Official Title: A Phase III, Prospective, Double-Blind, Randomized, Placebo Controlled Trial of Thrombolysis in Imaging-Eligible, Late-Window Patients to Assess the Efficacy and Safety of Tenecteplase (Timeless)

NCT Number: NCT03785678

Document Dates: Protocol Version 5: 09-March-2021

PROTOCOL

TITLE:	**A PHASE III, PROSPECTIVE, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF THROMBOLYSIS IN IMAGING-ELIGIBLE, LATE-WINDOW PATIENTS TO ASSESS THE EFFICACY AND SAFETY OF TENECTEPLASE (TIMELESS)**
PROTOCOL NUMBER:	ML40787
VERSION NUMBER:	5
EUDRACT NUMBER:	Not applicable
IND NUMBER:	139,995
TEST PRODUCT:	Tenecteplase (RO5490263)
MEDICAL MONITORS:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 21 October 2018
DATE AMENDED:	Version 2 (CIRB): 12 Nov 2018 Version 3: 6 June 2019 Version 4: 30 January 2020 Version 5: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
09-Mar-2021 16:53:35	[redacted]	[redacted]

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Protocol ML40787 has been amended primarily to add a cap to the enrollment of patients with an internal carotid artery (ICA) occlusion. Changes to the protocol, along with a rationale for each change, are summarized below:

- The endpoints for the safety objective were revised to clarify the timepoints for mortality rate and proportion of patients with parenchymal hematoma type 2 (Section 2).
- The exploratory endpoint "Overall survival at Day 90" was added per Food and Drug Administration (FDA) request (Sections 2 and 6).
- An inclusion criterion concerning neuroimaging was clarified: "MR" was changed to "MR perfusion." In addition, a cap was added so that the enrollment of patients with an ICA occlusion (including proximal and tandem ICA occlusions) is limited to no more than 15% of the target study population to maintain a representative comparison to similarly designed trials and evidence that reported a 6%–15% ICA occlusion rate (Section 4.1.1).
- Text was added to exclusion 8 to clarify when aneurysms are considered an exclusion criterion (Section 4.1.2).
- Text was added to exclusion 10 to clarify that COVID-19 positivity and/or suspected positivity are exclusion criteria since COVID could confounding the neurological or functional evaluation (Section 4.1.2).
- The text concerning treatment assignment procedures was revised to include the changes that will be made to screening and randomization process (Section 4.2.1).
- The system being used for treatment assignment was corrected from an "interactive voice or web-based response system (IxRS)" to an interactive web response system (IWRS)" throughout the protocol (Sections 4.2.1, 4.2.2, 4.3.3, and 9.4).
- A note was added to the list of concomitant therapies to be recorded was added to clarify that "vaccines" included COVID-19 vaccines (Section 4.4).
- The list of prohibited therapies was expanded to include anti-platelet agents for 24 hours after study drug administration to align with American Heart Association (AHA) guidelines in patients who may require a stent (Section 4.4.2).
- A sentence indicating that temperature is required prior to randomization was revised to remove "to rule out infection" as this phrase was inaccurate (Section 4.5.3).
- Computed tomography angiography (CTA) and computed tomography perfusion (CTP) were added as acceptable imaging systems for patients who cannot undergo magnetic resonance imaging (MRI) at first follow-up (Section 4.5.9, Appendix 1, and Appendix 7).
- Clarification was added to ensure baseline blood and urine samples are collected prior to randomization (Section 4.5.10).

- Text was revised to clarify and correct the definition of an sICH. Adverse Events of Special Interest list has been updated to match the sICH definition (Section 5.2.3).
- An additional adjustment variable (i.e., baseline mechanical thrombectomy planned status) was added to the analysis of efficacy endpoints to align with the study Statistical Analysis Plan (Sections 6.4, 6.4.1, 6.4.2, and 6.4.3).
- The list of secondary efficacy endpoints was reordered to match the hierarchical testing order (Section 6.4.2).
- The Schedule of Activities (Appendix 1) and Brain Imaging Requirements (Appendix 7) were updated to reflect revisions made in the protocol text.

Minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, PROSPECTIVE, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF THROMBOLYSIS IN IMAGING-ELIGIBLE, LATE-WINDOW PATIENTS TO ASSESS THE EFFICACY AND SAFETY OF TENECTEPLASE (TIMELESS)**
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SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, PROSPECTIVE, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF THROMBOLYSIS IN IMAGING-ELIGIBLE, LATE-WINDOW PATIENTS TO ASSESS THE EFFICACY AND SAFETY OF TENECTEPLASE (TIMELESS)**
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VERSION NUMBER:	5
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IND NUMBER:	139,995
TEST PRODUCT:	Tenecteplase (RO5490263)
PHASE:	Phase III
INDICATION:	Acute ischemic stroke
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the efficacy and safety of tenecteplase compared with placebo in patients with acute ischemic stroke (AIS) and evidence of salvageable tissue on their baseline computed tomography perfusion (CTP) scan or magnetic resonance imaging (MRI) who present in the 4.5- to 24-hour time window with an internal carotid artery (ICA) or middle cerebral artery (MCA; M1 or M2) occlusion. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Efficacy Objective	Corresponding Endpoint
• To compare the efficacy of tenecteplase with placebo	• Ordinal modified Rankin scale (mRS) score at Day 90
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of tenecteplase compared with placebo	• Proportion of patients with functional independence, defined as an mRS of 0–2, at Day 90 • Proportion of patients with angiographic reperfusion (TICI 2b or TICI 3) at completion of angiographic procedure (endovascular patients only) • Median National Institutes of Health Stroke Score (NIHSS) score at Day 90 (Appendix 3) • Proportion of patients with a Barthel Index (BI) score of ≥95 at Day 90 (Appendix 4) • Proportion of patients with good recovery based on the Glasgow Outcome Scale at Day 90 (Appendix 5) • Proportion of patients with reperfusion at 24 hours post-randomization, defined as >90% reduction in T_{max} >6s lesion volume • Proportion of patients with recanalization at 24 hours post-randomization, defined as complete recanalization on CT angiography (CTA)/magnetic resonance angiography (MRA)

Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of tenecteplase compared with placebo	• Median final infarct volumes at 72–96 hour *visit* or discharge (if patient is being discharged prior to 72 hours) • Median infarct growth at 72–96 hour *visit* or discharge (if patient is being discharged prior to 72–96 hour *visit*) • Ordinal mRS score at Day 90 by occlusion type (M1/ICA or M2 occlusions) • Ordinal mRS score at Day 30 and Day 90 by randomization site (non-endovascular capable center [nECC] or endovascular capable center [ECC]) • Proportion of patients where planned thrombectomy was not performed • Proportion of patients who are randomized at an nECC and transferred to an ECC for endovascular therapy for whom planned thrombectomy was not performed • Proportion of patients readmitted within 30 days from discharge • Proportion of patients requiring one pass with endovascular therapy device (endovascular patients only) • Mean Neuro-QoL scores by domain (Appendix 6) • *Overall survival at Day 90*
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of tenecteplase compared with placebo	• Incidence of symptomatic intracranial hemorrhage (sICH [a]) within 36 hours • Incidence and severity of adverse events • Mortality rate *up to* Day 30 and Day 90 • Proportion of patients with parenchymal hematoma type 2 (PH2) at *the* 72–96 hour *visit*

BI = Barthel Index; CT = computed tomography; *CTA = computed tomography angiography; ECC = endovascular capable center; MRA =* magnetic resonance *angiography; mRS = modified Rankin scale; nECC = non-endovascular capable center; Neuro-QoL = Quality of Life in Neurological Disorders (scale);* NIHSS = National Institutes of Health Stroke Scale; sICH = symptomatic intracranial hemorrhage; PH1 = parenchymal hematoma type 1; PH2 = parenchymal hematoma type 2*; TICI = thrombolysis in cerebral infarction (scale); T_{max} = time to maximum of the residue function .*

[a] sICH is defined as ≥4 points of clinical worsening on the NIHSS compared with the most proximal NIHSS reported, attributed to a *bleed* on CT scan (preferred) or MRI performed within 36 hours after study drug administration.

Study Design

Description of Study

This is a Phase III, prospective, double-blind, randomized, placebo-controlled trial of tenecteplase in patients with AIS who meet predefined imaging criteria. Patients who meet inclusion criteria will be randomized to tenecteplase (0.25 mg/kg, maximum 25 mg) or placebo, both administered as a single bolus injection over 5 seconds.

All patients will receive standard-of-care therapy according to American Heart Association / American Stroke Association *(AHA/ASA)* clinical guidelines (2018). For patients with ICA/M1 occlusions, this will include adjuvant endovascular therapy following study drug (tenecteplase/placebo) if criteria, as stipulated in the guideline, are met. Per guideline recommendations, patients with M2 occlusions generally will not undergo endovascular therapy following treatment with study drug (tenecteplase/placebo).

Study drug administration *is recommended to* occur before the start of endovascular therapy (defined as groin puncture):

- If it appears that it will be challenging to administer study drug prior to *the* femoral groin puncture for a planned thrombectomy, *it is recommended that* the patient *not be randomized*
- *However,* if the patient has *already* been randomized, and due to unforeseen circumstances the drug cannot be administered prior to groin puncture for the planned thrombectomy, the drug **must** be administered as soon as possible and prior to manipulation of the clot

To determine eligibility for randomization, all patients will undergo multimodal CT or MRI at baseline. Only patients with a vessel occlusion (ICA or MCA) and penumbral tissue will be randomized.

Randomization will be stratified by age (≤70 vs. >70 years), type of occlusion (ICA/M1 vs. M2), baseline NIHSS (≤15 vs. >15), and randomization site (*endovascular capable center [*ECC*]* vs. *non-endovascular capable center [*nECC*]*). The primary goal of this trial is to compare the effect of treatment with tenecteplase vs. placebo and standard of care on 90-day functional outcomes (i.e., ordinal mRS scores) in patients who present in the 4.5- to 24-hour time window with an ICA or MCA (M1, M2) occlusion and evidence of target mismatch on multimodal CT or MRI of the brain. U.S. Food and Drug Administration (FDA)-approved and validated perfusion imaging software for determination of core volumes will be used.

Both patients transferred from an nECC as well as patients admitted directly to an ECC are eligible for the study.

Patients will undergo two follow-up MRI scans. Patients who cannot undergo an MRI will undergo a multimodal CT at the first follow-up and a non-contrast CT at the second follow-up. The first follow-up scan will be obtained at approximately 24 *hours* (±6 hours) after randomization and will include an assessment of recanalization and reperfusion, per standard of care. The second MRI will be obtained between 72 to 96 hours after randomization for assessment of final infarct volumes.

All patients will be evaluated using mRS at discharge/Day 5, Day 30, and Day 90 after randomization for clinical outcome evaluation.

The primary analysis is to compare the efficacy of tenecteplase versus placebo in all patients at Day 90, as assessed by the mRS score with an ordinal analysis. As a key prespecified subgroup analysis, the trial will also assess the effect of tenecteplase separately in patients with ICA/M1 and in patients with M2 occlusions.

Number of Patients

Approximately 456 patients with AIS will be enrolled in this study at approximately 90 sites (consisting of both ECCs and nECCs) primarily in the U.S. and Canada.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Patient/legally authorized representative has signed the Informed Consent Form
2. Age ≥18 years
3. AIS symptom onset within 4.5 to 24 hours

   Stroke onset is defined as the time the patient was last known to be at their neurologic baseline. (Wake-up strokes are eligible if they present within the 4.5- to 24-hour time limits of last known well.)

   Note: All study-related treatment needs to be initiated within 24 hours.

4. Signs and symptoms consistent with the diagnosis of an acute anterior circulation ischemic stroke involving occlusion of the ICA, M1, or M2 vessels
5. Functionally independent (mRS 0–2) prior to stroke onset
6. Baseline NIHSS ≥5 and that remains ≥5 immediately prior to randomization
7. **Neuroimaging:** ICA or M1, M2 occlusion (carotid occlusions can be cervical or intracranial, with or without tandem MCA lesions) by *magnetic resonance angiography* (MRA) or *computed tomography angiography* (CTA) **AND** target mismatch profile on CT perfusion or *MR perfusion* (ischemic core volume <70 mL, mismatch ratio is ≥ 1.8 and mismatch volume is ≥ 15 mL)
   - The mismatch volume is determined by FDA-approved imaging software in real time based on the difference between the ischemic core lesion volume and the *time to maximum of the residue function* (T_{max}) >6s lesion volume. If both a CT perfusion and a multimodal MRI scan are performed prior to enrollment, the later of the 2 scans is assessed to determine eligibility. For patients screened with MRA, only an intracranial MRA is required (cervical MRA is not required). Cervical and intracranial CTA are typically obtained simultaneously in patients screened with CTA, but only the intracranial CTA is required for enrollment.
   - *Enrollment of patients with an ICA (including proximal and tandem ICA occlusions) will be capped at no more than 15% of the target study population.*

   Alternative neuroimaging:
   - If CTA (or MRA) is technically inadequate: T_{max} >6s perfusion deficit consistent with an ICA or M1, M2 occlusion **AND** target mismatch profile (ischemic core volume <70 mL, mismatch ratio ≥ 1.8 and mismatch volume ≥ 15 mL as determined by RAPID software)
   - If MR perfusion (MRP) is technically inadequate: ICA or M1, M2 occlusion by MRA **AND** diffusion-weighted imaging (DWI) lesion volume ≤ 25 mL for an M1 or ICA occlusion and ≤ 15 mL for an M2 occlusion. If MRA is technically inadequate, a CTA can be used if performed within 60 minutes prior to the MRI. Carotid occlusions can be cervical or intracranial; with or without tandem MCA lesions.
   - If CTP is technically inadequate: patient can be screened with MRI and randomized if neuroimaging criteria are met.
8. Ability to comply with the study protocol, in the investigator's judgement

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

General

1. Current participation in another investigational drug or device study
2. Known hypersensitivity or allergy to any ingredients of tenecteplase
3. Active internal bleeding
4. Known bleeding diathesis
5. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency; recent oral anticoagulant therapy with INR >1.7
6. Use of one of the new oral anticoagulants within the last 48 hours (dabigatran, rivaroxaban, apixaban, edoxaban)
7. Treatment with a thrombolytic within the last 3 months prior to randomization
8. Intracranial neoplasm (except small meningioma), arteriovenous malformation, or aneurysm

   Any patient with an aneurysm located anywhere where a catheter or wire may be used in the thrombectomy procedure should be excluded. Additionally, patients with proximally thrombosed aneurysms suspected to be the mechanism of thromboembolism of the affected vascular territory should not be considered for enrollment due to the need for additional surgical or endovascular treatment that may require additional antithrombotic therapy.

