

Protocol: Tenecteplase With Concomitant Anticoagulation for Severe Acute  
Respiratory Failure in Patients With COVID-19

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## PROTOCOL

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

GLOSSARY OF ABBREVIATIONS	
ADR	adverse drug reaction
AE	adverse event
AHA	American Heart Association
AIS	acute ischemic stroke
AV	arteriovenous
AMI	acute myocardial infarction
BFR	blood-flow rate
CCDS	company core data sheet
CT	computed tomography
CEC	Clinical Events Committee
CVCs	central venous catheters
DSMC	Data & Safety Monitoring Committee
EVT	endovascular treatment
ED <sub>50</sub>	effective dose at which 50% of a clot is lysed
GD	gestational day
HD	hemodialysis
HFNC	High Flow Nasal Cannula
ICH	International Conference on Harmonisation
IH	intracranial hemorrhage
IQR	interquartile range
IV	intravenous
MAD	Mutual Acceptance of Data
MCA	middle cerebral artery
NIPPV	noninvasive positive-pressure ventilation
NRB	non-rebreather mask
NOAEL	No-observed-adverse-effect-level
PAI-1	plasminogen activator inhibitor 1
PCI	percutaneous coronary intervention
p-PCI	primary percutaneous coronary intervention
SADR	serious adverse drug reaction
SAE	serious adverse event
sICH	symptomatic intracranial hemorrhage
t-PA	tissue plasminogen activator
USPI	United States Package Insert

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## **1. BACKGROUND**

### **1.1 BACKGROUND**

In less than five months since the emergence of a novel coronavirus (SARS-CoV-2) in December 2019, millions of patients worldwide have suffered acute respiratory conditions, many of whom ultimately require mechanical ventilation due to hypoxemic respiratory failure. This disease (COVID-19) has been associated with a hyperinflammatory and hypercoagulable state<sup>1</sup> leading to a range of thromboembolic complications from pulmonary embolism to ischemic stroke.<sup>2,3</sup> Furthermore, emerging data suggest that the associated acute respiratory failure is, at least in part, due to pulmonary vascular disease caused by micro- and/or macro-emboli creating pulmonary vascular shunting and dead-space ventilation.<sup>4,5</sup> The relatively preserved lung compliance, particularly in certain individuals and early in the disease course, has brought into question whether the respiratory failure is in fact caused by the traditional acute respiratory distress syndrome (ARDS).<sup>6,7</sup>

Given these observations, in the early phase of the COVID-19 pandemic hitting New York City, critically ill patients with severe hypoxemic respiratory failure due to COVID-19 were treated with intravenous thrombolysis with alteplase, tissue plasminogen activator (tPA). In a case series of four patients, rapid physiologic improvements in alveolar ventilation, oxygenation, and/or hemodynamics was noted.<sup>18</sup> Wang et al<sup>8</sup> also noted similar results with tPA in this patient population. In both of these case series, the physiologic effects of tPA were only temporary. It was only with the concomitant use of anticoagulation with heparin were these physiologic benefits sustained, likely because anticoagulation prevented immediate rethrombosis in this exceptionally prothrombotic condition.<sup>18</sup> Given that tPA is contraindicated for concomitant use with heparin infusion, this protocol is created to assess tenecteplase as a thrombolytic agent in patients with COVID-19, as there is a very long-standing literature documenting the safety of tenecteplase with concomitant heparin infusion. There is an additional logistic benefit to tenecteplase, in that it is given as a single bolus. The logistic challenges of providing a prolonged alteplase infusion to a COVID-19 patient, wherein the IV pumps are outside the room and the IV tubing is in excess of 7 feet long, is quite formidable.

### **1.2 CURRENT THERAPIES AND UNMET MEDICAL NEED**

Currently, there is no proven therapy for COVID-19 associated respiratory failure. A recent publication has suggested that systemic anticoagulation may help these patients<sup>19</sup>, but the data is far from definitive. Additionally, a case series and ongoing clinical trial (at other centers) is assessing the potential value of tPA thrombolysis in this patient population. We believe that TNK is uniquely situated to be of benefit for this population.

### **1.3 BACKGROUND ON TENECTEPLASE**

Tenecteplase (TNKase<sup>®</sup>) 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.

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Refer to the Tenecteplase Investigator's Brochure for details on nonclinical and clinical studies.

### **1.3.1 Approved Indication in US and Europe**

In the US, TNKase® (tenecteplase) is indicated for use in the reduction of mortality associated with AMI.

## **1.4 OVERVIEW OF CLINICAL DEVELOPMENT**

Tenecteplase has been previously developed in other indications and has been approved for the treatment of AMI. Tenecteplase is being developed by Genentech as a treatment for AIS 4.5 to 24 hours after stroke onset, in patients who show a salvageable brain pattern by advanced imaging technology.

Tenecteplase has been studied extensively in patients with acute myocardial infarction (AMI). The ASSENT-2 trial,<sup>9</sup> for example, analyzed 16,949 patients with AMI randomized to either IV bolus of tenecteplase or infusion of alteplase, followed by maintenance therapy with heparin for 48-72 hours (goal aPTT 50-75). All-cause mortality was nearly identical between the two groups; however, the authors noted a pragmatic advantage inherent with a single bolus of tenecteplase compared to an infusion of alteplase. Tenecteplase is also associated with a lower rate of systemic bleeding compared to alteplase. The ASSENT-3 and ASSENT-3 PLUS trials provide further confirmation of the safety of anticoagulation administration following tenecteplase,<sup>10,11</sup>

Tenecteplase has been studied for patients with pulmonary embolism.<sup>15</sup> In the PEITHO trial, the use of tenecteplase at a dose of 0.5 mg/kg with concomitant anticoagulation reduced the rate of hemodynamic decompensation in patients with intermediate-risk pulmonary embolism. This benefit, along with lower bleed rates, was particularly notable in participants younger than 75 years old. Eight of 13 (62%) participants who suffered stroke in PEITHO were > 75 years old; two of the eleven (18%) participants who suffered hemorrhagic stroke were < 75 years old. Completed and ongoing clinical studies of tenecteplase are summarized in the Tenecteplase Investigator's Brochure.

### **1.4.1 Acute Myocardial Infarction Clinical Development**

Tenecteplase is indicated for use in the reduction of mortality associated with AMI and has been approved since 2000. Completed and ongoing clinical studies of tenecteplase are summarized in the Tenecteplase Investigator's Brochure.

### **1.4.2 Acute Ischemic Stroke Clinical Development**

Tenecteplase is being evaluated for safety and efficacy in a Phase III in AIS stroke patients, 4.5–24 hours after symptom onset, who show a salvageable brain pattern by advanced imaging technology (Study ML40787). Study ML40787 TIMELESS (Thrombolysis in Imaging Eligible Late Window Patients to assess the efficacy and safety of Tenecteplase) is currently enrolling and plans to enroll 456 acute ischemic stroke patients in the US and Canada. Patients with large vessel occlusions, with a diffusion/perfusion mismatch, in the 4.5–24 hour window may be eligible to receive tenecteplase 0.25 mg/kg or placebo in conjunction with mechanical thrombectomy.



Completed and ongoing clinical studies of tenecteplase are summarized in the Tenecteplase Investigator's Brochure.

