PROTOCOL

TITLE:	**LOW-DOSE TENECTEPLASE IN COVID-19 PATIENTS WITH ACUTE PULMONARY EMBOLISM: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL**
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GLOSSARY OF ABBREVIATIONS	
ADR	adverse drug reaction
AE	adverse event
AHA	American Health Association
AIS	acute ischemic stroke
ALI	acute lung injury
ARDS	acute respiratory distress syndrome
AV	arteriovenous
AMI	acute myocardial infarction
BFR	blood-flow rate
CCDS	company core data sheet
CT	computed tomography
CVCs	central venous catheters
DIC	disseminated intravascular coagulation
EVT	endovascular treatment
ED_{50}	effective dose at which 50% of a clot is lysed
GD	gestational day
HD	hemodialysis
ICH	International Conference on Harmonisation
IH	intracranial hemorrhage
IQR	interquartile range
IV	intravenous
MAD	Mutual Acceptance of Data
MCA	middle cerebral artery
NOAEL	No-observed-adverse-effect-level
PAI-1	plasminogen activator inhibitor 1
PCI	percutaneous coronary intervention
PE	pulmonary embolism
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
VTE	venous thromboembolism

1. BACKGROUND

- There is a knowledge gap associated with the management of patients with COVID-19 lung injury and a laboratory picture compatible with disseminated intravascular coagulation (DIC). Clinical data to date support that COVID-19 is associated with a prothrombotic state that is not simply explained by an influx of more critically ill individuals.
- These patients suffer from severe respiratory failure; hypoxemia and ventilator dependence are the primary concerns; ARDS with respiratory failure is frequently the cause of death. Macroscopic and probable microvascular thromboembolic events are a major concern in this population.
- When DIC is associated with COVID-19, it predicts a very poor prognosis.
- We plan to evaluate the clinical efficacy and safety of low-dose IV bolus tenecteplase (TNK) together with anticoagulation compared with control patients on therapeutic anticoagulation alone in hospitalized adults diagnosed with COVID-19 and acute intermediate-risk PE. We believe that acute PE in the setting of active COVID-19 infections likely portend a poor prognosis.
- Prospective, multicenter, randomized two-arm trial enrolling consecutive patients who meet enrollment criteria.
- We hope to generate evidence that low-dose TNK together with anticoagulation is beneficial in these patients.
- The primary outcome will be based upon improvement in shock index with secondary endpoints focusing on other parameters.
- The planned sample size is 45 patients (5 sites). Subjects will be assessed daily while hospitalized. Subjects discharged from the hospital will be asked to attend study visits at Days 15 and 30 (telephone / telemedicine, clinic or inpatient ward).

1.1 BACKGROUND ON COVID-19 INFECTION, INFLAMMATION AND THROMBOSIS

COVID-19: Current statistics. At the present time (January 13, 2021) there are over 92.7 million cases of COVID-19 infection world-wide with nearly 2 million reported deaths. In the U.S., there have been 23.6 million cases and nearly 400,000 deaths reported (1). It is unclear if this pandemic will continue, be seasonal, or will worsen in the future based upon continued mutations. An interesting genetic fact is that it took the genome of the human species 8 million years to evolve by 1%. *Many animal RNA viruses can evolve by > 1% in a few days*. It is not surprising that we have seen the emergence of zoonotic viruses (2). The current COVID-19 pandemic has had catastrophic health, economic, and psychological impact on the entire world.

COVID-19: Clinical presentation and laboratory coagulation parameters. Before focusing on acute PE, we will briefly focus on aspects of COVID-19 infection and its relationship to inflammatory and coagulation parameters. A key feature of severe COVID-19 infection has been abnormal coagulation parameters, and a recent study has demonstrated that 71.4% of patients who die of COVID-19 meet International Society of

Thrombosis and Haemostasis (ISTH) criteria for disseminated intravascular coagulation (DIC) with a distinct minority (0.6%) of patients who survive meeting these criteria (3).

These patients clinically appear to have a predominantly prothrombotic state rather than a bleeding diathesis (4). They often have very high D-dimer levels, high fibrinogen and low antithrombin levels (5,6). In one large retrospective single-center review from China, while D-dimer levels were often normal at admission, they tended to be higher in critically ill patients (6). This suggests that fibrin deposition in the pulmonary microvasculature may contribute to the acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) and would be *particularly likely* to be seen in patients with ARDS and concomitant DIC as is observed in more than 70% of patients who succumb to COVID-19 (3).

