution (0-6) with sandwich estimation nested by site and participant, when applicable. Pairwise comparisons of mRS will be conducted at day 90 using a Dunnett correction. In addition, simple and interaction effects between pre-stroke, discharge, 30 and 90-day mRS by condition will be examined. Because superiority over placebo and lower dose is hypothesized, testing will reflect this superiority framework with one-tailed tests. Both NIHSS score and BI at Day 90 will be examined in a similar fashion assuming a binomial distribution (0-42 & 0-100) with sandwich estimation nested by site and participant (when applicable). Pairwise comparisons between conditions will be conducted at day 90 using a Dunnett correction. In addition, simple and interaction effects between pre-treatment, discharge, 30 and 90-day NIHSS scores and BI by condition will be examined. Because superiority over placebo and lower dose is hypothesized, testing will reflect this superiority framework with one-tailed tests. Mortality will be examined using Kaplan-Meier estimation with pairwise comparisons with a Dunnett correction with censoring on last known follow up. Because superiority over placebo and lower dose is hypothesized, testing will reflect this superiority framework with one-tailed tests. Marginal Cox Hazard regression will also be used to evaluate mortality with sandwich estimation and nesting within site.

	DWI volume and T2 will be modeled between conditions using generalized linear modeling assuming a normal or lognormal distribution (where appropriate) with sandwich estimation, where observations are nested by site and participant (when appropriate). Pairwise comparisons at post EVT, 48 hours (or early discharge), and 90 days. Simple and interaction effects will be examined across these three timepoints. Because superiority over placebo and lower dose is hypothesized, testing will reflect this superiority framework with one-tailed tests. Because the main aim of this is trial is to examine safety, efficacy analysis results are intended to yield estimates to inform powering for subsequent efficacy trial. Alpha is established at the 0.05 level and all interval estimates will be calculated for 95% confidence.
	Worsening of Stroke is determined as the number of participants experiencing at least one worsening of stroke divided by the number of participants observed over the 90-day period in that treatment group, between RNS60 and placebo control participants. This will be modeled using generalized linear modeling assuming a binary distribution with sandwich estimation, where observations are nested by site. Because superiority over placebo and lower dose is hypothesized, testing will reflect this superiority framework with one-tailed tests.

10 SUPPORTING DOCUMENTATION and OPERATIONAL CONSIDERATIONS

10.1 Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations including: United States Code of Federal Regulations (CFR; including Title 21 Parts 50, 54, 56, and 312), where applicable.
- Applicable guidelines issued due to the COVID-19 pandemic

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations

10.1.2 Financial Disclosure

As requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities, investigators and sub-investigators may provide the sponsor with sufficient, accurate financial information. This includes information on financial interests during the course of the study and potentially for 1-year after completion of the study. Routine care is expected to be paid for by the existing standard medical insurance system. This will include but is not limited to:

- Admission to hospital
- Baseline laboratory testing, pregnancy test, baseline NCCT and CTA, baseline CTP
- Endovascular procedure and angiography
- Follow-up limited-sequence MR brain imaging at 48h
- Follow-up laboratory testing
- Physician fees
- Treatment processes in the endovascular lab since they are considered standard of care
- Stroke unit care in hospital
- Nursing care
- Rehabilitation and home care if relevant
- Outpatient clinic follow-up at 90 days (routine)

The study fees are designed to cover the costs of study personnel, data collection, research study processes and treatments, the 30-day follow up visit, the 90-day follow-up visit, CRF completion, adverse event reporting, concomitant medication reporting, submission of imaging to the core lab and support of remote monitoring, if applicable. The study fees are inclusive of any local institutional overhead/indirect costs.

10.1.3 Informed Consent Process

See Section 5.5.2 for further details.