Studies have also demonstrated the benefit of tenecteplase in acute ischemic stroke. In the EXTEND-IA TNK trial,<sup>13</sup> tenecteplase combined with endovascular thrombectomy was associated with higher probability of radiographic reperfusion as well as long term functional outcomes in patients with large vessel intracranial occlusions as compared to alteplase. This benefit was seen at a lower dose (0.25 mg/kg) than the MI studies (0.5 mg/kg). A subsequent study, EXTEND-IA TNK II, found no increased risk but no clinical benefit in stroke to increasing the TNK dose to 0.4 mg/kg.<sup>13</sup> Further studies are in progress to assess a longer window to treatment time, including a Phase III clinical trial for patients with a salvageable penumbra on brain perfusion imaging.<sup>14</sup>

## **1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT**

Based on a recent JAMA publication, intubated COVID-19 patients in NYC can expect a mortality rate as high as 88%.<sup>16</sup> This dismal mortality rate has driven us to make clinical decisions regarding the use of off-label application of otherwise FDA approved medications in a hope to improve outcomes. Therefore, we undertook the off-label utilization of tenecteplase (at the lower EXTEND-IA TNK dosing) with concomitant heparin administration for the treatment of 5 refractory COVID-19 patients. We were highly encouraged by this experience in that all patients had improvement in oxygenation, alveolar ventilation, and hemodynamics within 24-48 hours. Four of the five patients had shock resolution, while the fifth patient had dramatic reductions in vasopressor requirements. No clinically significant bleeding was noted in any of these patients. As a result, we believe that a high-quality prospective Phase II, dose escalation trial is indicated.

To assess the efficacy of tenecteplase on critically ill patients with COVID-19 and hypoxic respiratory failure, we propose a multi-center, randomized, controlled, double-blind, dose-escalation trial comparing tenecteplase versus placebo. We intend to enroll 60 subjects: 40 randomized for intervention (20 each at doses of TNK, 0.25 mg/kg and 0.50 mg/kg) and 20 for placebo. Planned inclusion criteria are confirmed respiratory failure requiring mechanical ventilation for not greater than 48 hours, or non-rebreather (NRB), high-flow nasal cannula (HFNC), or non-invasive positive pressure ventilation (NIPPV) for less than 96 hours, with confirmed infection with SARS-CoV-2 virus (PCR positive within 14 days), elevated D-dimer (2 times upper limit of normal,<sup>17</sup> and lack of stringent exclusion criteria. Primary efficacy outcome will be clinical status assessment at 28 days (proportion of patients alive and free of respiratory failure). Primary safety outcome will be rate of ICH or major acute hemorrhage (defined as bleeding episode leading to hemodynamic compromise requiring emergency intervention [such as replacement of fluid and/or blood products, inotropic support, or surgical treatment], or life-threatening or fatal bleeding). Secondary outcomes include survival, ventilator-free days, respiratory failure-free days, vasopressor-free days, improvement in PaO<sub>2</sub>/FiO<sub>2</sub>, and ICU and hospital length of stay.



## **2. OBJECTIVES AND ENDPOINTS**

### **2.1 PRIMARY OBJECTIVE(S)**

The study objective is to evaluate the potential effect of tenecteplase on patients presenting with COVID-19. The hypothesis is that administration of the drug, in conjunction with heparin anticoagulation, will improve patients' clinical outcomes.

### **2.2 PRIMARY EFFICACY OUTCOME**

The primary efficacy outcome will be the proportion of patients alive and free of respiratory failure (defined as not requiring non-rebreather, high-flow nasal cannula, non-invasive positive pressure ventilation, or mechanical ventilation) at 28 days.

### **2.3 STUDY OUTCOMES**

The following outcomes will be tracked for the trial:

Primary outcome is: the proportion of patients alive and free of respiratory failure (not requiring non-rebreather, high-flow nasal cannula, non-invasive positive pressure ventilation, or mechanical ventilation) at 28 days

- A. Primary safety outcome: Occurrence of intracranial bleeding or major bleeding (Definition: A bleeding episode leading to hemodynamic compromise requiring emergency intervention (such as replacement of fluid and/or blood products, inotropic support, or surgical treatment), or life-threatening or fatal bleeding) within 72 hours of randomization. All outcomes will be assessed in a blinded fashion by the DSMC/CEC.
- B. Secondary outcomes include: 14-day in-hospital mortality, 28-day mortality, ventilator-free days, respiratory failure-free days (not requiring NRB, HFNC, NIPPV, or mechanical ventilation), vasopressor-free days, vasopressor requirements at 24 and 72 hours, P/F ratio at 24 hours and 72 hours, ICU-free days, hospital length of stay, new renal failure, need for renal replacement therapy
- C. Mortality: given a high mortality rate amongst this patient population, patients who die will be included in statistical analysis. Variables of interest will be calculated until the point these patients expire.

## **3. STUDY DESIGN**

### **3.1 DESCRIPTION OF THE STUDY**

This will be a placebo controlled, double-blind, randomized, Phase II dose escalation trial completed at up to 6 study centers. Subjects will be randomized in a 2:1 ratio to treatment or control in blocks of 15, performed twice per dose - low (0.25 mg/kg with maximum dose 25 mg) and high (0.50 mg/kg with maximum dose 40 mg), with randomization stratified by site.

### **3.2 END OF STUDY AND LENGTH OF STUDY**

The anticipated first patient, first visit will occur on June 15, 2020. Enrollment is anticipated to take approximately 5 months, with our last patient, first visit to occur on November 15, 2020. Follow up will be completed by December 15, 2020. It will take the study team approximately 2  
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months to clean and analyze the data, with a final study report expected by mid-February, 2021.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 8 months.

### **3.3 RATIONALE FOR STUDY DESIGN**

This is a phase II dose escalation study intended to evaluate the potential safety and efficacy of tenecteplase for the treatment of COVID-19 associated respiratory failure. This study is not powered for significance, but is instead designed to provide an estimate of the potential benefit-signal and better inform a subsequent phase III RCT.

#### **3.3.1 Rationale for Tenecteplase Dose and Schedule**

Tenecteplase is a triple combination mutant of alteplase, with a longer half-life, improved specificity for fibrin, and higher resistance to degradation by plasminogen-activator inhibitor.<sup>22</sup> One practical clinical advantage over other thrombolytic drugs is the ability to bolus a single dose of tenecteplase, compared to longer infusions required for efficacy (i.e. alteplase). Tenecteplase was first studied in acute myocardial infarction (AMI) in the 1990s. In the TIMI 10A trial, tenecteplase was found to be effective for coronary reperfusion in patients with AMI and had a safety profile comparable to wild-type tPA.<sup>23</sup> The follow up TIMI 10B trial randomized 886 patients with early ( $\leq 12$  hr) AMI to either bolus tenecteplase or bolus + infusion of tPA, plus coronary angiography and postprocedural heparin infusion.<sup>24</sup> The study authors found that overall rates of TIMI grade 3 reperfusion were similar between the two groups, but this finding was found in patients who received higher doses of tenecteplase (50 mg versus 30 mg), albeit with higher risk of symptomatic bleeding and intracranial hemorrhage. The risks of hemorrhage were reduced in both groups by lowering heparin infusion rates. A further safety assessment of tenecteplase, relative to alteplase, was published in 1999 through the ASSENT-1 trial, in which a total of 325 patients were given a single bolus of tenecteplase in escalating doses (30, 40, or 50 mg).<sup>25</sup> Overall rates of intracranial hemorrhage were low (0.77% overall), did not depend on dose, and were comparable to historical data on tPA. Overall, the authors recommend a weight-based dosing strategy for patients with AMI.