Acute venous thromboembolism (VTE) is common in COVID-19 patients as is central line thrombosis and vascular occlusion including ischemic limbs, and cerebrovascular accidents (5-7). We have seen clotted off CRRT lines and other vascular circuits. In one autopsy case, hemorrhagic necrosis was found on gross examination and was primarily present in "outer edge of the right lobe of the right lung (8)." However, clinical hemorrhage from the lung or other bleeding diathesis appear to be very rare in COVID-19 patients with acute lung injury and DIC. Unfortunately, almost no detailed autopsy data in COVID-19 lung injury are available.

Acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) in the pre-COVID era. While it is well-known that high-risk (massive) PE is common in critically ill patients and may benefit from systemic thrombolysis, acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) are characterized by excessive intra-alveolar fibrin deposition, driven, at least in part, by inflammation (9). The imbalance between activation of coagulation and inhibition of fibrinolysis in patients with ALI and ARDS was demonstrated prior to the "COVID era," and favors fibrin formation and appears to develop not just systemically, but also in the lung and airspace (TF ref). With the advent of COVID-19, *it appears that we are seeing ARDS with micro and macrothrombotic potential.*

A key aspect of the pathophysiology of ALI and ARDS in the "pre-COVID-19 era" is the presence of fibrin-rich exudative hyaline membranes which develop in lung alveoli due to activation of coagulation and inhibition of fibrinolysis; i.e., a *balance that is shifted in a procoagulant / antifibrinolytic direction* favoring fibrin formation (9). Despite extensive research in this area, the direct effects of activation of coagulation on inflammatory pathways and perpetuation of lung injury are not still well understood (10). While clinical studies targeting the coagulation cascade in patients with, or at risk of lung injury have been interesting and promising, there have been no major breakthroughs impacting on mortality (11). One reason for this lack of impact may have been the population of ALI/ARDS patients studied.

It has been demonstrated that BAL fluid from ARDS patients has decreased fibrinolytic activity compared with normal control subjects (12). Furthermore, plasminogen activator inhibitor-1 (PAI-1) levels in plasma and edema fluid have been shown to be higher compared with controls with hydrostatic pulmonary edema (13). PAI-1 levels have also been shown to be higher in the plasma of ARDS patients than in controls (14,15). Genetics may play a role in susceptibility as well (10,16). More work needs to be done to fully characterize the fibrinolytic pathway and its modulation in patients with ALI/ARDS as

potential therapies could also be directed at this pathway. The prothrombotic phenotype that we are seeing in COVID-19 patients appears particularly appropriate to study.

Thrombolytic therapy for ALI/ARDS in the pre-COVID era. Few well-controlled experimental and clinical studies on the role of fibrinolytic agents in modulating lung inflammation and injury have been completed and results of these studies have been mixed. In a pig model of lung injury induced by trauma, intravenous (IV) administration of urokinase or tissue-type plasminogen activator (tPA) was protective (17). Other models of lung injury have shown attenuation of bleomycin-induced fibrosis after administration of urokinase, either by inhalation, instillation or injection (18). An early-phase (non-COVID) clinical trial demonstrated the ability of both urokinase and tPA to improve lung function as evidenced by improvement in hypoxemia in a small group of ARDS patients (19). Finally, tPA has been shown to inhibit interleukin-1 induced acute lung leak in an animal model of lung injury, suggesting that tPA may suppress neutrophil activation in vivo and have anti-inflammatory effects (20). While data have been less impressive with urokinase, it may be that these plasminogen activators modulate lung inflammation and injury differentially depending on the underlying cause of lung injury or the route of administration of the drug.

There may be a number of reasons for unsuccessful human trials, prior to the COVID-19 era. These would appear to include heterogeneous patient populations, insufficient understanding of drug activity, interactions and metabolism in humans, and need for optimization of timing of therapeutic interventions, doses and duration of therapy. In addition, adverse effects in humans, which were not observed in experimental models, have also contributed to limited success with these strategies. In addition, many of the published clinical studies have been conducted in patients with *sepsis*, and have not been targeted specifically at ALI and ARDS. Finally, COVID-19 patients with lung injury appear to have a more severely prothrombotic tendency than patients with ALI/ARDS of other etiologies. We have witnessed this in our population of COVID patients and this concept is strongly supported in the rapidly evolving COVID literature, thus far.