10.1.4 Data Protection

Participants will be assigned a unique identifier by the CRO. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

Personal medical information may be reviewed for the purpose of verifying data recorded in the eCRF by the site monitors. Other properly authorized persons, such as the regulatory authorities, may also have access to these records. Personal medical information is always treated as confidential. The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

All imaging, evaluation forms, reports, and other records that leave the site are identified only by the site and participant number to maintain participant confidentiality. All records are kept in a locked file cabinet. Clinical information is not released without written permission of the participant, except as necessary for monitoring by the IRB, FDA, the sponsor, or the sponsor's designee.

All study investigators at the clinical sites, monitors and sponsor staff must ensure that the confidentiality of personal identity and all personal medical information of study participants are maintained at all times. Federal legislation in the U.S. (HIPAA) and local legislations must be followed.

10.1.5 Oversight Committees

Safety reviews may be performed routinely by the local study site PIs and/or sponsor's staff in the course of the trial. Any questions pertaining to the reported clinical data will be submitted to the investigator for resolution. Each step of this process will be monitored through the implementation of individual passwords to maintain appropriate database access and to ensure database integrity.

10.1.6 Data Safety Monitoring Board

An independent committee (composed of three individuals) will be assembled to follow the study charter as proposed above.

10.1.7 Dissemination of Clinical Study Data

Study information and tabular study results will be posted on the US National Institutes of Health's website www.clinicaltrials.gov within one year of study completion.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on the electronic CRF unless transmitted to the sponsor or designee electronically (e.g., imaging). The investigator is responsible for verifying that data entries are accurate and correct signing the CRF. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents. The investigator agrees to allow the monitor(s) direct access to all relevant documents, and to allocate his/her time and the time of staff to discuss findings, corrective actions and any relevant issues. In addition to contacts during the study, the monitor may also contact the site prior to the start of the study to discuss the protocol and data collection procedures with site personnel.

Except for an emergency situation in which proper care for the protection, safety and well-being of the study participants requires medical treatment, the study will be conducted as described in the approved protocol, ICH GCP, SOPs and regulatory requirements. All medical treatments will be recorded. Any deviation(s) from the protocol will be recorded and presented in the final clinical study report.

The sponsor will determine the extent, nature, and frequency of on-site visits that are needed to ensure that the study is being conducted in accordance with the approved protocol (and any amendments), GCP, and all applicable regulatory requirements. Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data. The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted

in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. This review may occur at the study site or remotely. Any records supplied by the site for the purpose of remote monitoring and remote source document verification must comply with local legislation and the process approved by the local IRB, when required.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for at least 5 years after the completion of the clinical trial, at least 2 years after the last approved marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug (whichever of the above requirements is the longest) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Source documents specification per site will be agreed prior to first participant enrolled at the site. Data reported in the eCRFs must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Any records supplied by the site for the purpose of remote monitoring and remote source document verification must be de-identified using only the unique trial specific participant identifier. This process will be aligned with local ethics and privacy requirements.

Any investigators shall supply the sponsor, upon request, with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that participant confidentiality is protected.

Definition of what constitutes source data may include: participant hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, signed consent forms, consultant letters, and source worksheets.

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: (1) Investigator's Study File; and (2) Participant Clinical Source Documents.

The Investigator's Study File will contain the Protocol/Amendments, CRFs, IRB and governmental approval with correspondence, all versions of IRB approved informed consent

forms, staff curriculum vitae and authorization forms and other appropriate documents / correspondence, etc.

The investigator must keep these two categories of documents on file according to local clinical trial regulation. All study documents for a regulated trial require storage for at least 5 years after the completion of the clinical trial, at least 2 years after the last approved marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP (whichever of the above requirements is the longest). After that period of time the documents may be destroyed, participant to local regulations.

The investigator and the sponsor will maintain the records of disposition of the drug and the clinic records in accordance with ICH GCP and each applicable regulatory agency. Clinic records will be retained at the site until informed by the sponsor to destroy the documents. If the clinical study must be terminated for any reason, the investigator will return all study materials to the sponsor and provide a written statement as to why the termination has taken place and notify the IRB.