Based on these positive safety trials, subsequent trials were published directly comparing tenecteplase and alteplase. ASSENT-2 was a double-blind, controlled trial randomizing 16,949 patients to either weight based tenecteplase bolus (0.5 mg/kg) or infusion with tPA, plus aspirin and heparin infusion.<sup>26</sup> The primary outcome of all-cause mortality at 30 days was similar for the two groups (6.18% and 6.15% for tenecteplase and tPA, respectively). Rates of intracranial hemorrhage were also similar between the two groups, although the risk of other hemorrhage was higher for tPA.

Given the positive results in the cardiac literature, tenecteplase has also been trialed for acute ischemic stroke; however, there has been limited adoption compared to alteplase following the NINDS trial in 1995.<sup>27</sup> Smaller phase II trials were performed throughout the 2010s, again suggesting equivalent efficacy regarding reperfusion with a similar safety profile between tenecteplase and alteplase. The first dose-escalation study was published in 2005 and assessed tenecteplase doses between 0.1 and 0.5 mg/kg.<sup>28</sup> Despite an increasing incidence of asymptomatic intracranial hemorrhage (ICH) between 0.1 and 0.4 mg/kg doses, no symptomatic ICH were seen. However, the 0.5 mg/kg tier was terminated prematurely given a high incidence



of symptomatic ICH (2 of 13 patients). Overall long-term functional outcomes were similar between the lower dose tenecteplase and historical controls treated with tPA.

The ATTEST trial randomized 104 patients with acute ischemic stroke to receive either TNK or tPA.<sup>29</sup> The primary endpoint of salvaged penumbra was identical between the two groups (68%), and rates of symptomatic intracranial hemorrhage were not statistically different (2% and 4% for TNK and tPA, respectively,  $p=0.55$ ). Another randomized controlled trial published in 2012 assessed either alteplase infusion or dose-escalated tenecteplase (0.1 or 0.25 mg/kg) in patients with acute ischemic stroke less than 6 hours after symptom onset.<sup>30</sup> Patients treated with tenecteplase had better rates of radiographic reperfusion as well as short- and long-term clinical improvement, with higher doses (0.25 mg/kg) performing better than lower. Rates of intracranial and non-intracranial hemorrhages were consistent in all three groups.

Most recently the EXTEND-IA TNK trial assessed 202 patients randomized to either tenecteplase bolus (0.25 mg/kg) or alteplase prior to endovascular thrombectomy for large vessel occlusion.<sup>31</sup> The primary outcome of angiographic reperfusion prior to thrombectomy (or absence of retrievable thrombus) was significantly greater in the TNK group, compared with tPA, present in 22% and 10%, respectively. Tenecteplase was also associated with improvement in 90-day functional outcomes, and similar rates of symptomatic intracranial hemorrhage.

Tenecteplase has also been assessed for use in treating pulmonary embolism (PE). In general, thrombolysis for PE has been shown to have minimal evidence for clinical benefit compared with heparin, except in those with the highest risks of recurrence or death.<sup>32</sup> In clinical trials, thrombolysis with alteplase has been associated with improvements in hemodynamic parameters (including pulmonary resistance and cardiac index) but have indeterminate effects on overall clinical outcomes given a paucity of data.<sup>33</sup> In one randomized, placebo-controlled trial of tenecteplase (at a dose of 0.5 mg/kg) plus heparin versus heparin alone, intermediate-risk patients with PE treated with TNK had lower risk of hemodynamic decompensation or death.<sup>34</sup> Symptomatic intracranial hemorrhage was more frequent in the TNK group, though occurred predominantly in patients older than 75 years old. Patients with submassive PE have also been found to have increased odds of good outcome after treatment with tenecteplase, compared with placebo, according to a randomized trial published in 2014.<sup>35</sup>

Based on this evidence, dosing guidelines for this trial will be as follows:

Patients will be monitored in the ICU immediately post-treatment and until 24 hours have passed and they are considered stable to downgrade to lower level of care.

- A. For patients already on therapeutic heparin, continue heparin infusion
- B. For patients not already on heparin or other anticoagulant, begin heparin with tenecteplase infusion starting with bolus dose of 60 Units/kg IV once (maximum dose of 5000 Units), followed by 12 Units/kg/hr (patients will only receive one dose of tenecteplase in total)
- C. For patients who were receiving enoxaparin at time of inclusion, tenecteplase infusion can be given immediately. Delay heparin to 12 hours after the most recent enoxaparin dose, beginning at an infusion rate of 12 Units/kg/hr. Do not administer a bolus dose of heparin.
  - Check PTT every 6 hours; adjust heparin to achieve target PTT between 2 and 2.5 times ULN



Patients will continue with the unfractionated heparin infusion for 24 hours from the beginning of the study. After 24 hours, they may be transitioned to low molecular weight heparin according to institutional standard of care.

### **3.3.2      Rationale for Patient Population**

This patient population has been chosen because they have objective indications of respiratory failure (intubation, NRB, HFNC, or NIPPV) but that failure is recent in onset. There has been increasing literature demonstrating the progressive thrombosis that occurs in multiple organ systems during COVID-19, including the lungs. By administering tenecteplase to this early stage respiratory failure population, who also have demonstrable thrombosis occurring (as indicated by their D-dimer) we hope to reverse the progressive pulmonary thrombosis that is occurring and thereby improve their outcome.

## **4.              MATERIALS AND METHODS**

### **4.1              PATIENTS**

Approximately 60 total patients with COVID-19 will be enrolled in this study. 40 intervention (20 low dose subjects at 0.25 mg/kg with maximum dose 25 mg, 20 high dose subjects at 0.50 mg/kg with maximum dose 40 mg), 20 control subjects.

#### **4.1.1              Inclusion Criteria**

Patients must meet the following criteria for study entry:

- Patient/legally authorized representative has completed the Informed Consent Form
- Age ≥18 years
- Ability to comply with the study protocol, in the investigator's judgment
- Respiratory failure secondary to COVID-19 requiring mechanical ventilation for no greater than 48 hours, or high-flow nasal cannula (HFNC), non-rebreather (NRB) mask or non-invasive positive pressure ventilation (NIPPV) for less than 96 hours
- Confirmed infection with SARS-CoV-2 virus (PCR positive within 14 days)
- Elevated D-dimer (>2 times upper limit of normal within past 72 hours)
- For patient who are intubated >12 hours prior to randomization or with any evidence of neurologic deficit a head CT within 12 hours demonstrating no evidence of acute or subacute infarct or hemorrhage

#### **4.1.2              Exclusion Criteria**

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

##### **General**

- Current participation in another investigational drug study within the prior 7 days
- Known hypersensitivity or allergy to any ingredients of tenecteplase
- Active internal bleeding
- Known bleeding diathesis