   Aneurysms located elsewhere in the intracranial vasculature do not constitute an exclusion criterion per se, subject to the standards of care and the discretion of the

treating physician. Additionally, previously treated intracranial aneurysms are not a criterion for exclusion, although, patients who underwent intracranial surgery within 2 months of screening are excluded.

9. Seizures at stroke onset if it precludes obtaining an accurate baseline NIHSS
10. Pre-existing medical, neurological, or psychiatric disease that would confound the neurological or functional evaluation

    COVID-19 positive and/or suspected (i.e., symptomatic) patients are not eligible unless previously tested positive for COVID-19 AND have been asymptomatic at a minimum 10 days from time of screening.
11. Severe, uncontrolled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg)
12. For patients with suspected coagulopathy, platelet count must be checked prior to randomization and patient is excluded if baseline platelet count <100,000/μL
13. Baseline blood glucose >400 mg/dL (22.20 mmol/L)
14. Baseline blood glucose <50 mg/dL (2.78 mmol/L) needs to be normalized prior to randomization
15. Clot retrieval attempted using a neurothrombectomy device prior to randomization
16. Intracranial or intraspinal surgery or trauma within 2 months
17. Other serious, advanced, or terminal illness with life expectancy less than 6 months (investigator judgment)
18. History of acute ischemic stroke in the last 90 days
19. History of hemorrhagic stroke
20. Presumed septic embolus; suspicion of bacterial endocarditis
21. Any other condition that, in the opinion of the investigator, precludes an endovascular procedure or poses a significant hazard to the patient if an endovascular procedure was to be performed
22. Pregnant

Imaging

23. Unable to undergo a contrast brain perfusion scan with either MRI or CT
24. Extensive early ischemic change (hypodensity) on non-contrast CT estimated to be >1/3 MCA territory, or significant hypodensity outside the T_{max} >6s perfusion lesion that invalidates mismatch criteria (if patient is enrolled based on CT perfusion criteria)
25. Significant mass effect
26. Acute symptomatic arterial occlusions in more than one vascular territory confirmed on CTA/MRA (e.g., bilateral MCA occlusions, or an MCA and a basilar artery occlusion)
27. Evidence of intracranial tumor (except small meningioma) acute intracranial hemorrhage, neoplasm, or arteriovenous malformation

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur 90 *days* (±14 days) after randomization of the last patient in (LPI) the study.

Length of Study

The total length of the study, from screening of the first patient to LPLV, is expected to be approximately 3 years.

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product (IMP) for this study is tenecteplase. The recommended total dose for this study is weight-based with 0.25 mg of tenecteplase per kg, not exceeding a

maximum dose of 25 mg. A single bolus dose should be administered over 5 seconds based on patient weight.

Comparator

Placebo is being used as the comparator since a thrombolytic is only FDA-approved in the United States for use out to 3 hours, and the standard of care guidelines support use out to 4.5 hours.

Statistical Methods

Primary Analysis

The primary endpoint is the ordinal mRS score at Day 90. The distribution of the mRS scores will be compared between the treatment groups by a proportional odds model controlling for the randomization strata *and baseline mechanical thrombectomy planned status*. If the proportional-odds assumptions are not met, alternative assumption-free ordinal analysis on the mRS score will be used (Agresti 1980; Howard et al. 2012; Churilov et al. 2014). Further details about the assumption-free method will be described in the Statistical Analysis Plan. Superiority of tenecteplase over placebo will be declared if the p-value of the estimated treatment effect from the proportional odds model is $\leq$0.049 (two-sided). An unadjusted analysis will also be performed using the Wilcoxon-Mann-Whitney test.

Determination of Sample Size

Approximately 456 patients will be enrolled in this study. Assuming the distribution of mRS scores at Day 90 in the two treatment arms and a 5% dropout rate in the study, approximately 228 patients in each treatment group will provide at least 90% power to detect the specified difference in the distribution of the mRS scores at the 2-sided overall 0.05 significance level based on the Wilcoxon-Mann-Whitney test. The final efficacy analysis will be performed at the 2-sided 0.049 significance level after adjustment for one interim efficacy analysis. This corresponds to being able to detect a common odds ratio of at least 1.76 (tenecteplase vs. placebo), with a total sample size of approximately 432 evaluable patients, assuming a 5% dropout rate.

Interim Analysis

Two safety only interim analyses are planned when the first 25 and 50 patients have completed the 72–*96*-hour *visit* assessment post-randomization, respectively. One efficacy interim analysis is planned when 50% (i.e., 228) of the total patients have completed the 90-day assessment to monitor both the efficacy and safety of tenecteplase vs. placebo. The safety data to be summarized in the safety interims include deaths, SAEs, non-serious AEs, treatment-related AEs, and AEs of special interest. The study may be halted if *an* excessive number of sICH events are observed, and the details of the suggested stopping boundaries for interim safety evaluations will be provided in the study *SAP*. At the efficacy interim analysis, where the primary efficacy analysis will be performed on 50% of patients, a type I error of 0.003 will be allocated for the interim efficacy evaluation based on the Lan-DeMets theory for α-spending function that approximates the O'Brien-Fleming boundary (DeMets and Lan 1994). Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC charter. If the study continues beyond the efficacy interim analysis, the critical value at the final primary efficacy analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, i.e., the final efficacy analysis will be performed at the 0.049 significance level to maintain an overall family-wise type 1 error rate of 0.05.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADL	activities of daily living
AHA	American Heart Association
AIS	acute ischemic stroke
AMI	acute myocardial infarction
ASA	American Stroke Association
BI	Barthel Index
CBC	complete blood count
CI	confidence interval
CRO	contract research organization
CT	computed tomography
CTA	computed tomography angiography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	computed tomography perfusion
DWI	diffusion-weighted imaging
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ECC	endovascular capable center
EVT	*endovascular treatment*
FDA	U. S. Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GOS	Glasgow Outcome Scale
GRE	gradient recalled echo
HIPAA	Health Insurance Portability and Accountability Act
ICA	internal carotid artery
ICH	International Council for Harmonisation, intracranial hemorrhage
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IQR	interquartile range
IRB	Institutional Review Board
ITT	intent-to-treat (population)
IV	intravenous
IWRS	Interactive Web Response System
LPI	last patient in (the study)
LPLV	last patient, last visit

Abbreviation	Definition
MCA	middle cerebral artery
MedDRA	Medical Dictionary for Regulatory Activities
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MRP	magnetic resonance perfusion
mRS	modified Rankin Scale
mTICI	*modified treatment in cerebral ischemia*
NCI	National Cancer Institute
nECC	non-endovascular capable center
Neuro-QoL	Quality of Life in Neurological Disorders
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
PCI	percutaneous coronary intervention
PH	parenchymal hematoma
PH1	*parenchymal hematoma type 1*
PH2	*parenchymal hematoma type 2*
SAP	Statistical Analysis Plan
sHT	symptomatic hemorrhagic transformation
sICH	symptomatic intracranial hemorrhage
SITS-MOST	Safe Implementation of Thrombolysis in Stroke-Monitoring Study
SD	*standard deviation*
SOC	*standard of care*
TICI	*thrombolysis in cerebral infarction*
T_{max}	*time to maximum of the residue function*
TNK	*tenecteplase*
tPA	tissue plasminogen activator
USPI	United States Package Insert

1. BACKGROUND

1.1 BACKGROUND ON ACUTE ISCHEMIC STROKE

Acute ischemic stroke (AIS) is the fifth leading cause of death in the U.S. Approximately 795,000 people suffer a stroke annually, with 23% due to recurrent stroke. Projections estimate that by the year 2030 an additional 3.4 million U.S. adults 18 years and older, representing 3.88% of the adult population, will experience a stroke, which is a 20.5% increase in prevalence from 2012 (Ovbiagele et al. 2013). Stroke is also the leading cause of serious, long-term disability. Approximately 2% of females and 3% of males are disabled from stroke (CDC 2017). From 2013 to 2014, the direct and indirect costs of stroke in the U.S. totaled $40.1 billion. It is projected that total direct medical costs will more than double, from $36.7 billion to $94.3 billion, between 2015 and 2035 (Benjamin et al. 2018).

Intravenous thrombolysis with alteplase remains the standard of care prior to thrombectomy for eligible patients within 4.5 hours of ischemic stroke onset (AHA/ASA 2018). However, alteplase succeeds in reperfusing large vessel arterial occlusion prior to thrombectomy in only a minority of patients (Campbell et al. 2018). Results of previous non-randomized studies have suggested that patients who have a mismatch between the volume of brain tissue that may be salvaged and the volume of infarcted tissue as seen on imaging could benefit from reperfusion of occluded proximal anterior circulation vessels, even when the reperfusion is performed more than 6 hours after the patient was last known to be well (Jovin T et al. 2011; Lansberg et al. 2015). Treatment benefit is strongly dependent on time-to-reperfusion and, as many patients have treatment delays due to inter-hospital transfers (or in some cases difficult vascular access), improved approaches to intravenous thrombolysis that decrease the need for transfer could substantially improve patient outcomes.

1.2 BACKGROUND ON TENECTEPLASE

Tenecteplase (TNKase®) is a modified form of human tissue plasminogen activator (tPA) that binds to fibrin and converts plasminogen to plasmin. In vitro studies demonstrated that in the presence of fibrin, tenecteplase conversion of plasminogen to plasmin is increased relative to its conversion in the absence of fibrin. This fibrin specificity decreases systemic activation of plasminogen and the resulting degradation of circulating fibrinogen compared with a molecule lacking this property, which could potentially decrease the incidence of bleeding.

1.2.1 Acute Myocardial Infarction

Following administration of 30, 40, or 50 mg of tenecteplase for use in mortality reduction associated with acute myocardial infarction (AMI), decreases in circulating fibrinogen (4%–15%) and plasminogen (11%–24%) were observed (refer to the tenecteplase U.S. Package Insert [USPI]). The clinical significance of fibrin specificity on safety (e.g., bleeding) or efficacy has not been established. Biological potency is

determined by an in vitro clot lysis assay and is expressed in tenecteplase-specific units. The specific activity of tenecteplase has been defined as 200 units/mg. In patients with AMI, tenecteplase administered as a single bolus exhibits a biphasic disposition from the plasma. Tenecteplase was cleared from the plasma with an initial half-life of 20 to 24 minutes. The terminal phase half-life of tenecteplase was 90 to 130 minutes. In 99 of 104 patients treated with tenecteplase, mean plasma clearance ranged from 99 to 119 mL/min (see the tenecteplase USPI). Refer to the Tenecteplase Investigator's Brochure for additional details on nonclinical and clinical studies.

1.2.2 Acute Ischemic Stroke

Two dose-ranging studies by Haley et al. in 2005 and 2010 included AIS patients treated with 0.25 mg/kg (maximum 25 mg). The study sizes were small (25 and 31 patients, respectively), and patients were not selected using advanced imaging. The 2005 study showed a symptomatic intracranial hemorrhage (sICH) rate of 0%, and the 2010 study showed an sICH rate of 6.5% (based on the *National Institute of Neurological Disorders and Stroke* [NINDS] definition).

In a Phase IIb study by Parsons et al. (2012), acute stroke outcomes were evaluated for tenecteplase (0.1 mg/kg, up to 10 mg or 0.25 mg/kg, up to 25 mg) or alteplase (0.9 mg/kg, up to 90 mg) in patients identified by computed tomography perfusion (CTP) criteria with an angiographically confirmed intracranial occlusion within a 6-hour window of symptom onset. The co-primary endpoints were the proportion of the perfusion lesion that was reperfused at 24 hours as seen on perfusion-weighted magnetic resonance imaging (MRI) and the extent of clinical improvement at 24 hours as assessed by the National Institutes of Health Stroke Scale (NIHSS). Compared with the alteplase group, the pooled tenecteplase group showed significant benefit for both co-primary endpoints. Infarct growth at 90 days was significantly less in the pooled tenecteplase arm (median 2 mL, IQR [–2 to 133]) than in the alteplase arm (median 12 mL, IQR [–1 to 113]; p=0.01). A higher proportion of patients in the pooled tenecteplase group (72%) compared with the alteplase group (44%) had an excellent or good recovery (modified Rankin Scale [mRS] score 0–2; p=0.02). Upon evaluation of the individual tenecteplase dose tiers, the data suggested an efficacy-dose response relationship leading to higher reperfusion and recanalization rates at the 0.25 mg/kg dose over the 0.1 mg/kg dose (Table 1). This trend translated into an increase in the number of patients with excellent recovery at 90 days (mRS 0–1 of 72% at Day 90 with 0.25 mg/kg and 36% with 0.1 mg/kg; p=0.011) without additional sICH (rate of 4% with both the 0.1 mg/kg and 0.25-mg/kg doses of tenecteplase). The improvement in mean percent reperfusion at 24 hours, complete recanalization at 24 hours, and mRS 0–2 at 90 days leads the Sponsor to believe that 0.25 mg/kg (maximum of 25 mg) is the best dose for AIS patients in this study.