Thus, more trials in targeted patient populations are necessary to investigate efficacy and safety. No data with tenecteplase exist but clinical data supporting its fibrinolytic activity in stroke (21), myocardial infarction (22), venous thromboembolism (23-25), and peripheral arteries and veins (26), and thus clear antifibrinolytic activity in numerous settings, together with administration by IV bolus make it ideal to study in COVID-19 related lung injury with DIC. A clear reason why bolus thrombolytic dosing is favored in the COVID era is based on reducing nursing exposure.

Finally, it should be noted that two separate documents have been published in March 2020, offering guidance about coagulation testing and management of coagulopathy and bleeding in COVID-19 patients (27,28). Both are based on clinical practice from the pre-COVID-19 era together with recent observations on COVID-19 patients. The two sets of recommendations are quite similar. The International Society of Thrombosis and Haemostasis (ISTH) suggests that patients with markedly elevated D-dimer level (arbitrarily defined as a 3-4-fold increase) should be considered for hospital admission even in the absence of other disease severity symptoms (27). In addition, it is recommended that all patients who require hospital admission for COVID-19 infection

should receive prophylactic dose low molecular weight heparin (LMWH), unless there are contraindications (e.g., active bleeding and platelet count < 25 x 10^9/L). While some institutions are setting threshold values upon which to start therapeutic dose anticoagulation based on certain D-dimer or fibrinogen thresholds (personal communication) there are not yet clinical trial data to support this. However, trials are ongoing (29-31).

Acute Pulmonary Embolism in the Setting of COVID-19 Infection.

See Section 1.5 below.

1.2 CURRENT THERAPIES AND UNMET MEDICAL NEED RELATED TO COVID-19 PNEUMONIA/ARDS AND DIC IN PATIENTS WITH ACUTE THROMBOEMBOLIC EVENTS

At this time, only remdesivir and convalescent plasma have Emergency Use Authorization by the United States Food and Drug Administration for the treatment of patients with COVID-19. Given the results of studies outlined above, intravenous tenecteplase, along with therapeutic anticoagulation (standard of care treatment), could provide efficacy and offer the potential to treat COVID-19 patients with thromboembolic disease more effectively than anticoagulation alone. Safety data have previously been generated on the use of tenecteplase higher than proposed dosages in other indications, including myocardial infarction and stroke. A study to assess safety and efficacy of intravenous tenecteplase plus standard of care in hospitalized patients with severe COVID-19 pneumonia and acute pulmonary embolism is justified to address the high unmet public health need and burden of disease in this severely ill population.

1.3 BACKGROUND ON TENECTEPLASE

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

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. Outside US and Canada (except Japan), METALYSE® (tenecteplase) is indicated for the thrombolytic treatment of AMI.

1.3.1.1 Acute Myocardial Infarction

Following administration of 30, 40, or 50 mg of tenecteplase for use in mortality reduction associated with acute myocardial infarction (AMI), decreases in circulating fibrinogen (4%–15%) and plasminogen (11%–24%) were observed (Refer to the Tenecteplase United States Package Insert [USPI]). The clinical significance of fibrin specificity on safety (e.g., bleeding) or efficacy has not been established. Biological potency is determined by an *in vitro* clot lysis assay and is expressed in tenecteplase-specific units. The specific activity of tenecteplase has been defined as 200 units/mg.

In patients with AMI, tenecteplase administered as a single bolus exhibits a biphasic disposition from the plasma. Tenecteplase was cleared from the plasma with an initial half-life of 20 to 24 minutes. The terminal phase half-life of tenecteplase was 90 to 130 minutes. In 99 of 104 patients treated with tenecteplase, mean plasma clearance ranged from 99 to 119 mL/min (see the tenecteplase USPI). Refer to the *Tenecteplase Investigator's Brochure* for additional details on nonclinical and clinical studies.

1.4 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.

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 to 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*.

1.4.3 Previous Clinical Development

Study N0747g (ASSENT-2; BI Study: 1123.4)

This Phase III, randomized, double-blind, double-dummy (i.e., patients received either tenecteplase and alteplase placebo or alteplase and tenecteplase placebo) mortality trial enrolled patients with AMI for study. The primary objective of the study was to compare the mortality of patients 30 days after treatment on the basis of a nonparametric method adjusted for age, baseline systolic blood pressure, baseline heart rate, baseline Killip class, and infarct location. The study has completed.