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- Use of one of the new oral anticoagulants within the last 24 hours (dabigatran, rivaroxaban, apixaban, edoxaban)
- Treatment with a thrombolytic within the last 3 months prior to randomization (exception for the use of Cathflo alteplase for occlusions of central venous catheters)
- Baseline platelet count  $<80,000/\text{L}$  (results must be available prior to treatment)
- Baseline blood glucose  $>400 \text{ mg/dL}$  ( $22.20 \text{ mmol/L}$ )
- Baseline blood glucose  $<50 \text{ mg/dL}$  needs to be normalized prior to randomization
- Intracranial or intraspinal surgery or trauma within 2 months
- Other, non-COVID-19 related, serious, advanced, or terminal illness (investigator judgment) or life expectancy is less than 6 months
- History of acute ischemic stroke in the last 90 days
- History of intracranial bleeding, including hemorrhagic stroke
- Presumed septic embolus; suspicion of bacterial endocarditis
- Mechanical ventilation  $> 48$  hours, HFNC, NIPPV, NRB, or any combination, for greater than 96 hours
- Mechanical ventilation, HFNC, NRB, or NIPVV (for reasons other than obstructive sleep apnea) within the prior 30 days (excluding 96 hours prior to randomization)
- Moribund status suggesting imminent vascular collapse and inability to survive  $> 72$  hours (investigator determination)
- Uncontrolled hypertension defined as systolic BP  $> 180 \text{ mm Hg}$  and/or diastolic BP  $> 110 \text{ mm Hg}$
- Age  $> 75$  years
- History of traumatic brain injury within 2 months
- Recent head trauma with fracture or brain injury
- History of Heparin Induced Thrombocytopenia (HIT) and/or other hereditary or acquired hemorrhagic diathesis or coagulation factor deficiency
- INR  $> 2$  or recent oral anticoagulant therapy with INR  $>1.7$
- Pregnancy or lactation within the prior 30 days; women of childbearing age ( $<55$  years old) should have documentation of a negative pregnancy test
- Chronic liver disease defined as  $> \text{Childs-Pugh Class B}$
- Patients with history of atrial fibrillation, mitral stenosis, or known left heart thrombosis
- Atrial fibrillation, mitral stenosis, or known left heart thrombosis
- Any other condition that, in the opinion of the investigator, precludes administration of tenecteplase or poses a significant hazard to the patient receives tenecteplase



## 4.2 METHOD OF TREATMENT ASSIGNMENT

This trial will be a randomized, blinded, placebo-controlled trial with an escalating-dose randomized design. Randomization will be completed as follows:

- Block randomization of 2:1 (treatment:control) in blocks of 15, performed twice per dose
- The first block of 15 patients (10 treatment at 0.25 mg/kg dose and 5 placebo control) will be assessed for safety trigger by the DSMC/CEC within 5 working days of the 15<sup>th</sup> patient completing 72 hours post treatment; if no safety trigger is met (as determined by DSMC/CEC), a second cohort of 15 patients will be enrolled (10 at the 0.25 mg/kg dose and 5 placebo control).
- If no safety trigger occurs after 30 patients enrolled (20 at the 0.25 mg/kg dose and 10 placebo control) then the first cohort 15 patients will be enrolled at the 0.50 mg/kg dose with randomization of 2:1 (treatment:placebo control). If no safety trigger occurs, the last cohort of 15 patients will be enrolled (10 at the 0.50 mg/kg dose and 5 placebo control).
- All SAE's will be reviewed by the DSMC/CEC every 15 patients enrolled and each death will be reviewed within 72 hrs of reporting. Safety trigger is defined as a greater than two patient differential in the occurrence of symptomatic intracranial hemorrhage or major acute bleeding event (defined below) within 72 hours between control and treatment arms.
- Randomization will be stratified according to site.

Tenecteplase and placebo will be provided by Genentech. They will be labeled accordingly, indicating which vials contain active drug and which contain placebo. The DCC research pharmacy will de-identify the drugs for distribution to each study center (with tracking of all product) and therefore will remain unblinded to treatment randomization and will be in charge of assigning the correct vials for dosing. Study staff, investigators, and subjects will remain blinded to treatment assignments.

## 4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is tenecteplase. This will be given to patients in combination with heparin, as outlined in section 3.3.1.





#### **4.3.1      Study Treatment Formulation, Packaging, and Handling**

##### **4.3.1.1      Tenecteplase**

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

Placebo will be supplied by Genentech as a sterile lyophilized powder in a 50 mg vial under partial volume that will be labeled as Tenecteplase Placebo 50mg.

For information on the formulation and handling of tenecteplase, see the local prescribing information for Tenecteplase or the Tenecteplase Investigator's Brochure.

#### **4.3.2      Study Treatment Dosage, Administration, and Compliance**

The treatment regimens are summarized in Section 3.3.1.

Any overdose or incorrect administration of tenecteplase or placebo should be noted in the patient's medical records and reported according to Section 5.5 (Special Situations Reports). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded in the patient's medical records.

##### **4.3.2.1      Tenecteplase**

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.

For information on the formulation and handling of tenecteplase, see the local prescribing information for Tenecteplase or the Tenecteplase Investigator's Brochure.

Please see section 3.3.1 for dosing schedule.

#### **4.4      CONCOMITANT THERAPY**

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, 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 treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded in the patient's medical records. Medications indicated as "prn" or "as needed" will not be reported in the EDC.

##### **4.4.1      Cautionary Therapy**

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, preventative vaccines, vitamins, nutritional supplements) used by a patient from 1 week prior to randomization to the patient's last visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.



Patients who use oral contraceptives or maintenance therapy for comorbidities should continue their use.

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.

#### **4.5              STUDY ASSESSMENTS AND PROCEDURES**

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 closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

#### **4.5.1          Informed Consent**

Written 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. Given the circumstances that may exist at sites due to COVID-19, sites will work with their IRBs to determine the best method of obtaining consent. This may be in person or electronically depending on requirements.

#### **4.5.2          Screening**

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

The following data points will be collected during the Screening timepoint.

- **Medical History, Concomitant Medication, and Demographic Data**

Medical history includes clinically significant diseases and procedures. All medication taken in the last 7 days prior to randomization (including prescription, over-the-counter, and

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herbal/homeopathic remedies and therapies) are to be recorded. Inpatient concomitant medications that are indicated as “prn” or “as needed” will not be recorded in the EDC. A detailed history of medication used for UC is required for the past 5 years.

Demographic data, including age, sex, and self-reported race/ethnicity will be collected.

- **Neurological Examinations**

A neurological examination will be performed according to the Schedule of Assessments. New or worsened abnormalities from screening will be recorded as adverse events if appropriate. In addition, a symptom-driven examination should be conducted as indicated in the Schedule of Assessments.

The neurological exam will be documented by a GCS score and NIHSS.

- **Vital Signs**

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure (via arterial line or BP cuff if arterial line is not in place), and temperature.

In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

- **Laboratory Samples**

Results from the following are required prior to randomization and should be processed locally:

- CBC: Platelet, WBC, Hb, Hct
- BMP: Na, K, Cl, HCO<sub>3</sub>, BUN, Cr
- Glucose (finger stick or lab)
- LFT: ALT, AST, Bili, Alk Phos, LDH, Total Protein, Albumin, D-dimer, fibrinogen, CRP, ferritin, troponin-I, BNP
- Coagulation: INR, aPTT, PT, anti-Xa
- Arterial Blood Gas: pH, pCO<sub>2</sub>, pO<sub>2</sub>, SaO<sub>2</sub>, Lactate
  - Will be conducted every 12 hours
- Thromboelastograms (when available according to standard practice)
- 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.