Table 1 Safety and Efficacy Outcomes of Tenecteplase

	TNK 0.1 mg/kg N=25	TNK 0.25 mg/kg N=25	P-value (TNK 0.1 mg/kg vs. TNK 0.25 mg/kg)	Alteplase 0.9 mg/kg N=25
sICH [a], n (%)	1/25 (4%)	1/25 (4%)	>0.99	3/25 (12%)
Mean % reperfusion at 24 hr (±SD)	69.3 ±31.2	88.8 ±23.1	0.0166	55.4 ±38.7
Complete recanalization at 24 hr, n (%)	8/23 (35%)	20/25 (80%)	0.002	8/22 (36%)
mRS 0–2 at 90 d, n (%)	15/25 (60%)	21/25 (84%)	0.114	11/25 (44%)
mRS 0–1 at 90 d, n (%)	9/25 (36%)	18/25 (72%)	0.011	10/25 (40%)

d=days; hr=hours; mRS=Modified Rankin Score; SD=standard deviation; sICH=symptomatic intracranial hemorrhage; TNK=tenecteplase.

[a] sICH defined as parenchymal hematoma with an National Institutes of Health Stroke Scale increase ≥4.

Source: Parsons et al. 2012.

*In t*he EXTEND-IA-TNK study—an Australian, Phase II, randomized trial—tenecteplase 0.25 mg/kg (maximum 25 mg) was compared with alteplase 0.9 mg/kg (maximum 90 mg) in patients with large vessel (internal carotid, basilar, or middle cerebral artery [MCA]) occlusion strokes prior to thrombectomy in the 0- to 4.5-hour time window (Campbell et al. 2018). This trial studied the efficacy and safety of tenecteplase 0.25 mg/kg in a patient population with more severe strokes, as indicated by a baseline median NIHSS score of 17. Symptomatic ICH rates were the same among the patient groups (1% each, defined by SITS Monitoring Study [SITS-MOST] criteria) (Table 2).

Table 2 Details of the EXTEND-IA-TNK Study

Design	Phase II, randomized, open-label, blinded-endpoint trial			
Objectives	To compare tenecteplase with alteplase in establishing reperfusion before EVT when administered within 4.5 hr of symptom onset			
Treatments	Tenecteplase 0.25 mg/kg IV, up to 25 mg Alteplase 0.9 mg/kg IV, up to 90 mg			
Endpoints	Primary • Reperfusion (mTICI 2b/3) or absence of retrievable thrombus at initial angiogram Secondary • mRS 0–1 at Day 90 • mRS at Day 90: ordinal full scale analysis • sICH within 36 hr • Mortality at 3 mo			
	Tenecteplase N=101	**Alteplase N=101**	**Adjusted OR (95% CI)**	**P-value**
mTICI 2b/3 or absence of retrievable thrombus at initial angiography, %	22%	10%	2.6 (1.1–5.9)	0.02
mRS 0–1 at 90 d, %	51%	43%	1.4 (0.8–2.6)	0.23
Median mRS score (IQR) on ordinal analysis [a] at 90 d	2 (0–3)	3 (1–4)	1.7 (1.0–2.8)	0.04
sICH [b] within 36 hr after treatment, %	1%	1%	1 (0.1–16.2)	0.99
Mortality within 3 mo, %	10%	18%	0.4 (0.2–1.1)	0.08

d=days; EVT=endovascular treatment; *hr=hour;* IQR=interquartile range; *IV=intravenous*; *mo=months;* mRS=modified Rankin Scale, mTICI=modified treatment in cerebral ischemia; NIHSS=National Institutes of Health Stroke Scale; OR=odds ratio; sICH=symptomatic intracerebral hemorrhage.

[a] The analysis was adjusted for the NIHSS score and age at baseline. The effect size was assessed with a common OR from ordinal logistic regression.

[b] sICH defined as a large parenchymal hematoma (blood clot occupying >30% of the infarct volume with mass effect) and an increase of 4 points or more on the NIHSS score.

Source: Campbell et al. 2018

EXTEND-IA-TNK demonstrated significantly higher rates of reperfusion and recanalization with 0.25 mg/kg tenecteplase compared with 0.9 mg/kg alteplase and translated into much improved clinical outcomes (Campbell et al. 2018). An individual patient data meta-analysis of trials found trends toward improved outcomes with 0.25 mg/kg tenecteplase (Huang et al. 2016). Safety, as assessed by sICH, was not significantly different overall.

A small Canadian study (N=16) tested 0.25 mg/kg (maximum dose 25 mg) of tenecteplase using imaging selection criteria and a novel thrombolytic agent. In this

study, one patient (6.3%) developed symptomatic hemorrhagic transformation (sHT). This HT rate seems comparable to previous trials of tenecteplase in ischemic stroke, suggesting the feasibility of treating patients outside of established treatment windows (Kate et al. 2018). In a randomized trial in patients with a penumbral pattern within 6 hours of onset, sHT occurred in 2/25 tenecteplase-treated patients (8%) and in 3/25 tPA-treated patients (12%) (Huang et al. 2015). Finally, a recent open-label pilot study reported that tenecteplase in minor ischemic stroke (NIHSS score <6) was associated with an sHT rate of 4% (1/25 patients treated with 0.25 mg/kg) (Coutts et al. 2015). The high rate of recanalization and low rate of hemorrhagic complications seen in EXTEND-IA-TNK (Campbell et al. 2018) and other studies suggest that tenecteplase (0.25 mg/kg–0.4 mg/kg) may be valuable.

After reviewing the published literature with tenecteplase in stroke, the dose of 0.25 mg/kg (maximum 25 mg) was selected for this trial.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Recent endovascular stroke trials have demonstrated benefit from endovascular therapy in patients with *MCA* or internal carotid artery (ICA) occlusions treated within 6 hours of symptom onset (SWIFT PRIME [Saver et al. 2015], MR CLEAN [Berkhemer et al. 2015], EXTEND-IA-TNK [Campbell et al. 2018], REVASCAT [Jovin et al. 2015], and ESCAPE [Goyal et al. 2015]). Two subsequent trials—DEFUSE 3 (Albers et al. 2018) and DAWN (Nogueira et al. 2017)—have shown benefit on computed tomography (CT) or MRI perfusion imaging in patients who were treated up to 24 hours after stroke with endovascular therapy and who had evidence of a clinical/ischemic core mismatch (i.e., mismatch between the severity of the clinical deficit and the infarct volume, as defined by Nogueira et al. 2017) or a perfusion/core mismatch (i.e., initial infarct volume [ischemic core] of less than 70 mL, a ratio of volume of ischemic tissue to initial infarct volume of 1.8 or more, and an absolute volume of potentially reversible ischemia [penumbra] of 15 mL or more [Albers et al. 2018]).

*American Heart Association/American Stroke Association (*AHA/ASA*)* 2018 clinical guidelines recommend that patients who present to the hospital in the early time window (within 4.5 hours) and meet criteria for *intravenous (*IV*)* alteplase are treated with alteplase prior to endovascular therapy. The advantage of alteplase-induced recanalization is that it can often be achieved more quickly than endovascular recanalization and can be initiated in any emergency room, whereas endovascular therapy often requires transfer to a hospital with neuro-endovascular capability.

According to the AHA/ASA clinical guidelines (2018), in selected acute stroke patients within 6–16 hours of last-known well time who have a large vessel occlusion in the anterior circulation and meet other DEFUSE 3 or DAWN eligibility criteria, mechanical thrombectomy is recommended; in selected acute stroke patients within 6–24 hours of last-known well time who have large vessel occlusion in the anterior circulation and meet

other DAWN eligibility criteria, mechanical thrombectomy with a stent retriever is reasonable.

While treatment with thrombolytics is standard of care for patients arriving within 0 to 4.5 hours, thrombolytics have not been shown to benefit patients who present beyond this time window (Emberson et al. 2014). Consequently, only a few patients in the recently completed late-window endovascular trials (DEFUSE 3 and DAWN) received IV thrombolytics.

A small study (TIAS; Kate et al. 2018) suggested the feasibility of treating patients far outside of established treatment windows with a novel thrombolytic agent (tenecteplase 0.25 mg/kg). Results showed that 9/16 patients (56.3%) had an improvement in NIHSS score by ≥4 points at 24 hours. The sICH rate was 6.3% (n=1). The median mRS score at 90 days was lower in the tenecteplase group (2 [range: 2–2.5]) than in the untreated mismatch (3 [range: 3–4]; $odds\ ratio$ [OR] 2.4; 95% CI 1.1–5.3; p=0.03) and non-mismatch (5 [range: 4–6]; OR 4.5; 95% CI 1.6–12.8; p=0.005) patients. The proportion of patients with mRS 0–2 was significantly higher in the tenecteplase group (73.3%) than in the untreated mismatch (22.2%) and non-mismatch (4.3%, p<0.001) groups. There were no deaths in the tenecteplase-treated and untreated mismatch groups.

Whether this "bridging" thrombolysis approach is beneficial compared with thrombectomy alone, when neurointervention is immediately available, has been questioned and is now the subject of randomized trials. However, for many institutions, thrombectomy involves transfer to an external hospital. There are also situations in which a planned thrombectomy is delayed or the neuro-interventionist is either unable to gain access to the cerebral circulation or unable to completely remove the thrombus. Improved IV thrombolysis options may increase the proportion of patients with early reperfusion prior to thrombectomy. This would have substantial clinical benefits and likely improve patient outcomes, and may reduce costs given the strong relationship between time to reperfusion and disability as well as potential reductions in the requirement for resource-intensive thrombectomy.

Tenecteplase is a three-point-mutated variant of alteplase bioengineered to achieve longer half-life, higher fibrin specificity, and increased resistance toward plasminogen activator inhibitor-1 (Logallo et al. 2015). In animal and in vitro models, tenecteplase has shown a better thrombolytic profile and potency compared with alteplase (Benedict et al. 1995). Due to the biochemical changes, tenecteplase can be administered as a 5-second bolus as opposed to alteplase, which is administered as a 1-hour infusion. The ease of administration of tenecteplase is of particular importance for patients who may need to be transported to another hospital for endovascular treatment. A meta-analysis has suggested a lower rate of sICH with 0.25 mg/kg tenecteplase compared with alteplase (Bivard et al. 2017). In a study by Campbell et al. (2018), 0.25 mg/kg tenecteplase was associated with higher recanalization rates than alteplase.

Consequently, favorable functional outcomes have been reported among AIS patients treated with tenecteplase compared with those who were treated with alteplase.

In this trial, the goal is to determine if pre-treatment with an IV thrombolytic (tenecteplase) increases the proportion of recanalization and results in good clinical outcomes. The trial will evaluate whether treatment with IV tenecteplase, administered between 4.5 and 24 hours of a patient's last-known well time (DEFUSE 3 [Albers et al. 2018] and DAWN [Nogueira et al. 2017]) is superior to placebo in patients who have a vessel occlusion and evidence of salvageable tissue on their baseline CTP or MRI. Placebo is being used as the comparator since a thrombolytic is only U.S. Food and Drug Administration (FDA)-approved in the United States for use out to 3 hours, and the standard of care guidelines support use out to 4.5 hours.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of tenecteplase compared with placebo in patients with AIS and evidence of salvageable tissue on their baseline CTP or MRI who present in the 4.5- to 24-hour time window with an ICA or MCA (M1 or M2) occlusion. Specific objectives and corresponding endpoints for the study are outlined below.

Table 3 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To compare the efficacy of tenecteplase with placebo	• Ordinal modified Rankin scale (mRS) score at Day 90
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of tenecteplase compared with placebo	• Proportion of patients with functional independence, defined as an mRS of 0–2, at Day 90 • Proportion of patients with angiographic reperfusion (TICI 2b or TICI 3) at completion of angiographic procedure (endovascular patients only) • Median NIHSS score at Day 90 (Appendix 3) • Proportion of patients with a Barthel Index (BI) score of ≥95 at Day 90 (Appendix 4) • Proportion of patients with good recovery based on the Glasgow Outcome Scale at Day 90 (Appendix 5) • Proportion of patients with reperfusion at 24 hours post-randomization, defined as >90% reduction in T_{max} >6s lesion volume • Proportion of patients with recanalization at 24 hours post-randomization, defined as complete recanalization on CT angiography (CTA)/magnetic resonance angiography (MRA)

Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of tenecteplase compared with placebo	• Median final infarct volumes at *the* 72–*96* hour *visit* or discharge (if patient is being discharged prior to 72 hours) • Median infarct growth at *the* 72–*96* hour *visit* or discharge (if patient is being discharged prior to *the* 72–*96* hour *visit*) • Ordinal mRS score at Day 90 by occlusion type (M1/ICA or M2 occlusions) • Ordinal mRS score at Day 30 and Day 90 by randomization site (non-endovascular capable center [nECC] or endovascular capable center [ECC]) • Proportion of patients where planned thrombectomy was not performed • Proportion of patients who are randomized at an nECC and transferred to an ECC for endovascular therapy for whom planned thrombectomy was not performed • Proportion of patients readmitted within 30 days from discharge • Proportion of patients requiring one pass with endovascular therapy device (endovascular patients only) • Mean Neuro-QoL scores by domain (Appendix 6) • *Overall survival at Day 90*
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of tenecteplase compared with placebo	• Incidence of symptomatic intracranial hemorrhage (sICH [a]) within 36 hours • Incidence and severity of adverse events • Mortality rate *up to* Day 30 and Day 90 • Proportion of patients with parenchymal hematoma type 2 (PH2) at *the* 72–*96* hour *visit*

BI =Barthel Index; CT=computed tomography; *CTA =computed tomography angiography; ECC =endovascular capable center; MRA=*magnetic resonance *angiography; mRS =modified Rankin scale; nECC =non-endovascular capable center; Neuro-QoL =Quality of Life in Neurological Disorders (scale);* NIHSS=National Institutes of Health Stroke Scale; sICH=symptomatic intracranial hemorrhage; PH1=parenchymal hematoma type 1; PH2=parenchymal hematoma type 2*; TICI =thrombolysis in cerebral infarction (scale); T_{max} =time to maximum of the residue function.*

[a] sICH is defined as ≥4 points of clinical worsening on the NIHSS compared with the most proximal NIHSS reported, attributed to a *bleed* on CT scan (preferred) or MRI performed within 36 hours after study drug administration.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, prospective, double-blind, randomized, placebo-controlled trial of tenecteplase in patients with AIS who meet predefined imaging criteria. Patients who meet inclusion criteria will be randomized to tenecteplase (0.25 mg/kg, maximum 25 mg) or placebo, both administered as a single bolus injection over 5 seconds.