Study N3698g (TROPICS 1)

Study N3698g was a Phase III, randomized, double-blind, placebo-controlled study of patients with dysfunctional central venous catheters. The primary efficacy endpoint of the study was the cumulative rate of catheter function restoration after 1 dose of study drug (placebo or tenecteplase) with up to a 120-minute dwell time. The study has completed.

Study N3699g (TROPICS 2)

This Phase III, open-label, single-arm study assessed CVC function and restoration after instillation of up to a maximum of 2 doses of the study drug (placebo or tenecteplase) with up to a 120-minute dwell time. The study has completed.

Study N3700g (TROPICS 3)

This Phase III, randomized (1:1), double-blind, placebo-controlled study evaluated the incidence of hemorrhagic, thrombotic, or infectious complications in 149 patients with dysfunctional tunneled hemodialysis catheters. The study has completed.

Study N3701g (TROPICS 4)

Study N3701g was a Phase III, open-label study of patients who required hemodialysis (HD), and who had a dysfunctional HD catheter. The primary outcome of the study was blood-flow rate (BFR) $\geq$ 300 mL/min and absolute change in BFR of $\geq$ 25 mL/min at an associated arterial pressure of $-$240 to $-$280 mmHg noted at both 30 min ($\pm$ 10 min) and at the end of HD. The study has completed.

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

ALI and ARDS are characterized by profound imbalances between coagulation and fibrinolysis. Fibrin deposition in the alveolar spaces is a hallmark of this clinical syndrome that most likely results from inflammation-induced activation of the coagulation cascade and impairment of fibrinolysis. In COVID-19 patients with lung injury, the more frequent development of a DIC picture increases this prothrombotic state and increases mortality. There is a knowledge gap associated with the management of patients with COVID-19

lung injury and a laboratory picture compatible with DIC. These patients suffer from severe respiratory failure; hypoxemia and ventilator dependence are the primary concerns; ARDS with respiratory failure is frequently the cause of death. Patients with COVID-19 may well be prothrombotic independent of their reduced mobility and critically ill status.

1.5.1 Acute Pulmonary Embolism in the Setting of COVID-19 Infection

Early data suggest that therapeutic anticoagulation may reduce mortality in COVID-19 patients without proven PE (32). Notably, compelling data from a very large (2,700 patient) cohort in May 2020 suggest that therapeutic anticoagulation may be associated with a lower mortality in COVID patients requiring mechanical ventilation (33). Randomized trial data are needed.

COVID VTE data also suggest an increase in acute DVT and PE; i.e., “macroscopic VTE” in COVID patients. This may well be explained by a prothrombotic tendency with this virus, rather than simply more critically ill patients (34,35). This is strongly supported by more anecdotal data in the New York area (personal communication). Thus, more aggressive therapy in these patients should be considered, on an individual careful basis as randomized data are collected.

A recent autopsy study of 12 COVID patients from Hamburg, Germany demonstrated that the cause of death was massive PE in four of the 12 cases. In the seven patients with DVT, all were bilateral (36).

Finally, it has been suggested that elevated maximum clot strength by TEG testing is predictive of COVID-19 status despite a high level of suspicion in negative patients with normal TEG results (37). While these results require a larger cohort for confirmation, TEG testing could improve confidence in negative COVID-19 testing results in suspected patients and ***perhaps suggest the need for more aggressive therapy in acute PE***.

The overall objective of the study is to evaluate the clinical efficacy and safety of IV bolus tenecteplase (TNK) in hospitalized adults diagnosed with COVID-19 lung infection and proven acute PE.

We propose a therapeutic strategy aimed at enhancing fibrinolysis in these patients. We believe that *low-dose* IV tenecteplase (0.25 mg/kg) followed by therapeutic anticoagulation could prove to hasten patient recovery and shorten hospitalization in those with COVID-19 induced lung infection and intermediate-risk acute PE with or without features of DIC. We will, however, measure inflammatory parameters and coagulation parameters in hopes of learning more about their role in COVID patients with acute PE.

We believe these PE patients can be successfully treated without significantly increasing the risk of major bleeding. We believe this could prove to improve recovery rates, shorten hospitalization time, and perhaps ultimately prove to improve survival as well as reducing post-ICU morbidity in these patients.