- **SARS-CoV-2 PCR Test**

A SARS-CoV-2 PCR Test will be conducted during screening to determine if the patient is COVID positive.

- **Respiratory Status / Ventilator Settings**

Respiratory or Ventilator settings will be collected at Screening.

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- Ventilator settings (if appropriate): RR, TV, PI (if PCV or PSV) FiO2, PEEP, Plateau Pressure
- NIPPV settings (if appropriate): RR, IPAP, EPAP, FiO2
- HFNC settings (if appropriate): FiO2, flow
- NRB settings (if appropriate): flow

- **Ordinal Scale Assessment**

The Ordinal Scale Assessment will be conducted daily to determine the patient's current status.

- **Imaging**

If the patient has a standard of care CT Scan or X-Ray performed, the imaging result will be captured in the Screening CRF.

#### **4.5.3      Pre-Randomization**

All study assessments during Pre-Randomization must be collected or confirmed within 2 hours of study drug administration.

- Neurological Exam
- Vitals
- Laboratory Samples

CBC: Platelet, WBC, Hb, Hct

BMP: Na, K, Cl, HCO3, BUN, Cr

Glucose (finger stick or lab)

LFT: ALT, AST, Bili, Alk Phos, LDH, Total Protein, Albumin, D-dimer, fibrinogen, CRP, ferritin, troponin-I, BNP

Coagulation: INR, aPTT, PT, anti-Xa

Thromboelastograms (when available according to standard practice)

- Respiratory Status / Ventilator Settings
- Ordinal Scale Assessment
- Concomitant medication review (excluding “prn” or “as needed” medications)

#### **4.5.4      Post-Randomization**

Post Randomization assessments will be collected every 6 hours up to 72 hours after study drug administration.

- Randomization and Study Drug Administration
- Neurological Exam



The subject will be evaluated every 15 minutes for the first hour following study drug administration. Evaluation will then occur every 30 minutes for 4 hours, then every hour for 12 hours. The neurological exam will be documented by a GCS score and NIHSS.

- Vitals

Vital signs should be measured every 15 minutes after study drug administration for one hour, then every hour for 4 hours, then every 6 hours.

- Laboratory Samples (q6 hours for 24 hrs and then daily for subsequent 48 hours)

Coagulation: INR, aPTT, PT, anti-Xa

Arterial Blood Gas: pH, pCO<sub>2</sub>, pO<sub>2</sub>, SaO<sub>2</sub>, Lactate

- Respiratory Status / Ventilator Settings
- Doses of all vasopressors every 6 hours for first 72 hours then daily
- Heparin Dosing

If subject was not previously on heparin, please begin infusion as specified in protocol. Begin heparin with tenecteplase infusion starting with bolus dose of 60 Units/kg IV once, followed by 12 Units/kg/hr. Heparin should be adjusted to achieve target PTT of 70-90 seconds.

- Concomitant medication review (excluding “prn” or “as needed” medications)

#### **4.5.5      Follow Up Period (Day 4 -27)**

The subject will have a daily follow up collecting all of the below assessments. If the patient reaches an aPTT value of 70-90 seconds, subsequently daily aPTT values will be record until discharge or Day 28.

- Neurological Exam
- Vitals
- Laboratory Samples (Standard of care)
- Respiratory Status / Ventilator Settings
- Ordinal Scale Assessment
- Imaging (Standard of Care)
- Concomitant medication review (excluding “prn” or “as needed” medications)

#### **4.5.6      End of Study (Day 28)**

The following assessments will be collected at the final End of Study timepoint if the patient is still admitted:

- Neurological Exam
- Vitals
- Laboratory Samples (Standard of care)

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Thromboelastograms (when available according to standard practice)

- Respiratory Status / Ventilator Settings
- Imaging (Standard of Care)
- Concomitant medication review (excluding “prn” or “as needed” medications)

The ordinal scale assessment will be completed at day 28 regardless of whether the patient is admitted or discharged.

#### **4.6 TREATMENT, PATIENT, AND STUDY DISCONTINUATION**

Patients must permanently discontinue study treatment (tenecteplase or placebo) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient’s potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient’s safety if he or she continues study treatment
- Investigator determines it is in the best interest of the patient
- Pregnancy
- Anaphylaxis or other severe hypersensitivity reaction
- Loss of clinical benefit as determined by the investigator after an integrated assessment of clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details)

The primary reason for study treatment discontinuation should be documented in the patient’s medical records. Patients who discontinue study treatment prematurely will not be replaced.

##### **4.6.1 Patient Discontinuation from Study**

Patients have the right to voluntarily withdraw from the study 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:

- Withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the Investigator

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 in the patient’s medical records. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.



If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

#### **4.6.2      Study Discontinuation**

The Investigator 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

### **5.            ASSESSMENT OF SAFETY**

#### **5.1            SAFETY PLAN**

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.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of tenecteplase, and the placebo, will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Refer to Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) during the study.

##### **5.1.1        Stopping Rules**

In the case of any Mortality during the 28 day follow up period, enrollment will be halted and DSMC/CEC review will be performed within 72 hrs of notification. The DSMC will then issue a report back to the study PI regarding their recommendation as to re-opening the study or permanently closing the study.

Should there occur, at any time during the study, a difference between the control and treatment cohorts of >2 intracerebral hemorrhages then the study will be halted. Per protocol, the DSMC/CEC will review all ICH's (SAE's). Following each of these individual case reviews (after analysis/interpretation locked), the DSMC/CEC statistician (who is unblinded, not the study statistician, who will remain blinded) will provide summary data on the ICH's according to cohort. If there is a greater than 2 ICH differential then the study will be halted. Additionally, the DSMC/CEC will be reviewing all enrollments, with summary statistics for each cohort (provided by the DSMC/CEC statistician) after each 15 patients are enrolled. They are empowered to halt study enrollment at each of these review points should there be safety concerns. After each of these planned DSMC/CEC reviews the DSMC/CEC will generate a formal report to provide to the study PI.

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## **5.1.2 Risks Associated with Tenecteplase**

Standard management of myocardial infarction 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.

### **5.1.2.1 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).

Should an arterial puncture be necessary during the first few hours following tenecteplase therapy, the use of an upper extremity vessel that is accessible to manual compression is preferable. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

Each patient being considered for therapy with tenecteplase should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

Guidelines for management of patients who develop bleeding are provided in [Table 1](#).

In addition, any ICH events (symptomatic and/or asymptomatic), 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 ).

### **5.1.2.2 Arrhythmias**

Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular

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premature depolarizations, ventricular tachycardia, etc.) are not different from those often seen in the ordinary course of AMI and may be managed with standard anti-arrhythmic measures. It is recommended that anti-arrhythmic therapy for bradycardia and ventricular irritability be available when tenecteplase is administered.

### **5.1.2.3 Thromboembolism**

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

### **5.1.2.4 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.

### **5.1.2.5 Use with Percutaneous Coronary Intervention**

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

## **5.1.3 Precautions**

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

### **5.1.3.1 Re-administration**

Re-administration of plasminogen activators, including tenecteplase, to patients who have received prior plasminogen activator therapy has not been systematically studied. Three of 487 patients tested for antibody formation to tenecteplase had a positive antibody titer at 30 days. The data reflect the percentage of patients whose test results were considered positive for antibodies to tenecteplase in a radioimmunoprecipitation assay and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to tenecteplase with the incidence of antibodies to other products may be misleading. Although sustained antibody formation in patients receiving one dose of tenecteplase has not been documented, re-administration should be undertaken with caution.