All patients will receive standard-of-care therapy according to AHA/ASA clinical guidelines (2018). For patients with ICA/M1 occlusions, this will include adjuvant endovascular therapy following study drug (tenecteplase/placebo) if criteria, as stipulated in the guideline, are met. Per guideline recommendations, patients with M2 occlusions generally will not undergo endovascular therapy following treatment with study drug (tenecteplase/placebo).

Study drug administration *is recommended to* occur before the start of endovascular therapy (defined as groin puncture):

- If it appears that it will be challenging to administer study drug prior to *the* femoral groin puncture for a planned thrombectomy, *it is recommended that* the patient *not be randomized*
- *However,* if the patient has *already* been randomized, and due to unforeseen circumstances the drug cannot be administered prior to groin puncture for the planned thrombectomy, the drug must be administered as soon as possible and prior to manipulation of the clot

To determine eligibility for randomization, all patients will undergo multimodal CT or MRI at baseline. Only patients with a vessel occlusion (ICA or MCA) and penumbral tissue will be randomized.

Randomization will be stratified by age (≤70 vs. >70 years), type of occlusion (ICA/M1 vs. M2), baseline NIHSS (≤15 vs. >15), and randomization site (*endovascular capable center [*ECC*]* vs. *non-endovascular capable center [*nECC*]*). The primary goal of this trial is to compare the effect of treatment with tenecteplase vs. placebo and standard of care on 90-day functional outcomes (i.e., ordinal mRS scores) in patients who present in the 4.5- to 24-hour time window with an ICA or MCA (M1, M2) occlusion and evidence of target mismatch on multimodal CT or MRI of the brain. FDA-approved and validated perfusion imaging software for determination of core volumes will be used.

Both patients transferred from an nECC as well as patients admitted directly to an ECC are eligible for the study.

Patients will undergo two follow-up MRI scans. Patients who cannot undergo an MRI will undergo a multimodal CT at the first follow-up and a non-contrast CT at the second follow-up. The first follow-up scan will be obtained at approximately 24 *hours* (±6 hours)

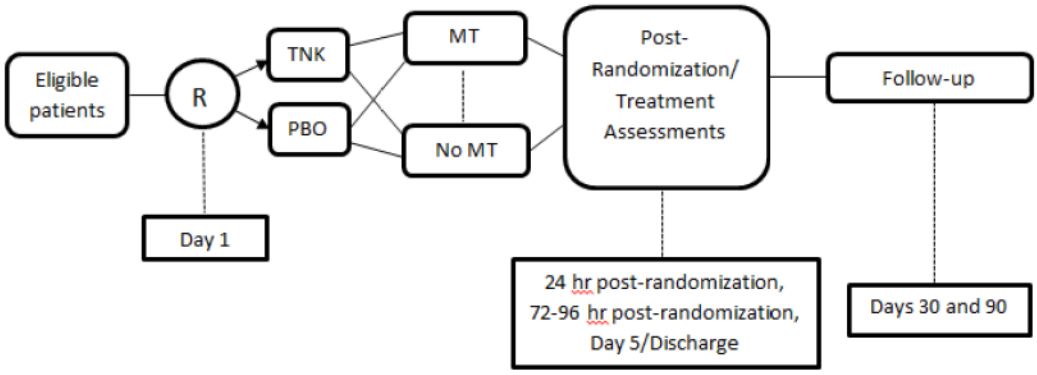
after randomization and will include an assessment of recanalization and reperfusion, per standard of care. The second MRI will be obtained between 72 to 96 hours after randomization for assessment of final infarct volumes.

All patients will be evaluated using mRS at discharge/Day 5, Day 30, and Day 90 after randomization for clinical outcome evaluation.

The primary analysis is to compare the efficacy of tenecteplase versus placebo in all patients at Day 90, as assessed by the mRS score with an ordinal analysis. As a key prespecified subgroup analysis, the trial will also assess the effect of tenecteplase separately in patients with ICA/M1 and in patients with M2 occlusions.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



hr=hour; MT=mechanical thrombectomy; PBO=placebo; R=randomized; TNK=tenecteplase.
Note: The primary endpoint will be assessed at the Day 90 visit.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur 90 $days$ ($\pm$14 days) after randomization of the last patient in (LPI) the study.

The total length of the study, from screening of the first patient to LPLV, is expected to be approximately 3 years.

In addition, the Sponsor may decide to terminate the study at any time.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Tenecteplase Dose and Schedule

The Sponsor proposes to assess if treatment with tenecteplase 0.25 mg/kg (maximum dose of 25 mg) and standard of care results in improved clinical outcomes (as assessed by mRS) when compared with standard of care alone.

Two dose-ranging studies by Haley et al. (2005 and 2010) included 56 patients (closely resembling the patients in the NINDS trial) treated with 0.25 mg/kg (maximum 25 mg) tenecteplase. Although the studies were small and the results varied, the 2005 study showed an sICH rate of 0% and the 2010 study showed an sICH rate of 6.5% (n=2/31). Advanced imaging was not used for patient selection in either study.

In a 2012 publication by Parsons et al., acute stroke outcomes were evaluated for tenecteplase (0.1 mg/kg, up to 10 mg or 0.25 mg/kg, up to 25 mg) or alteplase (0.9 mg/kg, up to 90 mg) in patients identified by *CTP* criteria and an associated large vessel occlusion in *CT angiography (CTA)* within a 6-hour window. Compared with the alteplase group, the pooled tenecteplase group showed significant benefit for both co-primary endpoints and the percentage of perfusion lesion that was reperfused 24 hours after treatment and extent of clinical improvement at 24 hours. Infarct growth at 90 days was significantly less in the pooled tenecteplase arm (median 2 mL, IQR [–2 to 133]) than in the alteplase arm (median 12 mL, IQR [=1 to 113]; p=0.01). A higher proportion of patients in the pooled tenecteplase group (72%) versus the alteplase group (44%) had an excellent or good recovery (mRS 0–2; p=0.02). Upon evaluation of the individual tenecteplase dose tiers, the data suggested that an efficacy-dose response relationship leading to higher reperfusion and recanalization rates at the 0.25-mg/kg dose over 0.1 mg/kg (Table 1). This trend translated into an increase in the number of patients with excellent recovery at 90 days (mRS 0–1 at 90 days of 72% with 0.25 mg/kg and 36% with 0.1 mg/kg; p=0.011) without additional sICHs (sICH rate of 4% with both the 0.1-mg/kg and 0.25-mg/kg doses of tenecteplase). The improvement in mean percent reperfusion at 24 hours, complete recanalization at 24 hours, and mRS 0–2 at 90 days leads the Sponsor to believe that 0.25 mg/kg (maximum 25 mg) is the correct dose for this patient population.

In the recently completed EXTEND-IA-TNK study, tenecteplase 0.25 mg/kg (maximum 25 mg) was compared with alteplase 0.9 mg/kg (maximum 90 mg) in large vessel (internal carotid, basilar, or MCA) occlusion strokes prior to thrombectomy in the 0–4.5 hour time window (Table 2). This trial established the efficacy and safety of tenecteplase 0.25 mg/kg in a patient population with more severe strokes, as indicated by a baseline median NIHSS of 17. Symptomatic ICH rates were the same among patient groups (1% each, defined by SITS-MOST criteria). This trial also leads the Sponsor to believe that an opportunity for patients may exist with a 0.25-mg/kg dose of tenecteplase.

To date, there is only one published trial using tenecteplase 0.25 mg/kg (maximum 25 mg) in the 4.5- to 24-hour window (Kate et al. 2018). This small trial included 16 patients treated with tenecteplase based on advanced imaging parameters. Patients without a mismatch served as comparators. The median baseline NIHSS score in the tenecteplase-treated group was 12 (8–15), and in the untreated mismatch (n=18) the baseline median NIHSS was 12 (7–12). There was one sICH (6.3%) in the tenecteplase-treated group. The proportion of patients with mRS 0–2 was significantly higher in the tenecteplase group (73.3%) than in the untreated mismatch group (22.2%). There were no reported deaths in tenecteplase-treated patients. Treatment with tenecteplase was associated with early reperfusion, recanalization, and penumbral tissue salvage. These surrogate outcome measures were associated with early clinical recovery at 24 hours and good functional outcomes at 90 days.

As a result, this study was designed to proceed with tenecteplase 0.25 mg/kg (maximum of 25 mg) versus placebo.

3.3.2 Rationale for Patient Population

Prior to the publication of the DAWN and DEFUSE 3 trials, a large percentage of patients admitted with symptoms of stroke were not treated because of lack of evidence to support treatment after 6 hours. The lack of treatment options made these patients susceptible to higher rates of continued disability.

DEFUSE 3 and DAWN suggested that this patient population, meeting the mismatch parameters, respond well to reperfusion in the 6- to 24-hour window and that such patients with a diffusion perfusion mismatch might also respond well to chemical reperfusion. Benefit in the 4.5- to 24-hour *window* with thrombolytic reperfusion was observed in the TIAS study (Kate et al. 2018).

This study will include both patients from ECCs and patients arriving at nECCs who could then be transferred to ECCs.

3.3.3 Rationale for Control Group

Because the evidence to support treatment with tenecteplase in the 4.5- to 24-hour window is limited to a small efficacy study (Kate et al. 2018), it is important to validate this treatment. Therefore, all patients will be randomized first to receive tenecteplase 0.25 mg/kg (maximum of 25 mg) versus placebo, and then endovascular eligible patients will receive mechanical thrombectomy. According to the guidelines, other than endovascular therapy, which has its limitations (i.e., it cannot always be guaranteed that a patient in this time window with a mismatch will be eligible for such treatment, that access can be obtained, or that the procedure will be a success), there are no treatment options for this patient population.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 456 patients with AIS will be enrolled in this study at approximately 90 sites (consisting of both ECCs and nECCs) primarily in the U.S. and Canada.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Patient/legally authorized representative has signed the Informed Consent Form
2. Age ≥18 years
3. AIS symptom onset within 4.5 to 24 hours

   Stroke onset is defined as the time the patient was last known to be at their neurologic baseline. (Wake-up strokes are eligible if they present within the 4.5- to 24-hour time limits of last known well.)

   Note: All study-related treatment needs to be initiated within 24 hours.
4. Signs and symptoms consistent with the diagnosis of an acute anterior circulation ischemic stroke involving occlusion of the ICA, M1, or M2 vessels
5. Functionally independent (mRS 0–2) prior to stroke onset
6. Baseline NIHSS ≥5 and that remains ≥5 immediately prior to randomization
7. **Neuroimaging:** ICA or M1, M2 occlusion (carotid occlusions can be cervical or intracranial, with or without tandem MCA lesions) by *magnetic resonance angiography (*MRA*)* or CTA **AND** target mismatch profile on *CTP* or *MR perfusion (MRP)* (ischemic core volume <70 mL, mismatch ratio is ≥ 1.8 and mismatch volume is ≥ 15 mL)
   - The mismatch volume is determined by FDA-approved imaging software in real time based on the difference between the ischemic core lesion volume and the *time to maximum of the residue function (*T_{max}*)* >6s lesion volume. If both a *CTP* and a multimodal MRI scan are performed prior to enrollment, the later of the 2 scans is assessed to determine eligibility. For patients screened with MRA, only an intracranial MRA is required (cervical MRA is not required). Cervical and intracranial CTA are typically obtained simultaneously in patients screened with CTA, but only the intracranial CTA is required for enrollment.
   - *Enrollment of patients with an ICA (including proximal and tandem ICA occlusions) will be capped at no more than 15% of the target study population.*

   Alternative neuroimaging:
   - If CTA (or MRA) is technically inadequate: T_{max} >6s perfusion deficit consistent with an ICA or M1, M2 occlusion **AND** target mismatch profile (ischemic core volume <70 mL, mismatch ratio ≥ 1.8 and mismatch volume ≥ 15 mL as determined by RAPID software)
   - If MRP is technically inadequate: ICA or M1, M2 occlusion by MRA **AND** diffusion-weighted imaging (DWI) lesion volume ≤ 25 mL for an M1 or ICA

occlusion and ≤ 15 mL for an M2 occlusion. If MRA is technically inadequate, a CTA can be used if performed within 60 minutes prior to the MRI. Carotid occlusions can be cervical or intracranial; with or without tandem MCA lesions.

- If CTP is technically inadequate: Patient can be screened with MRI and randomized if neuroimaging criteria are met.

8. Ability to comply with the study protocol, in the investigator's judgment

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

General

1. Current participation in another investigational drug or device study
2. Known hypersensitivity or allergy to any ingredients of tenecteplase
3. Active internal bleeding
4. Known bleeding diathesis
5. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency; recent oral anticoagulant therapy with INR >1.7
6. Use of one of the new oral anticoagulants within the last 48 hours (dabigatran, rivaroxaban, apixaban, edoxaban)
7. Treatment with a thrombolytic within the last 3 months prior to randomization
8. Intracranial neoplasm (except small meningioma), arteriovenous malformation, or aneurysm

   Any patient with an aneurysm located anywhere where a catheter or wire may be used in the thrombectomy procedure should be excluded. Additionally, patients with proximally thrombosed aneurysms suspected to be the mechanism of thromboembolism of the affected vascular territory should not be considered for enrollment due to the need for additional surgical or endovascular treatment that may require additional antithrombotic therapy.