10.1.10 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion at 90 days. A study site is considered closed when all required documents and study supplies have been collected and a 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 the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will permit any and all academic publications arising from the trial data provided that no publication containing unblinded trial data precedes publication of the overall trial results in a peer-review journal, they are approved by the trial executive committee, and the publication authors notify the sponsor at least 30 days prior to submittal for publication with a copy of such proposed publication for the sponsor's review and comment. Employees or consultants of the sponsor will only be named as authors in any such publication if the parties agree that it is appropriate under the usual conventions used by academic institutions for naming authors in scientific publications. Upon request of the sponsor the publication or disclosure shall be delayed for up to 60 days in order to allow for the filing of a patent application.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

A trial executive committee shall be formed and include at least the trial principal investigator and co-principal investigator, the statistical consultant, and representatives of the sponsor. The trial executive committee will be co-authors on all publications and presentations. The primary author list for the primary publication will consist of the executive committee and the site principal / qualified investigator at each of the sites. A formal publication policy will be presented and developed by the trial executive.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.12 Audits and Inspections

In accordance with the principles of ICH E6 Guideline for Good Clinical Practice, the study site may be inspected by regulatory authorities and/or audited by the sponsor or its designates. The investigator and relevant clinical support staff will be required to be actively involved in audits and inspections, including staff interviews, and to make all necessary documentation and data available upon request.

During the course of the study and/or after it has been completed, one or more investigator site audits may be undertaken by auditors from the sponsor or its delegates. The purpose of these audits is to determine whether or not the study is being/has been conducted and monitored in compliance with recognized ICH E6 Guideline for Good Clinical Practice, protocol and approved amendment requirements, applicable local SOPs, and local laws and regulations. It is the responsibility of the investigator and site staff to promptly address, by coordinating with the

sponsor, any deficiencies stemming out of regulatory inspections and sponsor or delegate audits, and to ensure that agreed-upon corrective and preventive actions are implemented as soon as possible.

An inspection by any regulatory authority may occur at any time during or after completion of the study. If an investigator is contacted by a regulatory authority for the purpose of conducting an inspection or to discuss any compliance issues, he/she is required to contact the sponsor immediately.

10.2 Appendix 3: Clinical Laboratory Tests and Imaging

10.2.1 Clinical Laboratory Tests

The tests detailed in Table 10-1 will be performed as per local hospital laboratory.

Table 10-1: Protocol-Required Safety Assessments

Laboratory Tests	Parameters
Hematology	Platelet count Hemoglobin Hematocrit
Chemistry	Blood Urea Nitrogen Coagulation Panel (PTT and INR) Liver function test panel (ALT, AST and Bilirubin) Serum creatinine Serum glucose
Electrolytes	Sodium Potassium Chloride Bicarbonate Magnesium
Pregnancy testing	Highly sensitive (serum or urine) human chorionic gonadotropin (β-hCG) pregnancy test (as needed for women of childbearing potential)
Electrocardiogram	Frequent premature ventricular contractions or PVCs (> 10/min), ventricular tachycardia (VT), hypoxia, ischemia
CXR	Monitor fluid

10.2.2 Imaging

At baseline all participants will undergo NCCT and CTA (with mCTA preferred) imaging for assessment of inclusion into the trial. If mCTA is not standard of care at the imaging facility, single phase CTA (CTA) can be used to confirm intracranial occlusion eligibility. If CTA is not available, CTP may be used. To evaluate for the presence or absence of collaterals, mCTA, single phase CTA or CTP can be utilized. The immediate post-thrombectomy (within approximately 2 hours) and 48-h MRI will be used to assess perfusion imaging and infarct volume and will include a minimum of axial DWI, gradient-echo (GRE), FLAIR, T2, and 3D T1 weighted dataset). The 48-h MR is considered a standard of care imaging procedure. If any MRI cannot be obtained (due to subject compliance or limitations) a CT will be performed.