### **5.1.3.2 Hypersensitivity**

Hypersensitivity, including urticarial/anaphylactic reactions, have rarely (<1%) been reported after administration of tenecteplase (e.g., anaphylaxis, angioedema, laryngeal edema, rash, and Tenecteplase—Icahn School of Medicine at Mount Sinai  
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urticaria). Monitor patients treated with tenecteplase during and for several hours after infusion. If symptoms of hypersensitivity occur, appropriate therapy should be initiated.

### **5.1.3.3 Drug Interactions**

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 direct oral anticoagulants, heparin and vitamin K antagonists) and drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole, and GP IIb/IIIa inhibitors) may increase the risk of bleeding if administered prior to, during, or after tenecteplase therapy.

### **5.1.3.4 Drug/Laboratory Test Interactions**

During tenecteplase therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent in vitro artifacts. Tenecteplase is an enzyme that, when present in blood in pharmacologic concentrations, remains active under in vitro conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis.

## **5.1.4 Management of Patients Who Experience Adverse Events**

### **5.1.4.1 Management Guidelines**

Guidelines for management of specific adverse events are outlined in Table 1.

**Table 1 Guidelines for Management of Patients Who Experience Bleeding**

Event	Action to Be Taken
Bleeding	<ul style="list-style-type: none"><li>• In the event of serious bleeding, heparin and antiplatelet agents should be discontinued immediately and treated appropriately. Heparin effects can be reversed by protamine.</li><li>• Intramuscular injections and nonessential handling of the patient should be avoided for the first few hours following treatment with tenecteplase.</li><li>• Venipunctures should be performed and monitored carefully.</li><li>• 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.</li></ul>

Refer to Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.



## **5.2 SAFETY PARAMETERS AND DEFINITIONS**

Safety assessments will consist of monitoring and reporting adverse events and serious adverse events per protocol. This includes all events of death and any study-specific issue of concern.

### **5.2.1 Adverse Events**

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with AMI that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Pre-Existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

### **5.2.2 Serious Adverse Events**

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

### **5.2.3 Adverse Events of Special Interest**

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). Non-serious adverse events of special interest for this study are as follows:

- Any ICH events (symptomatic and/or asymptomatic), if not already reported as an SAE
- The non-drug specific AESIs:

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- 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.
- 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 ASSESSING AND RECORDING SAFETY VARIABLES**

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

#### **5.3.1 Adverse Event Reporting Period**

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of any study procedures and ends 28 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

#### **5.3.2 Assessment of Adverse Events**

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to tenecteplase (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

##### **Yes**

There is a plausible temporal relationship between the onset of the AE and administration of tenecteplase, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to tenecteplase; and/or the AE abates or resolves upon discontinuation of tenecteplase or dose reduction.

##### **No**

Evidence exists that the AE has an etiology other than tenecteplase (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to tenecteplase administration (e.g., cancer diagnosed 2 days after first dose of tenecteplase).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

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Unexpected adverse events are those not listed in the P.I. or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

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

## **5.4 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS**

### **5.4.1 Data Safety Monitoring/CEC**

A Data Safety Monitoring Committee/Clinical Events Committee (DSMC/CEC), compiled of 1 neurosurgeon, 1 pulmonologist, and 1 cardiologist, will review safety events throughout the trial. Review of clinical events will be done in a completely blinded fashion. Each event will be reviewed by all DSMC/CEC members and if discrepancy exists in their determinations, then consensus adjudication will be required. The committee will meet to review all Serious Adverse Events (SAEs) and unexpected and related Adverse Events (AEs) every 15 patients. For each 15 patient interval assessment, summary statistics for each cohort will be provided to the DSMC/CEC (after completion of all blinded clinical events review). Following each of these individual case reviews (after analysis/interpretation locked), the DSMC/CEC statistician (who is unblinded, not the study statistician, who will remain blinded) will provide summary data on the ICH's according to cohort. If there is a greater than 2 ICH differential then the study will be halted. Additionally, the DSMC/CEC will be reviewing all enrollments, with summary statistics for each cohort (provided by the DSMC/CEC statistician) after each 15 patients are enrolled. The DSMC/CEC will review SAEs, both related and unrelated, as well as unexpected and related AEs. If a mortality or related serious adverse event occurs, the committee will meet within 72hrs of reporting to review. The committee will have the power to recommend a halt in study enrollment, should there be a safety concern.

### **5.4.2 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?"

### **5.4.3 Specific Instructions for Recording Adverse Events**

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

#### **5.4.3.1 Diagnosis versus Signs and Symptoms**

If known at the time of reporting, a diagnosis should be reported 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, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.



### **5.4.3.2 Deaths**

All deaths that occur during the protocol-specified AE reporting period (see Section 5.2.2), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

### **5.4.3.3 Preexisting Medical Conditions**

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

### **5.4.3.4 Hospitalizations for Medical or Surgical Procedures**

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

- 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 not necessary because of the patient requirement for outpatient

### **5.4.3.5 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 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.





**Table 2 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 <sup>a</sup>
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 <sup>b, c</sup>
4	Life-threatening consequences or urgent intervention indicated <sup>d</sup>
5	Death related to adverse event <sup>d</sup>

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](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

<sup>a</sup> Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

<sup>b</sup> 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.

<sup>c</sup> 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.

<sup>d</sup> 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.

#### **5.4.4 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 3):

- 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 3 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	<u>An adverse event will be considered related, unless it fulfills the criteria specified below.</u> 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.

#### **5.4.4.1 Pregnancies**

If a female patient becomes pregnant while receiving tenecteplase or within 90±14 days after the last dose of tenecteplase, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported to Genentech as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female patient exposed to the tenecteplase should be reported to Genentech, Inc. as an SAE.

#### **5.4.4.2 Post-Study Adverse Events**

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior tenecteplase exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

Case Transmission Verification will be performed by both parties during this period to ensure successful transmission of Single case reports.

#### **CASE TRANSMISSION VERIFICATION OF SINGLE CASE REPORTS**

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via Dr Hooman Poor emailing Genentech a Quarterly line-listing documenting single case reports sent by Dr Hooman Poor to Genentech in the preceding time period.





The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Dr Hooman Poor to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

### **AEs of Special Interest (AESIs)**

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- 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:
- Treatment-emergent ALT or AST  $> 3 \cdot \text{ULN}$  in combination with total bilirubin  $> 2 \cdot \text{ULN}$
- Treatment-emergent ALT or AST  $> 3 \cdot \text{ULN}$  in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), 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

### **Exchange of Single Case Reports**

Dr Hooman Poor will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product.



Investigators must report all the above-mentioned single case reports adequately to Genentech within the timelines described below. The completed MedWatch forms should be faxed/emailed immediately upon completion to Genentech at the following contacts:

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints with an AE should be sent to:

Fax: 650-238-6067

Email: usds\_aereporting-d@gene.com

All Product Complaints without an AE should be sent to:

Phone: 800-334-0290

It is understood and agreed that the Sponsor will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study. [MR{SF2}]

These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met.