   Aneurysms located elsewhere in the intracranial vasculature do not constitute an exclusion criterion per se, subject to the standards of care and the discretion of the treating physician. Additionally, previously treated intracranial aneurysms are not a criterion for exclusion, although, patients who underwent intracranial surgery within 2 months of screening are excluded.

9. Seizures at stroke onset if it precludes obtaining an accurate baseline NIHSS
10. Pre-existing medical, neurological, or psychiatric disease that would confound the neurological or functional evaluation

    COVID-19 positive and/or suspected (i.e., symptomatic) patients are not eligible unless previously tested positive for COVID-19 AND have been asymptomatic at a minimum 10 days from time of screening.

11. Severe, uncontrolled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg)

12. For patients with suspected coagulopathy, platelet count must be checked prior to randomization and patient is excluded if baseline platelet count <100,000/μL
13. Baseline blood glucose >400 mg/dL (22.20 mmol/L)
14. Baseline blood glucose <50 mg/dL (2.78 mmol/L) needs to be normalized prior to randomization
15. Clot retrieval attempted using a neurothrombectomy device prior to randomization
16. Intracranial or intraspinal surgery or trauma within 2 months
17. Other serious, advanced, or terminal illness with life expectancy less than 6 months (investigator judgment)
18. History of acute ischemic stroke in the last 90 days
19. History of hemorrhagic stroke
20. Presumed septic embolus; suspicion of bacterial endocarditis
21. Any other condition that, in the opinion of the investigator, precludes an endovascular procedure or poses a significant hazard to the patient if an endovascular procedure was to be performed
22. Pregnant

Imaging

23. Unable to undergo a contrast brain perfusion scan with either MRI or CT
24. Extensive early ischemic change (hypodensity) on non-contrast CT estimated to be >1/3 MCA territory, or significant hypodensity outside the T_{max} >6s perfusion lesion that invalidates mismatch criteria (if patient is enrolled based on CT perfusion criteria)
25. Significant mass effect
26. Acute symptomatic arterial occlusions in more than one vascular territory confirmed on CTA/MRA (e.g., bilateral MCA occlusions, or an MCA and a basilar artery occlusion)
27. Evidence of intracranial tumor (except small meningioma) acute intracranial hemorrhage, neoplasm, or arteriovenous malformation

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

Site personnel may screen all potential patients in the interactive web response systems (IWRS) in order to assign two study kit numbers (i.e., 1 placebo and 1 tenecteplase) to start the investigational medicinal product (IMP) preparation.

Once the patient *meets* all eligibility criteria (see Section 4.1.1 and Section 4.1.2) *and the consent is signed*, site personnel will *randomize the* patient *in IWRS and the system will inform which of the two assigned study kits will be administered. The other study kit will be destroyed or returned to Sponsor. Documentation of secondary*

review/verification of study kit administered and discarded should be collected for all dosed patients.

Patients will be randomized 1:1 to receive a single bolus injection of tenecteplase or placebo over 5 seconds. *Patients should* be treated as soon as possible after randomization. Patients are considered enrolled in the study once they have been randomized.

Patients not eligible after screening in IWRS will be recorded as screen failures and both study kits will be destroyed or returned to Sponsor.

Randomization will be stratified by age (≤70 vs. >70 years of age), type of occlusion (ICA/M1 vs. M2), baseline NIHSS (≤15 vs. >15), and randomization site (ECC vs. nECC). Permuted block randomization will be used to achieve the balance of treatment arm assignments within each randomization stratum.

4.2.2 Treatment Blinding and Unblinding

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, *IWRS* service provider, unblinded external statistician, and *independent Data Monitoring Committee (*iDMC*)* members.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the *IWRS*. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is tenecteplase.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Tenecteplase and Placebo

Tenecteplase and placebo will be supplied by the Sponsor as a sterile, lyophilized powder in a 50-mg vial under partial vacuum. Sites will be expected to provide the diluent, 10 mL Sterile Water for Injection.

For information on the formulation and handling of tenecteplase, see the local prescribing information for tenecteplase.

4.3.2 Study Treatment Dosage, Administration, and Compliance

Store lyophilized tenecteplase at controlled room temperature not to exceed 30°C (86°F) or under refrigeration 2°C–8°C (36°F–46°F). Do not use beyond the expiration date stamped on the vial.

Tenecteplase is for *IV* administration only. The recommended total dose for this study is weight-based with 0.25 mg of tenecteplase per kg, not exceeding a maximum dose of 25 mg. A single bolus dose should be administered over 5 seconds based on patient weight.

Administration of tenecteplase should be recorded on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with administration of any of the study treatments should be recorded on the Adverse Event eCRF.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (tenecteplase or placebo) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the *IWRS* to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Tenecteplase

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide Genentech IMP (tenecteplase) or any other study treatments or interventions to patients who have completed the study. The Roche Global Policy on

Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines *[including COVID-19 vaccines],* herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients enrolled in the trial cannot receive intra-arterial thrombolytic agents or intracranial stenting.

Devices used during endovascular procedure should be used according to the product instructions for use.

4.4.1 Cautionary Therapy

Formal interaction studies of tenecteplase with other drugs have not been performed. Patients studied in clinical trials of tenecteplase were routinely treated with heparin and aspirin. Anticoagulants (such as heparin and vitamin K antagonists) and drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole, and glycoprotein [GP] IIb/IIIa inhibitors) may increase the risk of bleeding if administered prior to, during, or after tenecteplase therapy.

The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not mentioned above.

4.4.2 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 30 days prior to initiation of study treatment, during study treatment, and until the patient's last study assessment.
- Oral or parenteral anticoagulants are prohibited for the first 24 hours after treatment with study drug, excluding 1) prophylactic doses, if administered per institutional practice and 2) low doses of IV heparin during the thrombectomy procedure, if this practice is considered standard of care for patients who have recently received an intravenous thrombolytic at the treating institution.

- Any additional thrombolytic is prohibited for the first 90 days after treatment with study drug with the exception of Cathflo® Activase®, if needed for central venous catheter occlusion management.
- *No anti-platelet agents for 24 hours after the study drug administration*

  If the patient has a cervical ICA occlusion, they may require a cervical angioplasty. Stenting the patient is strongly discouraged because of the need for dual anti-platelet therapy. However, if the vessel collapses after the angioplasty, then there is no choice but to stent, which would require dual anti-platelet therapy.

  According to the AHA Guidelines, the recommendation for use of aspirin (for non-tPA patients) is to give it within 24–48 hours, so that is compatible with waiting for 24 hours, even in participants receiving placebo.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient.

Patients will be monitored for safety and tolerability throughout the study.

4.5.1 Informed Consent Forms

Informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded.

Demographic data will include age, sex, self-reported race/ethnicity, and veteran status.

4.5.3 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure, and temperature. Temperature will be required prior to randomization and will be performed with subsequent frequency per SOC. The frequency of respiratory rate, pulse rate, and systolic and diastolic blood pressure measurements should reflect post-IV thrombolytic monitoring in AIS per SOC.

4.5.4 Modified Rankin Scale

A pre-stroke mRS will be estimated at baseline.

At discharge/Day 5, 30 and 90 days after randomization, patients will be evaluated using mRS preferably in the clinic. If an in-person visit is not feasible, the patient can be evaluated by telephone (Appendix 2).

4.5.5 National Institutes of Health Stroke Scale

Formal stroke scores or scales, such as the NIHSS, may be performed rapidly, have demonstrated utility, and may be administered by a broad spectrum of healthcare providers with accuracy and reliability. Use of a standardized scale quantifies the degree of neurological deficit, facilitates communication, helps identify patients for thrombolytic or mechanical intervention, allows objective measurement of changing clinical status, and identifies those at higher risk for complications such as ICF (Powers et al. 2018).

A baseline NIHSS will be used to determine stroke severity and study eligibility. The NIHSS assessment will then be performed at specific intervals per the schedule of activities in Appendix 1. See Appendix 3 for the NIHSS.

4.5.6 Barthel Index

The Barthel index (BI) is an ordinal scale used to measure performance in activities of daily living (ADL). A 10-item scale describing ADL and mobility (e.g., feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation, and stair climbing). Each performance item is rated on this scale with a given number of points assigned to each level or ranking. BI scoring ranges from 0 to 100, and lower scores representing greater dependency.

Patients will be assessed using the BI to measure their ability to perform activities of daily living at specific intervals per the schedule of activities in Appendix 1. See Appendix 4 for the BI.

4.5.7 Glasgow Outcome Scale

The *Glasgow Outcome Scale* (GOS) is a scale used to assess recovery of patients with brain damage. The scale has 5 categories, with scale ranging from low disability to death (Appendix 5). Patients will be assessed using the GOS at specific intervals per the schedule of activities in Appendix 1.

4.5.8 Neuro-QoL

Quality of Life in Neurological Disorders (Neuro-QoL) is a set of self-reported measures that assesses the physical, mental, and social effects experienced by adults living with neurological conditions (Appendix 6). Patients will be assessed using the Neuro-QoL per the schedule of activities in Appendix 1.

4.5.9 Brain Imaging

Brain imaging requirements for the study are provided in Appendix 7.

Study drug administration needs to occur within 90 minutes of qualifying RAPID brain imaging. If 90 minutes is exceeded, CTP/MRP imaging must be repeated to validate that the patient is still eligible for the study.

Patients will undergo two follow-up MRI scans. Patients who cannot undergo an MRI will undergo a multimodal CT/CTA/CTP at the first follow-up and a non-contrast CT at the second follow-up.

The first follow-up scan will be obtained at approximately 24 hours (±6 hours) after study drug administration and will include an MRA of the Circle of Willis to assess for recanalization and an MRP study to assess for reperfusion in addition to standard fluid-attenuated inversion recovery (FLAIR), gradient recalled echo (GRE), and DWI sequences, per standard of care.

The second follow-up scan will be obtained at the 72–96 hour visit after study drug administration and will only include FLAIR, GRE, and DWI for assessment of final infarct volumes.

4.5.10 Laboratory, Biomarker and Other Biological Sample Assessments

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis.

All baseline blood and urine samples must be collected prior to randomization.

Results from the following need to be checked prior to randomization:

- Platelet count (PLT; only in patients with suspected coagulopathy)
- Glucose (finger stick or lab)
- Coagulation: INR, aPTT, PT (only if the patient is taking an anticoagulant)
- Urine/serum pregnancy test
  - All women of childbearing potential will have a pregnancy test at screening. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

Results from the following are NOT required prior to randomization:

- Complete blood count (CBC), except platelets
- Chemistry panel (electrolytes)

Blood samples for pharmacokinetic measurement may be collected at selected sites.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw consent at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented by an investigator. Patients who withdraw from the study will not be replaced.

4.6.2 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.3 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Tenecteplase is not approved for AIS, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with tenecteplase in completed and ongoing studies. The anticipated important safety risks for tenecteplase are outlined below. Please refer to the Tenecteplase Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events are provided below.

An iDMC will be established to monitor patient safety in this study. The iDMC will meet at regular intervals (see Section 9.4.1) to review unblinded safety data, including serious adverse events, adverse events, and deaths (see following sections for details of the safety evaluations in this study).

5.1.1 Risks Associated with Tenecteplase

Standard management of stroke should be implemented concomitantly with tenecteplase treatment. Arterial and venous punctures should be minimized. Non-compressible arterial puncture must be avoided, and internal jugular and subclavian venous punctures should be avoided to minimize bleeding from the non-compressible sites. In the event of serious bleeding, heparin and antiplatelet agents should be discontinued immediately and treated appropriately. Heparin effects can be reversed by protamine.

5.1.1.1 Bleeding

The most common complication encountered during tenecteplase therapy is bleeding. This may be either superficial from punctures or damaged blood vessels or internal bleeding at any site or body cavity. Bleeding may result in life-threatening situations, permanent disability, or death.

- The incidence of ICH, especially sICH, in patients with AIS is higher in alteplase-treated patients than placebo-treated patients in published studies (for detailed information, see the alteplase USPI).

The type of bleeding associated with thrombolytic therapy can be divided into two broad categories:

- Internal bleeding, involving intracranial and retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts
- Superficial or surface bleeding, observed mainly at vascular puncture and access sites (e.g., venous cutdowns, arterial punctures) or sites of recent surgical intervention

Management of Bleeding

Patients will be excluded for the presence of conditions related to risks of bleeding (as outlined in Section 4.1.2, Exclusion Criteria).

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, may be lysed during tenecteplase therapy. In the event of serious bleeding (not controlled by local pressure) in a critical location (intracranial, gastrointestinal, retroperitoneal, or

pericardial), study drug should be discontinued immediately, and any concomitant heparin or antiplatelet agents should be discontinued immediately and appropriate treatment initiated.

Guidelines for management of patients who develop bleeding are provided in Table 4.

In addition, any $sICH$ events, if not already reported as an SAE by the investigator, are considered non-serious adverse events of special interest for this study (Section 5.2.3) and should be reported and submitted to the Sponsor (Section 5.4.2).

5.1.1.2 Risk of Hypersensitivity

Hypersensitivity, including urticarial/anaphylactic reactions, has been reported after administration of tenecteplase (e.g., anaphylaxis, angioedema, laryngeal edema, rash, and urticaria). When such reactions occur, they usually respond to conventional therapy. Monitor patients treated with tenecteplase during and for several hours after infusion.