The baseline NCCT and CTA and all brain/neurovascular imaging conducted up to the Day 90 MR will be rendered anonymous and sent to the central core imaging lab. The core imaging lab staff will review the imaging as per an Imaging Charter in order to ensure adherence to the imaging guidelines and enrollment criteria for training purposes. The core imaging lab will confirm determination of baseline ASPECT scores, as well as reperfusion rates (TICI scores) and infarct growth from immediately after thrombectomy to 48h. In addition, overall injury to the

affected hemisphere will be compared between groups by comparing volume loss/gliosis between the 90-d and post-thrombectomy MRI.

For all interval times assessed from imaging, the time zero will be the first slice of the NCCT scan. Imaging date and time will be collected in the CRF.

Notes:

The use of a dynamic CTA or multiphase CTA data acquisition protocol is preferred.
Baseline NCCT and CTA may be completed at a hospital affiliated with the trial site.

10.3 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition
An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Adverse Drug Reaction (ADR) In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. ***Unexpected Adverse Drug Reaction*** An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).
Events <u>Meeting</u> the AE Definition
• A new illness • The worsening of a concomitant illness • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing condition worsens in frequency or intensity, or if in the assessment of the treating physician there is a change in its clinical significance, this change should be reported as an AE (exacerbation). This applies equally to recurring episodes of pre-existing conditions (e.g., asthma) if the frequency or intensity increases post-randomization.

10.3.1 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death All deaths occurring during the follow up to Day 90 will be reported as an SAE. When reporting a death, the event or condition that caused or contributed to the fatal outcome should be reported as a single medical concept.
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Results in a congenital anomaly/birth defect
f. Other situations: a SAE can also be an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.2 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the CRF pages and SAE reports. • There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant

study identification number, will be redacted on the copies of the medical records before submission to the sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: Awareness of sign or symptom but easily tolerated.
- Moderate: Discomfort sufficient to cause interference with normal activities.
- Severe: Incapacitating, with inability to perform normal activities.

An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

AE Causality/ Relationship

Related	A clinical event, including laboratory test abnormality, where there is a "reasonable possibility" that the SAE was caused by the study drug, meaning that there is evidence or arguments to suggest a causal relationship.
Possibly:	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unrelated:	This category is applicable to AEs which are judged to be clearly and incontrovertibly due to extraneous causes (diseases, environment, etc.) and do not meet the criteria for drug relationship listed for the above-mentioned conditions.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study the investigator may be requested by the sponsor to provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.3 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) **in order to report the event within 24 hours**‡. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to Redacted **Clinical Safety:** **SAE Reporting Phone Line**: +1-Redacted **Safety Fax**: +Redacted
SAE Reporting to the Sponsor via Paper CRF
If the eCRF system is not available, a paper SAE form should be directed within 24 hours to: Redacted Clinical Safety Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

‡ In cases where an SAE is reported on a Friday, where possible the investigator will aim to send the notification prior to the weekend. If not possible, or if the event occurs on a weekend or a holiday, notification will be sent on the first business day after the event.

10.4 Appendix 5: Collection of Pregnancy Information

Male participants with partners who become pregnant:

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study drug. After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the Pregnancy Reporting Form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 4 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant:

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the Pregnancy Reporting Form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 4 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.2.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention but will continue to be followed to the end of the trial.