- **SADRs**

Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

- **Other SAEs**

Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **AESIs**

AESIs requiring expedited reporting shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.

- **Special Situation Reports**

- o **Pregnancy reports**

While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

- o **Pregnancies in Female Partners of Male Patients**

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Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 30 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

In addition to all AEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Genentech/Roche even in the absence of an Adverse Event within thirty (30) calendar days:

- Data related to product usage during breastfeeding
- Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error (including potentially exposed in case of medication errors or intercepted medication errors) or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Lack of therapeutic efficacy
- Drug interaction
- Use of a Medicinal Product in a Pediatric and Elderly population
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported

- Product Complaints

All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

#### **5.4.5 MedWatch 3500A Reporting Guidelines**

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (Section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication



#### **5.4.5.1 Follow-up Information**

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at <https://www.fda.gov/media/69876/download>

#### **5.4.6 Reporting to Regulatory Authorities, Ethics Committees and Investigators**

Hooman Poor, MD, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

Genentech will be responsible for the expedited reporting of safety reports originating from the Study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

Hooman Poor, MD will be responsible for the distribution of safety information to its own investigators, where relevant.

#### **Additional Reporting Requirements for IND Holders**

For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

#### **7 Calendar Day Telephone or Fax Report**

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of tenecteplase. An unexpected adverse event is one that is not already described in the tenecteplase Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

#### **15 Calendar Day Written Report**

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of tenecteplase. An unexpected adverse event is one that is not already described in the tenecteplase Investigator Brochure.



Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

**FDA fax number for IND Safety Reports:**

Fax: 1 (800) FDA 0178

**All written IND Safety Reports submitted to the FDA by the investigator must also be faxed to Genentech Drug Safety:**

Fax: (650) 225-4682 or (650) 225-4630

**And to the coordinating center:**

[Denise.Balili@mountsinai.org](mailto:Denise.Balili@mountsinai.org) or fax: 646-537-9656

**For questions related to safety reporting, please contact Genentech Drug Safety:**

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

## **5.5 AGGREGATE REPORTS**

### **IND ANNUAL REPORTS**

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: [ctvist\\_drugsafety@gene.com](mailto:ctvist_drugsafety@gene.com)

hyperlink to email: [ctvist\\_drugsafety@gene.com](mailto:ctvist_drugsafety@gene.com)

### **Other Reports**

Hooman Poor will forward a copy of the Publication to Genentech upon completion of the Study.

*Note: Investigators should also report events to their IRB as required.*

### **Randomization Codes for Blinded Clinical Trials**

The blind will be broken for ADR reports that are Serious and Unexpected, unless otherwise agreed with applicable regulatory authorities.

## **5.6 STUDY CLOSE-OUT**

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study

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report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned

Clinical Operations contact for the study: [lytics-gsur@gene.com](mailto:lytics-gsur@gene.com)

hyperlink to email: [lytics-gsur@gene.com](mailto:lytics-gsur@gene.com)

[lytics-gsur@gene.com](mailto:lytics-gsur@gene.com)

And to Genentech Drug Safety CTV oversight mail box at: [ctvist\\_drugsafety@gene.com](mailto:ctvist_drugsafety@gene.com)

hyperlink to email: [ctvist\\_drugsafety@gene.com](mailto:ctvist_drugsafety@gene.com)

## QUERIES

Queries related to the Study will be answered by Hooman Poor, MD. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. Hooman Poor, MD agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

## 6. STATISTICAL CONSIDERATIONS

### 6.1 DETERMINATION OF SAMPLE SIZE

Assuming a total of 60 subjects enrolled with a 2:1 ratio in the tenecteplase:control arms and a good outcome rate of 15% in the control arm, this study has approximately 70% power to detect an absolute difference of 35% in the good outcome rate between the combined tenecteplase arms (40 patients) and the control arm (20 patients) and approximately 55% power to detect an absolute difference of 35% between each of the tenecteplase arms (20 patients) and the control arm (20 patients), at the 2-sided 0.05 significance level based on the Fisher's exact test. Good outcome rate is defined as the proportion of patients who are alive and free of respiratory failure at 28 days. If the true rate of symptomatic ICH or major bleeding requiring transfusion is 3%, the chance of observing at least one of these events in 20 patients is at least 45%. The chance of observing at least one event in 20 patients increases to at least 70% if the true event rate is 6%.

### 6.2 PRIMARY EFFICACY VARIABLE

Data will be analyzed according to clinical status at day 28. Outcome will be the proportion of patients who are alive and free of respiratory failure (no use of HFNC, NIPPV, Intubation). All other patients, those on HFNC, NIPPPV, or mechanical ventilation, or dead, will be assessed as

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failures for the purposes of the primary analysis. In the case of missing data, a last carry forward methodology will be used.

### **6.3 PRIMARY SAFETY VARIABLE**

Data will be analyzed according to the occurrence, at any time between tenecteplase administration and day 28, of intracranial hemorrhage or major bleeding event (defined above). Outcome will be the proportion of patients who have suffered no intracranial hemorrhage or major bleeding event. Those patients who have suffered an intracranial hemorrhage or major bleeding event will be assessed as failures for the purposes of the safety analysis.

### **6.4 ONGOING SAFETY ANALYSIS**

Should there occur, at any time during the study, a difference between the control and treatment cohorts of >2 intracerebral hemorrhages then the study will be halted. Per protocol, the DSMC/CEC will review all ICH's (SAE's). Following each of these individual case reviews (after analysis/interpretation locked), the DSMC/CEC statistician (who is unblinded, not the study statistician, who will remain blinded) will provide summary data on the ICH's according to cohort. If there is a greater than 2 ICH differential then the study will be halted. Additionally, the DSMC/CEC will be reviewing all enrollments, with summary statistics for each cohort (provided by the DSMC/CEC statistician) after each 15 patients are enrolled. They are empowered to halt study enrollment at each of these review points should there be safety concerns. After each of these planned DSMC/CEC reviews the DSMC/CEC will generate a formal report to provide to the study PI.

### **6.5 METHOD OF ANALYSIS**

Continuous and categorical variables will be presented and summarized by using means with standard deviations and frequencies with percentages respectively. Tukey's method for pairwise comparison and large sample based multiple comparison of logits will be performed for continuous variables. Logistic regression modeling will be used for covariates adjustments and subgroup analyses. Survival functions will be estimated by applying Kaplan-Meier method. Statistical testing will be performed at two-sided 5% level of significance.

## **7. INVESTIGATOR REQUIREMENTS**

### **7.1 RETENTION OF RECORDS**

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

For studies conducted outside the U.S. under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.





## **7.2 STUDY MEDICAL MONITORING REQUIREMENTS**

This clinical research study will be monitored both internally by the PI and externally by the Icahn School of Medicine IRB. In terms of internal review, the PI will continuously monitor and tabulate AEs. Appropriate reporting to the Icahn School of Medicine IRB will be made. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Stopping rules for toxicity and/or response are met,
- Risk/benefit ratio is not altered to the detriment of the patients,
- Appropriate internal monitoring of AEs and outcomes is done,
- Over-accrual does not occur,
- Under-accrual is addressed with appropriate amendments or actions, and
- Data are being appropriately collected in a reasonably timely manner.