Management of Hypersensitivity

If symptoms of hypersensitivity occur, appropriate therapy should be initiated.

5.1.1.3 Thromboembolism

The use of thrombolytics can increase the risk of thrombo-embolic events in patients with high likelihood of left heart thrombus, such as patients with mitral stenosis or atrial fibrillation.

5.1.1.4 Cholesterol Embolization

Cholesterol embolism has been reported rarely in patients treated with all types of thrombolytic agents; the true incidence is unknown. This serious condition, which can be lethal, is also associated with invasive vascular procedures (e.g., cardiac catheterization, angiography, vascular surgery) and/or anticoagulant therapy. Clinical features of cholesterol embolism may include livedo reticularis, “purple toe” syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel infarction, and rhabdomyolysis.

5.1.1.5 Arrhythmias

Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard anti-arrhythmic measures. It is recommended that anti-arrhythmic therapy for bradycardia and/or ventricular irritability be available when tenecteplase is administered.

5.1.1.6 Use with Percutaneous Coronary Intervention

In patients with large ST segment elevation myocardial infarction, physicians should choose either thrombolysis or percutaneous coronary intervention (PCI) as the primary treatment strategy for reperfusion. Rescue PCI or subsequent elective PCI may be performed after administration of thrombolytic therapies if medically appropriate; however, the optimal use of adjunctive antithrombotic and antiplatelet therapies in this setting is unknown.

5.1.1.7 Other Adverse Reactions

The following adverse reactions have been reported among patients receiving tenecteplase in clinical trials. These reactions are frequent sequelae of the underlying disease, and the effect of tenecteplase on the incidence of these events is unknown.

These events include cardiogenic shock, arrhythmias, atrioventricular block, pulmonary edema, heart failure, cardiac arrest, recurrent myocardial ischemia, myocardial reinfarction, myocardial rupture, cardiac tamponade, pericarditis, pericardial effusion, mitral regurgitation, thrombosis, embolism, and electromechanical dissociation. These events can be life-threatening and may lead to death. Nausea and/or vomiting, hypotension, and fever have also been reported.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Management Guidelines

Guidelines for management of specific adverse events are outlined in Table 4.

Table 4 Guidelines for Management of Patients Who Experience Bleeding

Event	Action to Be Taken
Bleeding	• In the event of serious bleeding, heparin and antiplatelet agents should be discontinued immediately and treated appropriately. Heparin effects can be reversed by protamine. • Intramuscular injections and nonessential handling of the patient should be avoided for the first few hours following treatment with tenecteplase. • Venipunctures should be performed and monitored carefully. • Should an arterial puncture be necessary during the first few hours following tenecteplase therapy, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital

signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the International Council on Harmonisation guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 and Section 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies or venipuncture)
- Any bleeding that does not qualify as an adverse event of special interest (see Section 5.2.3), including hemorrhagic infarction 1 and 2 (HI1 and HI2), subarachnoid hemorrhage (SAH), and intraventricular hemorrhage (IVH).

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
    - This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)

- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to *National Cancer Institute Common Terminology Criteria for Adverse Events* [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Non-serious adverse events of special interest for this study are as follows:

- Any *sICH (defined as ≥4 points of clinical worsening on the NIHSS compared with the most proximal NIHSS reported, attributed to a bleed on CT scan [preferred]* or *MRI performed within 36 hours after study drug administration)* if not already reported as an SAE. (All other hemorrhages, including HI1, HI2, SAH, and IVH should be reported as an AE.)
- The non-drug specific AESIs:
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4–Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 90 *days* (±14 days) after the dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 6 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as a diagnosis (e.g., "injection-site reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than injection reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the

single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF (i.e., on a separate eCRF page). For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported on a separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality rate is a safety endpoint. All deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (i.e. no more than 24 hours after learning of the event; see Section 5.4.2). The *iDMC* will monitor the frequency of deaths from all causes.

When reporting a death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8.1 Deaths due to Progression of Disease

In order to fully assess mortality as a safety endpoint, deaths due to progression of disease will be evaluated separately. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the Investigator solely to the progression of disease (i.e., the qualifying stroke) will be documented and will include the investigator's assessment of the primary cause of death.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Progression of Acute Ischemic Stroke

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events, unless death is the outcome (see Section 5.3.5.8.1). These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on neuroimaging. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of tenecteplase in a quantity that is 10% greater than the assigned dose
- Medication error: accidental deviation in the administration of tenecteplase
- In some cases, a medication error may be intercepted prior to administration of tenecteplase

Special situations are not in themselves adverse events, but may result in adverse events. All special situations associated with tenecteplase, regardless of whether they

result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter “tenecteplase” and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter “tenecteplase” and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter “tenecteplase” and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter “tenecteplase” and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). Adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)

- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information:

Medical Monitor: [redacted], M.D.
[redacted](South San Francisco)

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 $days$ ($\pm$14 days) after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur >90 $days$ $(\pm 14$ days$)$ after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 90 $days$ $(\pm 14$ days$)$ after the dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported to the Sponsor. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Congenital Anomalies/Birth Defects and Abortions

Any abortion and any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 90 *days* [±14 days] after the dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Tenecteplase Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary efficacy analysis will be based on the intent-to-treat (ITT) population, defined as all randomized patients who provided informed consent, and analyzed according to the randomized treatment assignment. Safety analyses will be based on safety population, defined as all randomized patients who received any amount of study drug, and analyzed according to the actual treatment received.

One efficacy interim analysis will be conducted when 50% of the patients have completed the 90-day follow-up after randomization. At this interim, efficacy of tenecteplase will be compared with placebo based on the primary efficacy endpoint (see Section 6.6).

Final study analysis will be performed when all patients have completed or discontinued from the study, all data from the study are in the database, and the database is locked. Details of all statistical issues and planned statistical analyses will be specified in the Statistical Analysis Plan (SAP), which will be finalized prior to the data-cut of the planned efficacy interim analysis.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is to demonstrate superiority of tenecteplase over placebo, when administered between 4.5 to 24 hours of last-known well time, in patients who have a vessel occlusion and evidence of salvageable tissue on their baseline CTP or MRI. The primary efficacy endpoint is the mRS score at Day 90. The distribution of the ordinal mRS scores will be compared between the two treatment groups.

Approximately 456 patients will be enrolled in this study. Assuming the distribution of mRS scores at Day 90 in the two treatment arms as shown in Table 7 and a 5% dropout rate in the study, approximately 228 patients in each treatment group will provide at least 90% power to detect the specified difference in the distribution of the mRS scores at the 2-sided 0.049 significance level (after adjustment for one interim efficacy analysis; see Section 6.6). This calculation is based on the East® 6.4.1 software. This corresponds to being able to detect a common odds ratio of at least 1.76 (tenecteplase vs. placebo),

with a total sample size of approximately 432 evaluable patients, assuming a 5% dropout rate.

Table 7 Assumed Distribution of 90-Day mRS in Sample Size Determination

mRS	0	1	2	3	4	5	6
Tenecteplase (% of patients)	17	20	16	15	13	7	12
Placebo (% of patients)	13	13	12	14	18	12	18

mRS=modified Rankin Scale.

The sample size estimation is highly dependent on the distribution assumption of 90-day ordinal mRS score for both treatment arms; thus, additional power calculation is provided with 456 total patients for different distribution scenarios on the mRS at Day 90. As shown in Table 8, compared with the assumption used in current sample size calculation (Table 7), Scenario 1 (from the DEFUSE 3 trial) assumes a more optimistic outcome in the tenecteplase treatment arm than the placebo arm, while Scenario 2 (from the EXTEND-IA-TNK trial) assumes less treatment difference between the two treatment arms. The resulting power for both scenarios are shown in Table 9.

Table 8 Distribution of 90-Day mRS from Different Scenarios

	Scenario 1						
Tenecteplase (% of patients)	10	16	18	15	18	8	14
Placebo (% of patients)	8	4	4	16	27	16	26
	Scenario 2						
Tenecteplase (% of patients)	28	21	14	14	8	6	10
Placebo (% of patients)	18	23	9	12	14	7	18

mRS=modified Rankin Scale.

Table 9 Power Consideration by 90-Day mRS Distribution Scenarios

mRS distribution assumption	Evaluable Sample size	Type I Error	Power
Scenario 1	432 (456*0.95)	0.049	>99%
Scenario 2	432	0.049	>88%

mRS=modified Rankin Scale.

6.2 SUMMARIES OF CONDUCT OF STUDY

Patient disposition (number of patients randomized, treated, and completed study) and reasons for premature study discontinuation will also be summarized by treatment group.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics, such as age, sex, race, randomization site, and baseline stroke characteristics (such as baseline NIHSS, type of occlusion), will be summarized for all randomized patients who provided informed consent using descriptive statistics. Summaries will be presented overall and by treatment group.

6.4 EFFICACY ANALYSES

The analysis population for the efficacy analyses will consist of all randomized patients who provided informed consent (i.e., ITT population), with patients grouped according to their assigned treatment.

Efficacy analyses will be stratified by the randomization strata *and adjusted for mechanical thrombectomy planned status at baseline (Yes vs. No),* unless otherwise noted. For the purpose of the primary efficacy analysis, patients with missing mRS scores at Day 90 will be imputed. Robustness of the primary analysis results will be explored by the tipping point approach, where departures from the missing at random (MAR) assumption will be assessed. Details of the imputation model and sensitivity analyses will be pre-specified in the SAP of the study.

6.4.1 Primary Efficacy Endpoint

The primary endpoint is the ordinal mRS score at Day 90. The distribution of the mRS scores will be compared between the treatment groups by a proportional odds model controlling for the randomization strata *and baseline mechanical thrombectomy planned status*. If the proportional-odds assumptions are not met, alternative assumption-free ordinal analysis on the mRS score will be used (Agresti 1980; Howard et al. 2012; Churilov et al. 2014). Further details about the assumption-free method will be described in the SAP. Superiority of tenecteplase over placebo will be declared if the p-value of the estimated treatment effect from the proportional odds model is $\leq$0.049 (two-sided). An unadjusted analysis will also be performed using the Wilcoxon-Mann-Whitney test.

6.4.2 Secondary Efficacy Endpoints

For the following binary secondary efficacy endpoints, treatment groups will be compared using logistic regression models adjusted by the randomization strata *and baseline mechanical thrombectomy planned status*, as appropriate:

- Proportion of patients with functional independence, defined as an mRS of 0–2 at Day 90 from randomization

- Proportion of patients with angiographic reperfusion (TICI 2b/3 or TICI 3) at completion of angiographic procedure (endovascular patients only)
- Proportion of patients with recanalization at 24 hours post-treatment, defined as complete recanalization on CTA/MRA
- *Proportion of patients with reperfusion at 24 hours post-treatment, defined as >90% reduction in T_{max} >6s lesion volume*
- Proportion of patients with a BI score ≥95 at Day 90 from randomization
- *Proportion of patients with good recovery based on the GOS at Day 90 from randomization*

For the following continuous secondary endpoint, treatment groups will be compared using the van Elteren's test, adjusting for the randomization stratification factors:

- Median NIHSS at 24 hours, 72–96 hours, 30 days, and 90 days

Key secondary endpoints will be compared between the two treatment groups, gated on the success of the primary efficacy comparison (2-sided p-value ≤0.049). Hypothesis testing of the key secondary endpoints will be performed in a sequential manner at the 2-sided significance level of 0.049. Additional details of the hierarchical testing of the secondary endpoints will be provided in the SAP.

6.4.3 Exploratory Analyses

The mRS score at Day 90 will be analyzed in the following subgroups:

- Occlusion type (ICA/M1 or M2 occlusions)
- Randomization site (ECC or nECC)
- Proportion of patients where planned thrombectomy was not performed (including patients with partial or complete recanalization of the qualifying vessel occlusion which includes patients who did not go to angiography suite because non-invasive imaging demonstrated recanalization, or patients who have undergone catheter angiography and are found to no longer to have an occlusion of the qualifying vessel)
- *Overall survival at Day 90*

For each of the above-mentioned subgroups, the distribution of the mRS scores will be compared between the treatment groups by a proportional odds model controlling for the randomization strata *and baseline mechanical thrombectomy planned status*, as appropriate.

For patients who are randomized at an nECC and transferred to an ECC for endovascular therapy, the proportion of patients where planned thrombectomy was not performed will be compared between treatment groups using a logistic regression model adjusted by baseline age group and baseline NIHSS.

For the following continuous exploratory endpoints, treatment groups will be compared using the van Elteren's test, adjusting for the randomization stratification factors *and baseline mechanical thrombectomy planned*:

- Median final infarct volumes at *the 72–96 hour visit* or discharge (if patient is being discharged prior to *the 72–96 hour visit*); and
- Median infarct growth at *the 72–96 hour visit* or discharge (if patient is being discharged prior to *the 72–96 hour visit*).

The appropriate scoring algorithm will be employed to score the Neuro-QoL responses and scores will be compared between the treatment groups. Details of the exploratory analyses will be provided in the SAP.

6.5 SAFETY ANALYSES

Safety analyses will be performed for all randomized patients who receive tenecteplase or placebo, with patients grouped according to the treatment actually received.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE, v5. Preferred terms (PTs) for ICH will be based on the latest version of the MedDRA Standardized Medical Query (SMQ) "haemorrhagic central nervous system vascular conditions."

Incidence and severity of treatment-emergent adverse events, including incidence of hemorrhage, and other adverse events of special interest will be summarized by treatment group. A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after study drug administration.

Deaths and primary cause of death will be summarized.

The iDMC (see Section 9.4.1) will evaluate safety at periodic safety reviews and recommend to the Sponsor whether the study should be modified or stopped early. All summaries and analyses will be prepared by the independent statistical entity and presented by treatment arm for the iDMC's review. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. There will be no adjustment for the overall type 1 error rate due to the safety reviews by the iDMC as efficacy data will not be reviewed.