2. OBJECTIVES AND ENDPOINTS

2.1 PRIMARY ENDPOINTS

The primary endpoint is percent improvement in **shock index** (HR/SBP) 6 hours after the TNK/placebo bolus. For example, a patient may start with a heart rate of 100/min and systolic BP of 100 mm Hg (shock index = 1) and after therapy, HR might be 90, with systolic BP of 110 mm Hg (shock index of 0.81), an improvement of 19%.

2.2 SECONDARY ENDPOINTS

1. Clinical status at 24 hours after administration of TNK/placebo based upon 7-point scale. Assessment of patient status using an ordinal scale will be recorded at baseline and once daily in the morning while hospitalized. The ordinal scale categories are as follows:
   - Level 1: Discharged (or "ready for discharge" on ambient air or $\leq$ 2L supplemental O2)
   - Level 2: Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental O2
   - Level 3: Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental O2
   - Level 4. ICU or non-ICU, requiring non-invasive ventilation or high-flow O2
   - Level 5. ICU, requiring intubation and mechanical ventilation
   - Level 6: ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g. vasopressors, renal replacement therapy)
   - Level 7: Death
2. Clinical status at Day 7 after administration of TNK/placebo based upon the same 7-point ordinal scale.
3. Clinical status at Day 28 after administration of TNK/placebo based upon the same 7-point ordinal scale.
4. O2 sat / FIO2 ratio 6 hours and 24 hours after administration of TNK/placebo, as a practical, noninvasive, and reliable surrogate for pO2 / FIO2 (see refs).
5. Percentage change in shock index 24 hours after TNK/placebo
6. Percent change in RV/LV ratio by echocardiogram 24 hour after TNK/placebo
7. Number of post-enrollment days with O2 requirement $\leq$ 4L/min at Day 7
8. Number of post-enrollment days with no O2 requirement at Day 7
9. Change in D-dimer level 24 hours after enrollment
10. Change in D-dimer level at Day 7 (if obtained)
11. Change in ferritin, C-reactive protein (CRP), IL-6 levels 24 hours after TNK/placebo dose
12. Post-enrollment documented new clinical thrombotic events at Day 7
13. All-cause mortality at day 7 and day 30

2.2.1 Exploratory Efficacy Objectives

1. We will examine characteristics of patients prior to bolus by measuring static measurements of hemostasis including D-dimer, PT/PTT, INR, and fibrinogen. In addition, thromboelastography (TEG) will be performed (TEG 6s or TEG 5000) if sites have the ability to perform this test.
2. If TEG is available at a site, it will be performed immediately prior to study drug administration, 10 minutes (+ 5 min) after the bolus and 24 (+/- 6) hours after study drug administration. The 24 hour TEG is optional. *If the initial, pre-bolus TEG is not performed for any reason, the following post-bolus TEG(s) need not be performed.*

2.3 SAFETY ENDPOINTS

Safety outcomes will be defined as:

1. **Hemorrhagic stroke** (including hemorrhagic conversion of ischemic stroke) within 7 days after randomization, extracranial major (moderate or severe) bleeding within 7 days, and serious adverse events within 30 days.
2. **Major bleeding** (excluding intracranial hemorrhage) within 7 days of TNK administration is defined as moderate or severe bleeding:
    - **Moderate bleeding:** A bleeding episode requiring blood transfusion(s), but not deemed life-threatening and not leading to hemodynamic compromise requiring emergency fluid replacement, inotropic support, or interventional treatment.
    - **Severe bleeding:** 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 (such as diffuse alveolar hemorrhage). In addition, any bleeding in a critical site (e.g., intracranial, pericardial, retroperitoneal). Bleeding in critical sites will be noted separately.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a prospective, double-blind, placebo-controlled study randomizing patients with acute intermediate-risk PE who meet enrollment criteria in a 2:1 manner into intervention (TNK) versus placebo arms, respectively. We will have up to 5 sites. After 18 patients are enrolled, a safety assessment will be performed by an independent Data and Safety Monitoring Board, and if a safety issue arises, it will be considered and discussed among the Investigators. The planned sample size is 45 patients (30 treatment and 15 control). Subjects will be assessed daily while hospitalized. Subjects discharged from the hospital will be asked to attend study visits at Days 14 and 30 (telephone / telemedicine, clinic or inpatient ward).

The overall objective of the study is to evaluate the clinical efficacy and safety of IV bolus tenecteplase (TNK) and therapeutic anticoagulation compared with placebo and therapeutic anticoagulation in hospitalized adults diagnosed with COVID-19 infection and acute intermediate-risk PE.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for last follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 1 month after the last patient is enrolled.