10.5 Appendix 6: Abbreviations

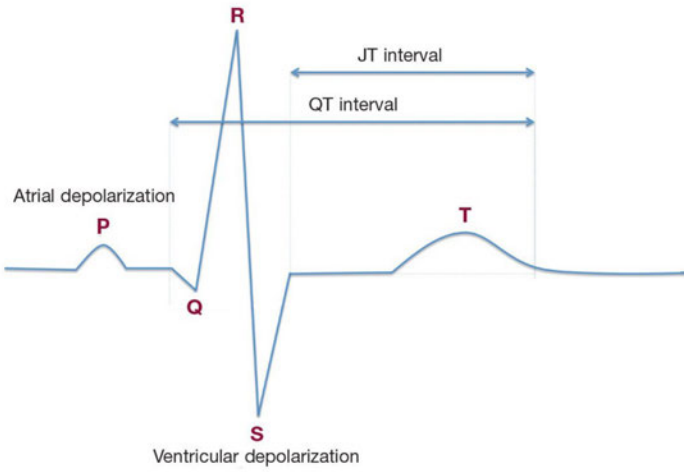
AHA	American Heart Association
AIS	Acute Ischemic Stroke
AE	Adverse Event
ASPECTS	Alberta Stroke Program Early Computerized Tomography Score
β-hCG	Beta-human Chorionic Gonadotropin
BI	Barthel Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Computed Tomography
CTA	Computed Tomographic Angiography
CTP	Computed Tomographic Perfusion
CXR	Chest X-ray
DWI	Diffusion Weighted Imaging
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol health-related quality of life
EVT	Endovascular Thrombectomy
FDA	Food and Drug Administration
FLAIR	Fluid Attenuated Inversion Recovery
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
ICA	Internal Carotid Artery
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
LAR	Legally Authorized Representative
LFT	Liver Function Tests
LVO	Large Vessel Occlusion
MAP	Mean Arterial Pressure
MCA	Middle Cerebral Artery
mCTA	Multiphase Computed Tomography Angiography

MedDRA	Medical Dictionary for Regulatory Activities
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
n	Number of Observations
NaCl	Sodium Chloride
NCCT	Non-contrast Computed Tomography Scan
NIHSS	National Institutes of Health Stroke Scale
pH	Potential Hydrogen
PI	Principal Investigator
PP	Per Protocol
QA	Quality Assurance
RR	Risk Ratio
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TICI	Thrombolysis in Cerebral Infarction Score
USA/US	United States of America
VAS	Visual Analogue Scale

10.6 Appendix 7: Adjusted QTcF Calculation

QTcF Measurement Adjustment in Patients with a Widened QRS Complex > 110 ms

The duration of the ECG QT interval reflects the combination of cardiac depolarization which is measured as duration of the QRS interval and cardiac repolarization, which is defined by the JT interval.



Normal values for the rate-corrected QTc interval are defined largely from populations of subjects with normal QRS durations, without bundle branch blocks or intra-ventricular conduction delays. In the setting of a widened QRS complex (> 110 ms), however, using the QTcF interval measurement may lead to overestimating cardiac repolarization, since the QTcF would be prolonged due to the contribution from the widened QRS complex. In other words, the QTcF interval could be prolonged despite cardiac repolarization being normal (i.e., a normal JTc interval). For example, if the QRS duration was 150 ms and the QTcF was 500 ms, cardiac repolarization is not meaningfully prolonged when it is considered that a normal QRS duration is conservatively 90 ms. So, in this case 60 ms (150 ms – 90 ms) of the QTcF of 500 ms is due to excessive QRS prolongation and thus the QTcF "*adjusted*" for the QRS widening is 440 ms (500 ms – [150 ms – 90 ms]).

Thus, in subjects with a QRS duration > 110 ms, a QTcF adjusted for the widened QRS duration can be used to assess if a patient meets criteria for protocol exclusion, drug hold, or discontinuation using the below formula:

***Adjusted QTcF* = measured QTcF – [measured QRS – 90 ms]**

Another example:
QTcF= 505 ms
QRS= 157 ms

Adjusted QTcF = 505 ms – [157 ms – 90 ms] = 438 ms

***Note: Adjusted QTcF calculation should be done by someone qualified and experienced in making this calculation.*

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12 INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Randomized, Blinded, Placebo-controlled, Parallel Group Design to Determine the Safety of RNS60 in Large Vessel Occlusion Stroke Patients Undergoing Endovascular Thrombectomy. (RNS60 Stroke Trial) and agree to abide by all provisions set forth therein.

I agree to comply with the current International Conference on Harmonisation Guidelines for Good Clinical Practice and the laws, rules, regulations and guidelines of the community, state or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor.