6.6 INTERIM ANALYSES

6.6.1 Planned Interim Analyses

Two safety only interim analyses are planned when the first 25 and 50 patients have completed the *72–96 hours visit* assessment post-randomization, respectively. One efficacy interim analysis is planned when 50% (i.e., 228) of the total patients have

completed the 90-day assessment to monitor both the efficacy and safety of tenecteplase vs. placebo. The safety data to be summarized in the safety interims include deaths, SAEs, non-serious AEs, treatment-related AEs, and AEs of special interest. The study may be halted if an excessive number of sICH events are observed, and the details of the suggested stopping boundaries for interim safety evaluations will be provided in the study SAP. At the efficacy interim analysis, where the primary efficacy analysis will be performed on 50% of patients, a type I error of 0.003 will be allocated for the interim efficacy evaluation based on the Lan-DeMets theory for α-spending function that approximates the O'Brien-Fleming boundary (DeMets and Lan 1994). Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC charter. If the study continues beyond the efficacy interim analysis, the critical value at the final primary efficacy analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, i.e., the final efficacy analysis will be performed at the 0.049 significance level to maintain an overall family-wise type 1 error rate of 0.05.

Details of the statistical methodology for the efficacy interim analyses will be documented in the study SAP. The iDMC charter will document potential recommendations the iDMC can make as a result of the analyses (e.g., stop the study for positive efficacy, stop the study for safety concerns). During the interim analyses, the Sponsor will remain blinded to individual treatment assignment. The interim analyses will be conducted by an independent statistical entity and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter to ensure integrity of study conduct.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. A contract research organization (CRO) will support data management of this study, including discrepancy management and quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor or CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system. Local laboratory data from sites will be directly captured via EDC.

A Central Reader (Core Lab) will be used to perform adjudication of imaging. Refer to the Central Reader Charter for additional details.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Genentech will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent

Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

Each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 90 sites will participate to enroll approximately 456 patients. Screening, randomization, and drug assignment will be performed by an *IWRS*.

Accredited local laboratories will be used for routine monitoring.

An iDMC will be employed to monitor and evaluate patient safety and treatment efficacy during the study.

9.4.1 Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will be assembled to monitor patient safety, treatment efficacy, and study conduct. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the iDMC roles and responsibilities. Unblinded data summaries for iDMC review will be provided by an independent statistical entity external to the Sponsor. While the iDMC will review unblinded summaries, the Sponsor will remain blinded to treatment group until the time of formal study unblinding.

During the conduct of the study, regularly scheduled safety data reviews by the iDMC will occur. After the first patient is enrolled, safety review will occur after the first 25 patients have completed the *72–96 hours visit* assessments post-randomization and again after the first 50 patients have completed the *72–96 hours visit* assessments post-randomization. Thereafter, the iDMC will meet at a frequency determined by the iDMC and the Sponsor according to the emerging safety profile. The iDMC or Sponsor may also request ad hoc reviews at any time to address potential safety concerns.

The iDMC will also review unblinded efficacy data at the planned interim efficacy analysis when 50% of the patients have completed 90-day follow-up post-randomization (see Section 6.6.1). At this review, the iDMC will evaluate the benefit-risk profile of tenecteplase treatment through reviewing unblinded safety and efficacy data.

The iDMC may recommend stopping the study early or amending the study for either significant safety concerns or outstanding efficacy results. The final decision of acting upon the iDMC's recommendations will rest with the Sponsor. The policies and procedures will be detailed in the iDMC Charter.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving

an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

	Screening and Treatment Visit	Visit 24 (±6) Hours After Randomization	Visit 72–96 Hours After Randomization [p]	Discharge or Day 5 after Randomization *(whichever occurs earlier)*	Follow-Up [a]	
					30 (±7) Days	90 (±14) Days
Informed consent	x					
Medical history and baseline conditions [b]	x				x	x
Demographic data [b]	x					
Vital signs [c]	x					
Actual Weight [d]	x					
Glucose [d]	x					
Coagulation [d]	x					
CBC [e]	x					
Chemistry Panel [e]	x					
Pregnancy test [f]	x					
mRS [g]	x			x	x	x
NIHSS [h]	x	x	x	x	x	x
Brain imaging [i, m]	x	x	x			
Barthel Index [j]				x	x	x
GOS [k]				x	x	x
Neuro-QoL [l]						x
Study drug administration [m]	x					
Concomitant medications [n]	x	x	x	x	x	x
Adverse events [h, o]	x	x	x	x	x	x

Appendix 1
Schedule of Activities (cont.)

AIS=acute ischemic stroke; CBC=complete blood count; CT=computed tomography; DWI=diffusion-weighted imaging; eCRF=electronic Case Report Form; FLAIR=fluid-attenuated inversion recovery; GOS=Glasgow Outcome Scale; GRE=gradient recalled echo; *IV=intravenous;* MRA=magnetic resonance angiography; MRI=magnetic resonance imaging; MRP=magnetic resonance perfusion; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale*; sICH=symptomatic intracranial hemorrhage; SOC=standard of care.*

[a] Patients should return to the clinic for follow-up 30 and 90 days after treatment. At Day 90, patients should have the study completion visit. If an in-person visit is infeasible, *only* the mRS should be performed by telephone. *All questionnaires can be collected by telemedicine except the Neuro-QoL.*

[b] Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. Demographic data will include age, sex, self-reported race/ethnicity, and veteran status.

[c] Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure, and temperature. Temperature will be required prior to randomization and will be performed with subsequent frequency per SOC. The frequency of respiratory rate, pulse rate, systolic and diastolic blood pressure measurements should reflect post-IV thrombolytic monitoring in AIS per SOC.

[d] Patients should be weighed before randomization. Glucose (finger stick or blood draw) and coagulation tests (INR, aPTT, PT [only if the patient is taking an anticoagulant]) should be done. Results are required prior to randomization.

[e] Platelet count results must be checked prior to randomization in patients with suspected coagulopathy. Electrolytes will also be collected. All other CBC and electrolyte results are NOT required prior to randomization.

[f] All women of childbearing potential will have a urine/serum pregnancy test at screening. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[g] A pre-stroke mRS will be estimated a baseline. Thirty and 90 days after treatment, patients should be evaluated using mRS preferably in the clinic; if an in-person visit is not feasible, the patient can be evaluated by telephone (Appendix 2).

[h] A baseline NIHSS will be used to determine stroke severity and study eligibility. This assessment will be performed per institutional practice during hospitalization, upon hospital discharge and at the listed follow-up visits. In the event of an *ICH* event that occurs within 36 hours of drug administration, a NIHSS assessment is *to* be completed. See Appendix 3 for NIHSS. Please refer to Appendix 7 for brain imaging requirements.

[i] Patients will undergo two follow-up MRI scans *(MRI/MRA/MRP at the first follow up and MRI at the second follow up).* Patients who cannot undergo an MRI will undergo a multimodal CT/*CTA/CTP* at the first follow-up and a non-contrast CT at the second follow-up. The first follow-up scan will be obtained at approximately 24 (±6) hours after *randomization.* The second follow-up scan will be obtained at 72–96 hours after *randomization.* See Appendix 7 for brain imaging requirements.

[j] See Appendix 4 for the Barthel Index.

[k] See Appendix 5 for GOS.

[l] See Appendix 6 for Neuro-QoL.

[m] Study drug administration needs to occur within 90 minutes of qualifying RAPID brain imaging. If 90 minutes is exceeded, CTP/MRP imaging must be repeated to validate that the patient is still eligible for the study. Study drug administration *is recommended to* occur before the start of endovascular therapy (defined as groin puncture). If it appears that it will be challenging to administer study drug prior to femoral groin puncture for a planned thrombectomy, *it is recommended that* the patient *not be randomized. However,* if the patient has *already* been randomized, and due to unforeseen circumstances the drug cannot be administered prior to groin puncture for the planned thrombectomy, the drug must be administered as soon as possible and prior to manipulation of the clot.

[n] In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded.

[o] New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[p] Activities may be performed at discharge, if discharge is prior to *the 72–96 hour visit. If the patient is discharged within 24 hours of the 24-hour visit, no 72–96 hour visit image collection is required.*

Appendix 2
Modified Rankin Scale

Q01	Modified Rankin Scale		○ (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
Q02	First/Given name of mRS assessor (50 character max)		
Q03	Last/Family name of mRS assessor (50 character max)		
Q04	*If visit is 'Day 30' or 'Day 90'*	Was the assessor blinded to treatment received?	○ No ○ Yes
General Comments:			
Name of person who collected data: If this worksheet is a source document, sign/date here:			

Appendix 2
Modified Rankin Scale (cont.)

Structured assessment of modified Rankin scale

Has the patient made a complete recovery with **absolutely no** residual signs or symptoms of stroke?

YES → mRS score = 0

NO ↓

Can the patient perform every regular activity that they could undertake prior to the stroke? Regular is defined as more frequently than monthly; includes work, social and leisure activities (eg driving a car, dancing, reading or working)

YES → mRS score = 1

Please briefly document what neurological symptoms/signs are present?

NO ↓

Can the patient perform all their activities of daily living without assistance?
ie mobility, dressing, bathing, toileting, feeding, preparing simple meals, travelling locally without supervision.
Can the patient be safely left alone for a period of at least 1 week?

YES → mRS score = 2

What usual activities have ceased?

NO ↓

Can the patient mobilise (with gait aid if necessary) and perform activities of daily living independently BUT requires supervision or assistance for more complex tasks e.g. shopping, cooking, cleaning, managing finances that means they need to be visited more frequently than weekly

YES → mRS score = 3

What activities require assistance?

NO ↓

Does the patient require assistance for personal activities of daily living (walking, dressing, feeding, toileting) but can be safely left alone for a period of a few hours during the day?

YES → mRS score = 4

What activities require assistance?

How long could the patient manage without a visit?

NO ↓

Does the patient have severe disability requiring 24hr/day carer availability?

YES → mRS score = 5

Death = mRS score 6

If in doubt, the more severe score should be allocated and please provide as much information as possible.

General Comments:

Name of person who collected data:
If this worksheet is a source document, sign/date here:

Appendix 3
National Institutes of Health Stroke Scale

NIH_Stroke_Scale

N I H
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.	_____

Rev 10/1/2003

Appendix 3
National Institutes of Health Stroke Scale (Cont.)

N I H
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**	_____

Rev 10/1/2003

Appendix 3
National Institutes of Health Stroke Scale (Cont.)

N I H
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:_____	_____

Rev 10/1/2003

Appendix 3
National Institutes of Health Stroke Scale (Cont.)

N I H
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 _____(___ ___)

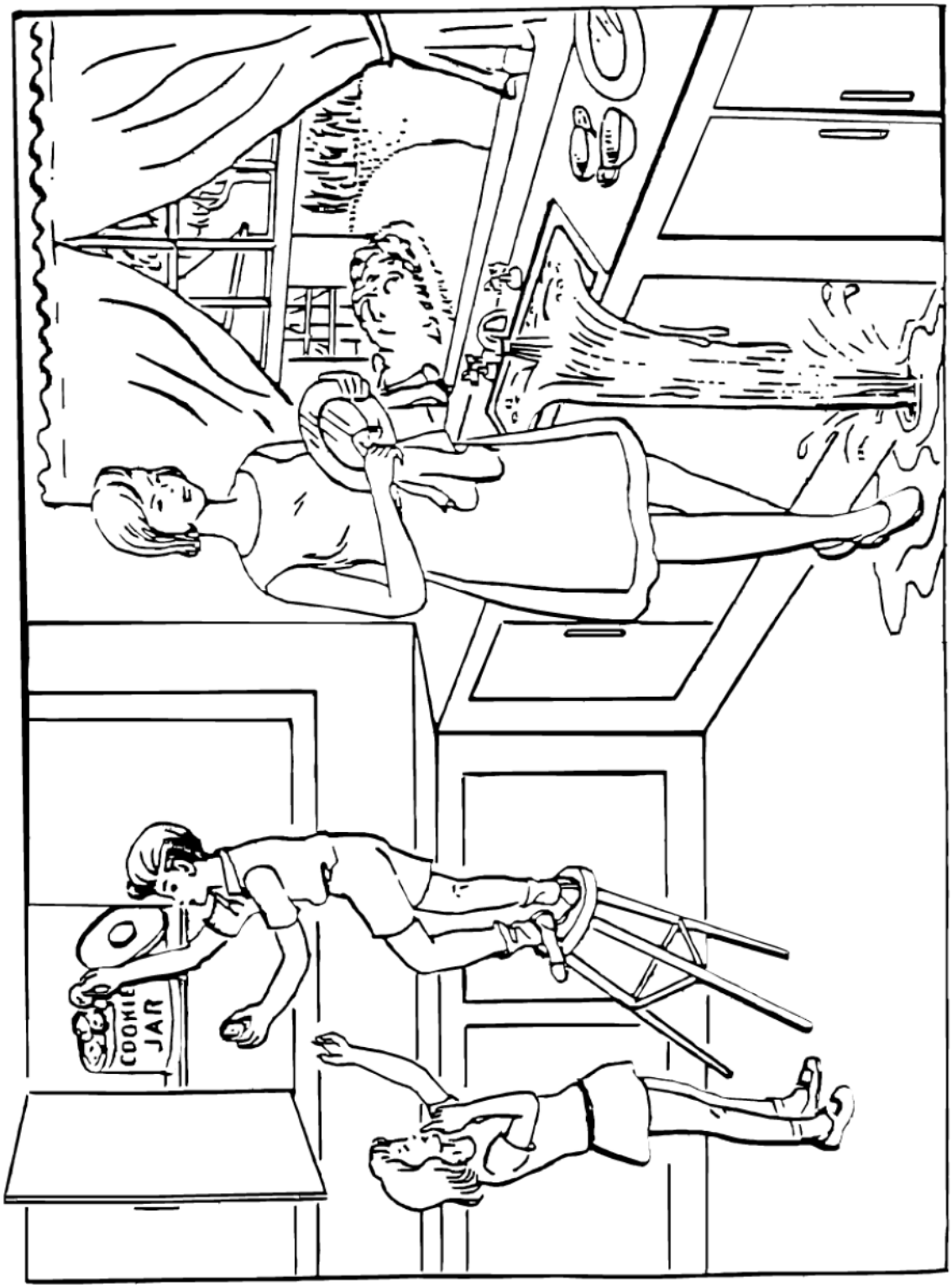
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient 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.	_____

_____

_____

Rev 10/1/2003

Appendix 3
National Institutes of Health Stroke Scale (Cont.)