3.3 RATIONALE FOR STUDY DESIGN

These are described in Section 1.2 and Section 1.5.

3.3.1 Rationale for Tenecteplase Dose and Schedule

We are treating patients with intermediate-risk PE, thus, lower dose TNK is prudent.

3.3.2 Rationale for Patient Population

COVID-19 appears to be a prothrombotic state. These patients are very susceptible to acute VTE and we believe they may be susceptible to a pulmonary microvascular process as well, which potentially could occur with or without the acute “macroscopic” PE. Intermediate-risk PE have a higher rate of poor outcomes than low-risk PE and could potentially benefit from more aggressive therapy. We believe COVID patients with acute intermediate-risk PE could be at even higher risk for deterioration.

3.3.3 Rationale for Double-blind, Placebo-controlled Study

This design was chosen because of the critical importance of an accurate assessment of the risk/benefit. In this patient population, we are acutely aware of the bleeding risk of anticoagulation and while TNK could increase this risk compared with placebo, our team and the clinical teams will be following the patients very closely clinically. It is also standard of care in such patients to check a CBC daily to monitor for potential bleeding or thrombocytopenia. Thus, we feel that being blinded to treatment choice will be safe. Based on the lack of available evidence regarding response to anticoagulation in COVID PE patients and the lack of proven benefit from thrombolysis in these patients, administration of placebo is ethical.

3.3.4 Rationale for Biomarker Assessments

Assessment of biomarkers in this study (D-dimer, ferritin, IL-6, C-reactive protein,) is proposed to obtain further mechanistic insights into the pathophysiology of acute COVID-19 pneumonia that could 1) enhance understanding of disease processes, 2) assist development of patient risk stratification tools (via laboratory serologies), 3) aid in the development of novel treatments for the disease, and 4) inform potential phase 3 trial design, to name a few. These biomarkers are selected for this study given the association with thrombosis and systemic inflammation, two hypothesized mechanisms of COVID-19 disease progression. The biomarkers are scheduled for assessment pre and post-intervention. Thromboelastography (TEG) will be tested before and after TNK/placebo as well, at sites that have TEG testing available.

4. MATERIALS AND METHOODS

4.1 PATIENTS

4.1.1 Study Population / Duration

Forty-five male or non-pregnant female adults older than 18 years of age but ≤75 years with COVID- 19 who meet all eligibility criteria will be enrolled at up to 5 sites. Study participants will be randomized in a 2:1 manner to either intervention (TNK) or control/standard-of-care arms, respectively. The total number enrollees into each treatment arm will be 30 TNK and 15 control subjects. The estimated time from screening (Day 1 to end of study) for an individual subject is approximately 30 days. If, based on initial study results, it appears appropriate to include additional sites, this can be considered.

4.1.2 Inclusion Criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

1. Male or non-pregnant female adult ≥18 years of age, but ≤ 75 years of age at time of enrollment.
2. Laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen ≤ 28 days prior to randomization, OR person under investigation (PUI) of COVID-19 with pulmonary infiltrates and elevated ferritin and CRP level.
3. Acute intermediate-risk pulmonary embolism defined as:
    - Presence of acute pulmonary embolism confirmed by diagnostic imaging (computed tomographic angiography, ventilation-perfusion scan, or invasive pulmonary angiography) AND

- Presence of clot burden with at least one lobar artery involved OR bilateral with at least segmental branches OR unilateral clot in at least multiple segmental branches.

4. Subject (or legally authorized representative) provides written informed consent prior to the performance of any study procedures.

5. In the Investigator's judgement, patient has the ability to comply with the study protocol, and understands and agrees to comply with planned TNK bolus versus placebo.

4.1.3 Exclusion Criteria

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

1. Anticipated transfer to another hospital (which is not a study site) within 72 hours

2. Allergy or contraindications to TNK

3. Contraindications to systemic anticoagulation

4. Active bleeding

5. Known significant bleeding risk (although recent exposure to aspirin or any other antiplatelet therapy is not an exclusion criterion). *While there is no specific hemoglobin cut-off value for enrollment, Investigators will gauge the severity / stability of the Hgb and exclude patients deemed inappropriate*.