Routine monitoring will be carried out via a periodic team conference among investigators during which toxicity data, including all SAEs, will be reviewed and other issues relevant to the study such as interim assessment of accrual, outcome, and compliance with study guidelines, will be discussed. Monitoring will be carried out on an ongoing basis. The severity, relatedness, and whether or not the event is expected will be reviewed.

## **7.3 STUDY MEDICATION ACCOUNTABILITY**

The Sponsor Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62 and Genentech requirements.

All unused remaining product at the end of the study should be disposed of at the study site according to institutional standard operating procedure. If there is no SOP at the site for drug destruction, return study drug with the Inventory of Returned Clinical Material form as directed by Genentech.

## **7.4 DATA COLLECTION**

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are recorded on the appropriate forms and in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed, and dated by the study coordinator or PI. All source documents will be available for inspection by the FDA and the Icahn School of Medicine IRB.

## **7.5 DATA MONITORING**

The entire study will be conducted using an electronic data acquisition method where all clinical data on enrolled subjects will be data entered (single-keyed) by the site personnel into a web-based data management system, REDCap. In order to provide user-friendly and easy-to-navigate interfaces, the REDCap data capture screens are designed based upon individual CRFs. Prior to study start, the system is validated to ensure the data entry screens mirror the CRFs and that the pre-programmed data rules appropriately detect incorrect data. The data will be managed after data entry via data queries from the study monitor. Monitoring will be conducted in real time, allowing for early identification of adverse events and protocol Tenecteplase—Icahn School of Medicine at Mount Sinai  
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deviations. This user-friendly web-based database system, developed and validated by the study team, will be used for subject data entry, data validation, project progress monitoring, subject tracking, coordination of safety review, randomization, user customizable report generation and secure data transfer.

## **8. ETHICAL CONSIDERATIONS**

### **8.1 COMPLIANCE WITH LAWS AND REGULATIONS**

Patients who comply with the requirements of the protocol, are tolerating study treatment, and may be receiving benefit will be offered dosing beyond Cycle 1 at the investigator's discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Such patients may have the option to receive MPDL3280A treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in [Section 4.6](#).

### **8.2 INFORMED CONSENT**

The informed consent document must be signed by the patient or the patient's legally authorized representative before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each patient's study file and must be available for verification by study monitors at any time.

### **8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE**

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant AEs.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the Investigator's Brochure and that are considered possibly or probably related to the tenecteplase or study drug by the investigator. Some IRBs may have other specific AE requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Genentech (e.g., IND safety report, Investigator's Brochure, safety amendments and updates, etc.).



#### **8.4 CONFIDENTIALITY**

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the patient or 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.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Genentech representatives and collaborators, and the IRB/Ethics Committee (EC) for each study site, if appropriate.



## 9. REFERENCES

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## Appendix 1

### Study Flowchart

	Screening	Enrollment/Randomization <sup>a</sup>		Follow Up Period (Day 4 to 27 post randomization)	End of Study (Day 28 OR Discharge)
		Pre-Randomization (must be collected within 2 h of study drug administration)	Post Randomization q6 hr. to 72 hr.		
Informed Consent	x				
Demographics	x				
Medical History	x				
Inclusion/Exclusion Criteria	x	x			
Weight for Dosing	x				
Vital Signs <sup>b</sup>	x	x	x	x	x
PCR COVID Test	x				
Lab Testing <sup>c</sup>	x	x	x <sup>d</sup>	SOC	SOC
Arterial Blood Gas <sup>e</sup>	x	x	x <sup>*</sup>	SOC	
Respiratory Status/Ventilator Settings <sup>f</sup>	x	x	x	x <sup>**</sup>	x
Ordinal Scale	x	x	x	x	x
Neurological Exam <sup>g</sup>	x	x	x	x	x
Vasopressor Dosing	x	x	x	x	
TNK-tPA Dosing			x		
Heparin Dosing <sup>h</sup>	x <sup>***</sup>	x <sup>***</sup>	x	x	
Imaging <sup>i</sup>	SOC		SOC	SOC	SOC
Pregnancy Test <sup>j</sup>	x				
Adverse Events/ SAE Review <sup>k</sup>	x	x	x	x	x
Concomitant Medications	x	x	x	x	x



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## Appendix 1: Study Flowchart

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- a. Randomization will be done using an escalating-dose randomized design. It will be block randomization of 10:5 (treatment:control) performed twice per dose of TNK-tPA. If no safety triggers occur after 20 patients enrolled at the low dose, then the high dose enrollment will be undertaken with block randomization of 10:5.
- b. Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressure and temperature. Vitals are to be measured within 60 minutes prior to each tenecteplase infusion and, if clinically indicated, during or after the infusion.
- c. Labs to be collected include: CBC: Platelet, WBC, Hb, Hct; BMP: Na, K, Cl, HCO<sub>3</sub>, BUN, Cr; Glucose (finger stick or lab); LFT: ALT, AST, Bilirubin, Alkaline Phosphatase, LDH, Total Protein, Albumin, D-dimer, fibrinogen, CRP, ferritin, troponin-I; Coagulation: INR, aPTT, Anti-Xa, PT (only if the patient is taking an anticoagulant); Thromboelastograms
- d. Only coagulation labs need to be checked every 6 hours post randomization which includes: INR, aPTT, PT (only if the patient is taking an anticoagulant)
- e. Arterial blood gases to be collected include: Arterial Blood Gas: pH, pCO<sub>2</sub>, pO<sub>2</sub>, SaO<sub>2</sub>, Lactate
- f. Ventilator/Respirator Setting settings to be collected include: RR, TV, PEEP, Plateau Pressure; NIPPV settings (if appropriate): RR, IPAP, EPAP, FiO<sub>2</sub>; HFNC settings (if appropriate): FiO<sub>2</sub>, flow
- g. Neurological exams are to be performed every time room access is breached.
- h. For patients already on therapeutic heparin, continue heparin infusion. For patients not already on heparin or other anticoagulant, begin heparin with tenecteplase infusion starting with bolus dose of 60 Units/kg IV once, followed by 12 Units/kg/hr. For patients who were receiving enoxaparin at time of inclusion, tenecteplase infusion can be given immediately. Delay heparin to 12 hours after the most recent enoxaparin dose, beginning at an infusion rate of 18 Units/kg/hr. Do not administer a bolus dose of heparin and check PTT every 6 hours; adjust heparin to achieve target PTT of 70-90 seconds.
- i. All image collection should follow institution specific standard of care guidelines.
- j. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ( $\geq 12$  continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). 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.
- k. All AEs that occur after signing the ICF and up to the EOS visit must be recorded. AEs for this study protocol include: bleeding, hypersensitivity, thromboembolism, cholesterol embolization and arrhythmias. post-permanent SD discontinuation.
  - \* To be performed q12h.
  - \*\* To be performed daily until a 2 point improvement in the ordinal scale assessment OR until 27 days OR until death OR discharge.
  - \*\*\* For patients already on heparin.



## Appendix 2

### Safety Reporting Fax Cover Sheet



#### **SAFETY REPORTING FAX COVER SHEET**

##### **GENENTECH SUPPORTED RESEARCH**

AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Patient Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]
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SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET



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## **Appendix 3**

### **FDA MedWatch 3500 Form**

This form is included in the study start-up zip file to be sent to sites via email.



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