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.

Appendix 3
National Institutes of Health Stroke Scale (Cont.)

MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

Appendix 4
Barthel Index

Barthel-Index_AU1.0_Eng

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):	_____

Provided by the Internet Stroke Center — www.strokecenter.org

Barthel Index - United States/English - Mapi.
ID8240 / Barthel-Index_AU1.0_eng-USori.doc

Appendix 4
Barthel Index (Cont.)

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

Mahoney FI, Barthel D. "Functional evaluation: the Barthel Index."
Maryland State Medical Journal 1965;14:56-61. Used with permission.

Loewen SC, Anderson BA. "Predictors of stroke outcome using objective measurement scales."
Stroke. **1990;21:78-81.**

Gresham GE, Phillips TF, Labi ML. "ADL status in stroke: relative merits of three standard indexes."
Arch Phys Med Rehabil. **1980;61:355-358.**

Collin C, Wade DT, Davies S, Horne V. "The Barthel ADL Index: a reliability study."
Int Disability Study.**1988;10:61-63.**

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Appendix 4
Barthel Index (Cont.)

Barthel-Index_AU1.0_Sp

ÍNDICE DE BARTHEL

Nombre del Paciente: _____
Nombre del Evaluador: _____
Fecha: _____

Actividad	Puntaje

ALIMENTACIÓN
0 = no puede solo
5 = necesita ayuda para cortar, extender la manteca, etc., o requiere dieta adaptada a sus necesidades
10 = independiente _____

BAÑARSE
0 = dependiente
5 = independiente (o en la regadera/ducha) _____

ASEO
0 = necesita ayuda con el cuidado personal
5 = independiente para lavarse la cara/los dientes/peinarse/afeitarse (se le provee de implementos) _____

VESTIRSE
0 = dependiente
5 = necesita ayuda pero puede hacer alrededor de la mitad sin ayuda
10 = independiente (incluyendo botones, cremalleras/cierres, cordones, etc.) _____

CONTROL INTESTINAL
0 = incontinente (o necesita de enemas)
5 = accidente ocasional
10 = continente _____

CONTROL DE LA VEJIGA
0 = incontinente, o con catéteres e incapaz de arreglárselas solo
5 = accidente ocasional
10 = continente _____

USO DEL INODORO
0 = dependiente
5 = necesita alguna ayuda, pero puede hacer algo solo
10 = independiente (para sentarse y pararse, vestirse, limpiarse) _____

TRANSFERIRSE (DE LA CAMA A LA SILLA Y VICEVERSA)
0 = no puede, sin equilibrio cuando está sentado
5 = necesita mucha ayuda (una o dos personas, físicamente), puede sentarse
10 = poca ayuda (verbal or física)
15 = independiente _____

MOVILIDAD (EN SUPERFICIES NIVELADAS)
0 = no se moviliza o < de 50 yardas/45 m
5 = independiente con la silla de ruedas, incluyendo rincones, > de 50 yardas/45 m
10 = camina con ayuda de una persona (verbal o física) > de 50 yardas/45 m
15 = independiente (pero puede necesitar alguna ayuda, por ejemplo, un bastón) > 50 yardas/45 m _____

ESCALERAS
0 = no puede solo
5 = necesita ayuda (verbal, física, con artefactos de ayuda)
10 = independiente _____

TOTAL (0–100): _____

Provisto por el Internet Stroke Center — www.strokecenter.org

Barthel Index - United States/Spanish - Version of 24 Dec 14 - Mapi.
ID8240 / Barthel-Index_AU1.0_spa-US.doc

Appendix 4
Barthel Index (Cont.)

Índice ADL de Barthel: Instrucciones

1. El índice debe usarse como un informe de lo que el paciente hace y no como un informe de lo que el paciente podría hacer.
2. El objetivo principal es establecer un nivel de independencia de todo tipo de ayuda, física o verbal, aunque sea poca o por cualquier razón.
3. La necesidad de supervisión indica que el paciente no es independiente.
4. El desempeño de un paciente debe ser establecido utilizando la mayor evidencia disponible. Las preguntas al paciente, amigos/familiares y enfermeras son las fuentes habituales, pero la observación directa y el sentido común son también importantes. Sin embargo, no es necesario efectuar pruebas directas.
5. Por lo general, el rendimiento del paciente durante las 24 a 48 horas anteriores es importante, pero de vez en cuando es relevante controlarlo durante períodos más prolongados.
6. Las categorías medias implican que el paciente efectúa más del 50 por ciento del esfuerzo.
7. Se permite el uso de elementos de ayuda para ser independiente.

Referencias

Mahoney FI, Barthel D. "Functional evaluation: the Barthel Index."
Maryland State Medical Journal 1965;14:56-61. Usado bajo permiso.

Loewen SC, Anderson BA. "Predictors of stroke outcome using objective measurement scales."
***Stroke*. 1990;21:78-81.**

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Collin C, Wade DT, Davies S, Horne V. "The Barthel ADL Index: a reliability study."
***Int Disability Study*.1988;10:61-63.**

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Appendix 5
Glasgow Outcome Scale

GLASGOW OUTCOME SCALE

Patient Name: _____
Rater Name: _____
Date: _____

Note: The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no *obvious cortical* function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

TOTAL (1–5): _____

References

Jennett B, Bond M. "Assessment of outcome after severe brain damage."
Lancet 1975 Mar 1;1(7905):480-4

Appendix 6
Neuro-QoL

Neuro-QOL Item Bank v1.0 – Lower Extremity Function (Mobility) – Short Form

Lower Extremity Function (Mobility) – Short Form

Please respond to each question or statement by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
	Are you able to get on and off the toilet?...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Are you able to step up and down curbs?...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Are you able to get in and out of a car?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Are you able to get out of bed into a chair?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Are you able to push open a heavy door?..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Are you able to run errands and shop?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Are you able to get up off the floor from lying on your back without help?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Are you able to go for a walk of at least 15 minutes?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Appendix 6
Neuro-QoL (cont.)

Neuro-QOL Item Bank v1.0 – Depression – Short Form

Depression – Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
NQDEP12	I felt depressed……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQDEP23	I felt hopeless……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQDEP07	I felt that nothing could cheer me up……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQDEP27	I felt that my life was empty……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQDEP02	I felt worthless……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQDEP19	I felt unhappy……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQDEP21	I felt I had no reason for living……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQDEP34	I felt that nothing was interesting……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix 6
Neuro-QoL (cont.)

Neuro-QOL Item Bank v1.0 – Ability to Participate in Social Roles and Activities – Short Form

Ability to Participate in Social Roles and Activities – Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
NQPRF01	I can keep up with my family responsibilities……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF03	I am able to do all of my regular family activities……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF08	I am able to socialize with my friends…..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF09	I am able to do all of my regular activities with friends……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF17	I can keep up with my social commitments……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF25	I am able to participate in leisure activities……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF32	I am able to perform my daily routines…..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF34	I can keep up with my work responsibilities (include work at home)….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix 6
Neuro-QoL (cont.)

Neuro-QOL Item Bank v2.0 – Cognition Function– Short Form

Cognition Function– Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely (once)	Sometimes (2-3 times)	Often (once a day)	Very often (several times a day)
	I had to read something several times to understand it……..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	My thinking was slow……	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	I had to work really hard to pay attention or I would make a mistake……..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	I had trouble concentrating……..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

	How much DIFFICULTY do you currently have…	None	A little	Somewhat	A lot	Cannot do
	reading and following complex instructions (e.g., directions for a new medication)?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	planning for and keeping appointments that are not part of your weekly routine, (e.g., a therapy or doctor appointment, or a social gathering with friends and family)?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	managing your time to do most of your daily activities?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	learning new tasks or instructions?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Appendix 7
Brain Imaging Requirements

The purpose of this appendix is to provide imaging processing standards to help ensure that brain imaging data are obtained in a manner that complies with the TIMELESS protocol. Images must be sent to a central reader in order to provide more uniform reading and interpretation of results for this multi-center study, leading to a more precise estimate of treatment effect. Furthermore, because TIMELESS is a randomized, controlled trial, imaging readers will be blinded to a patient's treatment assignment to eliminate bias.

All sites are required to use RAPID software to provide brain imaging assessments. There will be no software variations, allowing for calibration standards across sites in order to ensure imaging consistency and quality control.

IMAGING REQUIRED

At baseline:

- Aspects scores documented, if applicable
- If screened by CT: Computed tomography (CT) to rule out hemorrhage
- **Neuroimaging:** internal carotid artery (ICA) or M1, M2 occlusion by magnetic resonance angiography (MRA) or CT angiography (CTA) **AND** target mismatch profile on CT perfusion *(CTP)* or MR *perfusion (MRP)* imaging (MRI) (ischemic core volume $<$70 mL, mismatch ratio is $\geq$1.8 and mismatch volume is $\geq$15 mL). Carotid occlusions can be cervical or intracranial with or without tandem MCA lesions
  - The mismatch volume is determined by the software in real time based on the difference between the ischemic core lesion volume and the T_{max} $>$6s lesion volume. If both a *CTP* and a multimodal MRI scan are performed prior to enrollment, the later of the 2 scans is assessed to determine eligibility. Only an intracranial MRA is required for patients screened with MRA; cervical MRA is not required. Cervical and intracranial CTA are typically obtained simultaneously in patients screened with CTA, but only the intracranial CTA is required for enrollment.
  - Anatomic Definitions for M1 and M2
    - M1: Horizontal segment of the proximal MCA from the bifurcation of the ICA (into the anterior and middle cerebral arteries) to the genu of the MCA branch or branches at the entrance to the insula
    - M2: Vertical MCA branches in the Sylvian fissure originating at the genu and extending to the next genu at the level of the operculum

Appendix 7
Brain Imaging Requirements (cont.)

- **Alternative neuroimaging:**
  - If CTA (or MRA) is technically inadequate: T_{max} >6s perfusion deficit consistent with an ICA or M1, M2 occlusion **AND** target mismatch profile (ischemic core volume <70 mL, mismatch ratio ≥1.8 and mismatch volume ≥15 mL as determined by RAPID software)
  - If MR perfusion (MRP) is technically inadequate: ICA or M1, M2 occlusion by MRA AND diffusion-weighted imaging (DWI) lesion volume ≤25 mL for an M1 or ICA occlusion and ≤15 mL for an M2 occlusion. If MRA is technically inadequate, a CTA can be used if performed within 60 minutes prior to the MRI. Carotid occlusions can be cervical or intracranial; with or without tandem MCA lesions
  - If CTP is technically inadequate: patient can be screened with MRI and randomized if neuroimaging criteria are met.
- *DSA images: baseline, mechanical thrombectomy, and post thrombectomy images obtained during angiogram to determine the required TICI scores*

24-hour imaging:

- An MRI will be performed 18–30 hours (approximately 24 *hours [*±6 hours*]*) post-randomization to assess reperfusion, recanalization, and ischemic core growth. This will include an MRA of the Circle of Willis to assess for recanalization and an MRP study to assess for reperfusion in addition to standard fluid-attenuated inversion recovery (FLAIR), gradient recalled echo (GRE), and DWI sequences per standard of care. At the investigator's discretion, a repeat CTP may be performed at 18–30 hours if MRI is not possible (e.g., due to unstable medical condition).
  - Patients who cannot undergo an MRI*/MRA/MRP* will undergo a multimodal CT*/CTA/CTP* instead.

***Occurrence of an ICH event* within 36 hours:**

- *In the event of an ICH event that occurs* within 36 hours of *drug administration, a NIHSS assessment is to be completed (see* Appendix 3 *for the NIHSS)*

72–*96* hour imaging:

- The second MRI will be obtained at 72–96 hours after randomization and will only include FLAIR, GRE, and DWI for assessment of final infarct volumes.
  - *Patients who cannot undergo a MRI will undergo a non-contrast CT*

Appendix 8
Modified Thrombolysis in Cerebral Infarction (TICI) Scale

Table 1 presents the Modified Thrombolysis in Cerebral Infarction (TICI) scale as it is currently adopted for emergent large vessel occlusion (ELVO).

Table 1. Modified Thrombolysis in Cerebral Infarction (TICI) Scale

Scale	*Description*
0	*No perfusion or anterograde flow beyond site of occlusion*
1	*Contrast passes the area of occlusion but fails to opacify the entire cerebral bed distal to the obstruction during angiographic run*
2	*Partial perfusion wherein the contrast passes the occlusion and opacifies the distal arterial bed but rate of entry or clearance from the bed is slower than non-involved territories* *2A: <50% of territory visualized* *2B: ≥50% of territory is visualized* *2C: Near complete perfusion except for slow flow in a few distal cortical vessels or presence of small distal cortical emboli*
3	*Complete reperfusion with normal filling*

Source: Spiotta et al. 2019.

Reference:

Spiotta AM, Fiorella D, Arthur AS, et al. The semiotics of distal thrombectomy: towards a TICI score for the target vessel. J Neurointerv Surg. 2019;11(3):213–214.