6. Major GI or GU bleed within the past 3 weeks

7. History of hemorrhagic stroke

8. History of acute ischemic stroke in the last 90 days

9. High-risk (massive) acute PE (PE associated with hypotension (systolic BP < 90 mmHg for > 15 min).

10. PE associated with syncope and any degree of head trauma

11. PE meeting criteria for intermediate-risk PE and thus for enrollment, but with clinical evidence of deterioration such that the Investigator deems the patient not appropriate for enrollment.

12. Administration of thrombolytic agent within the previous 7 days

13. Pulmonary thrombectomy within the previous 30 days

14. Uncontrolled hypertension defined as systolic blood pressure >180 mm Hg and/or diastolic blood pressure >110 mm Hg at randomization

15. Severe ARDS (P/F ratio < 100)

16. Platelet count lower than 80,000/mm^3

17. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency; recent oral anticoagulant therapy with INR >1.7
18. Arterial puncture at a non-compressible site within the past 5 days
19. Prior brain surgery
20. Severe trauma in the prior 2 weeks
21. Major surgery in the prior 2 weeks
22. Brain malignancy / metastases, brain tumor in past 5 years
23. Brain AVM or ruptured aneurysm at any time
24. Acute myocardial infarction or history of myocardial infarction within the past 3 weeks or cardiac arrest during hospitalization
25. Cardiac tamponade
26. Lumbar puncture with in past 7 days
27. Known abdominal or thoracic aneurysm
28. Acute or chronic renal failure requiring dialysis
29. Chronic liver failure (acutely elevated liver function tests not an exclusion criterion)
30. Bacterial endocarditis at time of study entry
31. Seizure during pre-hospital course or during hospitalization for COVID-19
32. Currently on ECMO
33. Pregnancy, lactation or parturition within the previous 30 days
34. Patients, in whom, in the opinion of the Investigator, are critically ill from concomitant comorbid cardiopulmonary disease, and unlikely to benefit.
35. Any other condition that the Investigator felt would place the patient at increased risk if the investigational therapy were initiated
36. Previous enrollment in this study

4.2 METHOD OF TREATMENT ASSIGNMENT

After informed consent is obtained, screening and assessment procedures will be completed to confirm a patient's eligibility for participation in the study. The study site will obtain the patient's medical record number/unique patient identification number, and treatment assignment to either interventional (TNK) or placebo arms of the study will be randomly determined. Patients will be allocated to the interventional versus placebo arms in a 2:1 manner as per a computer generated randomization schedule. A total of 30 TNK subjects versus 15 placebo controls will be enrolled. Randomization will be via a central randomization system created in REDCap. Allocation concealment will be ensured, as

the service will not release the randomization assignment to the unblinded pharmacy team until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed.

4.3 STUDY TREATMENT

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

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Tenecteplase

Tenecteplase will be supplied by Genentech, Inc. 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.

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

4.3.1.2 Placebo or Other Assigned Treatment

Placebo for tenecteplase will be supplied by Genentech, Inc. 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.

The placebo arm treatment will consist of an intravenous syringe identical to that of TNK using the local prescribing information for tenecteplase.

Protocol Specified Therapy/Other Study Drug(s) – NONE

4.3.2 Study Treatment Dosage, Administration, and Compliance

Any overdose or incorrect administration of tenecteplase 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.

ANTICOAGULATION AND TNK DOSING

- Once a patient is diagnosed with suspected PE, therapeutic anticoagulation with either standard UFH or LMWH will be initiated, per the judgment of the treating physicians (and then the patient will be evaluated for enrollment and informed

consent obtained). The patient will be subsequently randomized to either TNK or placebo and both will receive continued anticoagulation.

- The dose regimen for TNK for the PEITHO PE trial was *approximately* 0.5 mg/kg. In this study, TNK will be administered as a lower dose protocol as outlined below, after the patient is randomized into the TNK study arm. It will be delivered as a bolus over 5 seconds. In the setting of acute PE, if there is deterioration at any point to high-risk (massive) PE status, treatment appropriate for that setting will be determined and initiated by the managing team.

Low dose Protocol

0.25 mg/kg (10 mg / 2000 U / 2mL) (maximum dose of 25 mg)

4.3.3 Blinding and Unblinding Procedures

Patients will receive TNK or identical-appearing placebo. At randomization, unblinded Pharmacy Staff will see treatment assignments via the randomization dashboard in REDCap.