Name of Site Principal Investigator	Signature
Name of Clinical Site	Date

13 ADDENDUM

13.1 COVID-19 Considerations

Minimizing Risk to Participants and Staff
The protocol includes the following adaptations to minimize risk while prioritizing the overall well-being and best interests of all involved in the trial. This protocol was written considering the impact of COVID-19 on trial participants, site staff and sponsor staff. With these priorities in mind, the protocol design will still permit assessment of safety of RNS60.

- **Minimize the number of study visits** to align with the trial endpoints
- **Minimize the number of trial specific activities**. The trial was designed to align with standard of care protocols for acute stroke. For example, obtaining data from standard of care assessments conducted during routine stroke care, for the collection and reporting of some safety outcomes (vital signs, laboratory results) and imaging outcomes.
- **Conduct visits by telemedicine or by telephone** at Day 30 and Day 90, where permitted, when a participant is unable to attend the site physically. This will permit the timely collection of efficacy endpoints (mRS, NIHSS, BI and EQ-5D-5L) and safety data (AE and SAE collection). If the contact is made by phone, only the NIHSS assessment will not be completed, all other assessments will be obtained.
- **Use of remote electronic consent,** where permitted, to obtain initial consent from the LAR, who may not be able to enter the hospital, and to obtain regained capacity consent from participants who did not consent prior to their discharge from hospital.
- **Use of electronic Clinical Outcome Assessments (eCOA)** for the conduct of the mRS, NIHSS, BI and EQ-5D-5L assessments at Day 30, and Day 90 timepoints. This will permit site staff to collect trial endpoints even if they are not permitted into the hospital, reduce data entry time and reduce the time on-site for CRAs in order to monitor the data.

In addition to the above items included in the protocol, ongoing risk assessments and monitoring of the COVID-19 situation will be conducted by the sponsor with input from the investigators. These ongoing assessments include changes to any of the following:

- Potential impact on trial participants
- Potential impact on trial site staff, including local or central IRBs
- Potential impact on sponsor/CRO staff conducting site monitoring and central review of data.

The outcome of these ongoing assessments could result in site-specific mitigation plans, which could include:

- Suspension of enrollment at that site
- Suspension of on-site visits by participants at that site, replacing the physical data capture with some remote measures (telephone or telemedicine, where permitted)
- Suspension of on-site visits being conducted by the CRA, replacing the monitoring with remote review of data and telephone contacts with the site
- Other mitigation plans, as appropriate.

13.2 Assessment Questionnaires

Below is a sample of the assessment questionnaires and instructions to be used in the trial.

Modified Rankin Scale (mRS)	Clinician Reported Outcome English example
National Institute of Health Stroke Scale (NIHSS)	Clinician Reported Outcome English example.
Barthel Index	Clinician Reported Outcome English example.
EQ-5D-5L	Patient Reported Outcome USA, English Interviewer Administered example See https://euroqol.org/ for device, country, and language specific versions

MODIFIED RANKIN SCALE (MRS)

Rater Name: _____

Date: _____

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

TOTAL (0–6): _____

Rater Sign / pager:_____

Provider Sign / MD# / pager:_____

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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 _____(___ ___)

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.	_____

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**	_____

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:_____	_____

NIH STROKE SCALE

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

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

Hospital _____(___ ___-___ ___)

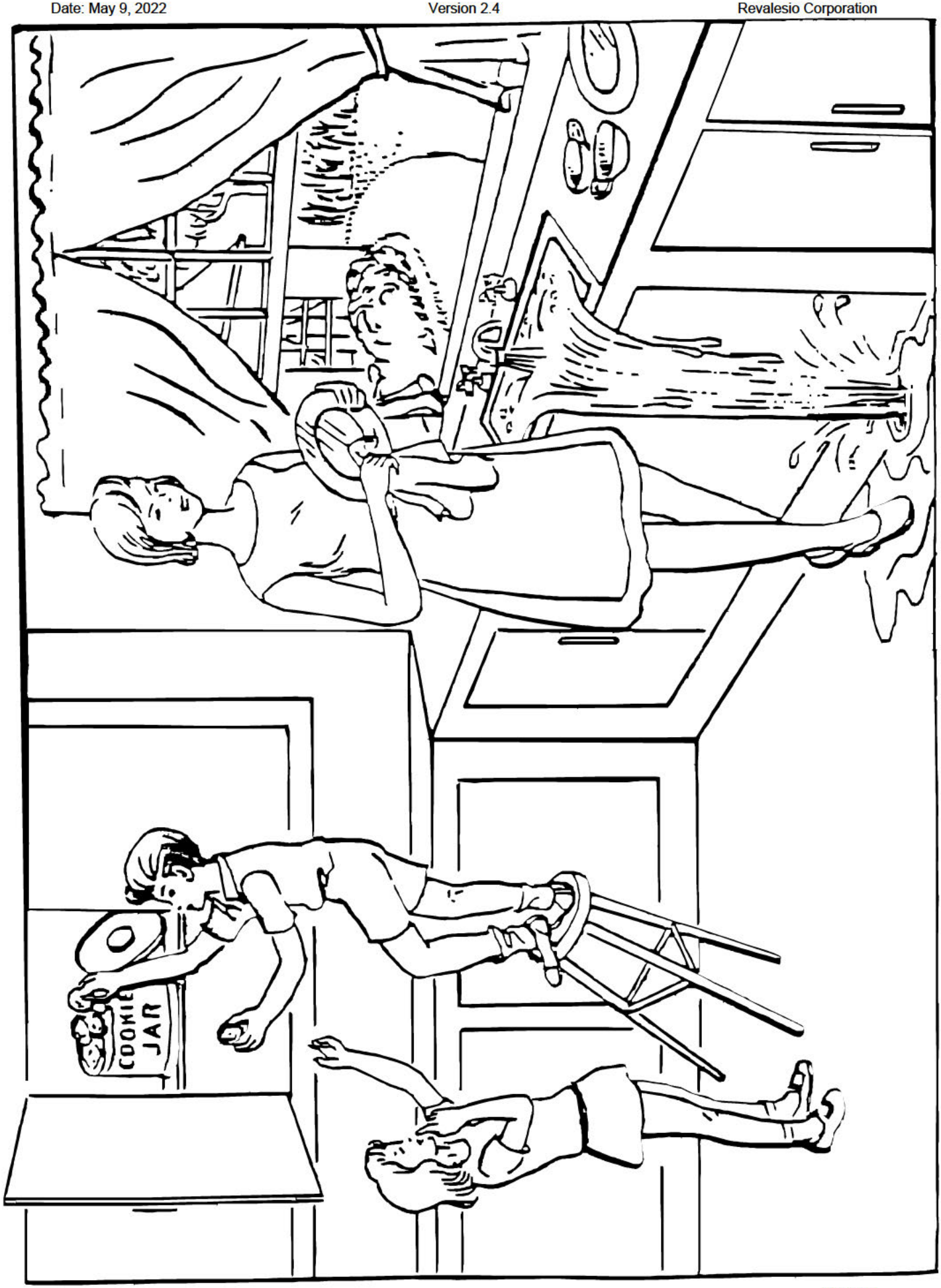
Date of Exam ___ ___/___ ___/___ ___

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.	_____

_____

_____


COOKIE
JAR

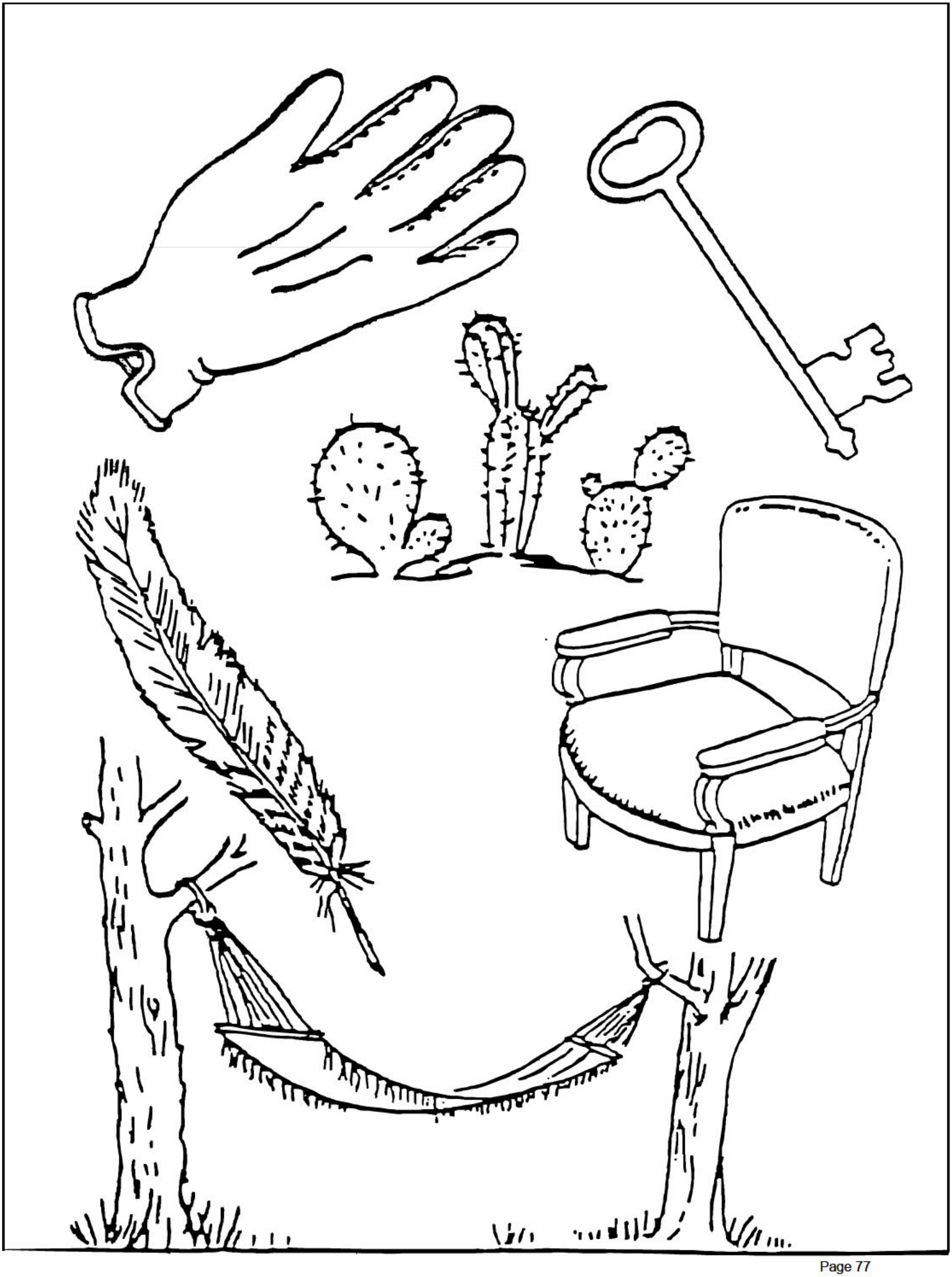
You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.



MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

THE BARTHEL INDEX

Patient Name: _____
Rater Name: _____
Date: _____

Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
BATHING 0 = dependent 5 = independent (or in shower)	_____
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	_____
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	_____
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	_____
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	_____
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	_____
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	_____
TOTAL (0–100):	_____

The Barthel ADL Index: Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 per cent of the effort.
7. Use of aids to be independent is allowed.

References

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Copyright Information

EQ-5D-5L

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