In the case of an emergency where, in the opinion of the Investigator, discontinuation of study drug bolus is not possible or sufficient and the study treatment must be unblinded in order to evaluate further a course of medical treatment, the Investigator can perform the unblinding according to site-specific procedures, consistent with DSMB recommendations

4.3.4 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 2 weeks 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 in REDCap.

Patients who use oral contraceptives or maintenance therapy for comorbidities should continue their use. No additional anticoagulants should be administered concomitantly with the therapeutic anticoagulation prescribed. Antiplatelet drugs should be continued if deemed appropriate by the clinical team.

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.

4.3.5 Additional Medication

Any medications required for treating COVID-19 infection or any underlying comorbid conditions should continue to be administered as standard of care unless otherwise indicated.

4.3.6 Prohibited Therapy

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

- No additional anticoagulants should be administered concomitantly with the therapeutic anticoagulation prescribed.
- *Antiplatelet drugs should be continued if deemed appropriate by the clinical team.*

4.4 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. Patients should be assessed for toxicity prior to the dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable. Patients will be closely monitored for safety and tolerability throughout the study.

4.4.1 Informed Consent Forms and Screening Log

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.

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.

4.4.2 Medical History, Concomitant Medication, and Demographic Data

Medical history includes clinically significant diseases and procedures. All medication taken in the last 2 weeks prior to randomization (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies) are to be recorded.

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

4.4.3 Physical Examinations

A complete physical examination, performed at screening, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded in the patient's medical records.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events in the patient's medical records and in the REDCap EDC.

4.4.4 Vital Signs

Vital signs will include measurements of temperature, pulse rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation.

Vital signs should be measured within 60 minutes prior to study drug bolus, within 15 minutes after the bolus, and 60 minutes after the bolus. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

4.4.5 Laboratory, Biomarkers, and Other Biological Samples

Please reference Appendix 1 for a summary of lab collection. Samples for the laboratory tests referenced below will be sent to the study site's local laboratory for analysis. There are no samples that will be sent to a central lab in this study.

Results from the following are required prior to enrollment (- 3 days):

- Urine/serum pregnancy test
    - If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
    - *A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).*
- Complete blood count (CBC)
- Chemistry Panel with liver function tests (LFTs)

Results from the following are required on Day 1 pre-bolus (- 3 days):

- CBC
- Chemistry panel
- COVID-19 panel: D-dimer, C-reactive protein (CRP), Creatine Kinase (CK), Ferritin, Troponin, IL-6
- Coagulation panel: PT/PTT, Fibrinogen, INR

If site has the capacity to run Thromboelastography (TEG), this test should be collected immediately prior to administration of TNK/placebo, 10 min (+5min) after, and 24 hours after (encouraged, not mandatory).

- TEG is a noninvasive test that quantitatively measures the ability of whole blood to form a clot. The principle of this *in vitro* test is to detect and quantify dynamic changes of the viscoelastic properties of a blood sample during clotting under low shear stress. In contrast to traditional, static measurements of hemostasis (e.g., PT, aPTT, INR, fibrinogen level, and fibrin degradation products), TEG allows for an assessment of near real-time, in-vivo clotting capacity, providing the interpreter information regarding the dynamics of clot development, stabilization, and dissolution. It is feasible that this test may enlighten us with regard to the DIC picture in COVID-19 infection and perhaps shed light on good candidates for the COVID lung injury patients who might benefit from thrombolysis.
- If the pre-bolus TEG is not performed, please do not obtain follow-up TEG samples.

Results from the following labs should be collected 24 hours (+/- 6 hours) post-bolus:

- COVID-19 labs: D-dimer, CRP, Ferritin, IL-6

Results from the following lab tests should be collected Days 2-7 (or discharge, if sooner):

- CBC
- Chemistry panel
- Results if completed for Standard of Care: LFTs, Coagulation labs, or COVID-19 labs

If follow-up visits are in person, the following lab tests should be collected:

- CBC
- Chemistry panel
    - LFTs are collected only at Day 30
- SARS-CoV-2-specific neutralizing antibody titer
    - This test is collected only at Day 30 and is strictly for those patients who were persons under investigation (PUIs) at time of enrollment and have not had any positive SARS-CoV-2 PCR or public health assay at the time

of the Day 30 visit or if they not had a positive COVID-19 antibody titer in the past 40 days.

4.4.6 Echocardiograms

Echocardiogram results will be obtained at screening and 24 +/- 6 hours after the bolus.

4.5 TREATMENT, PATIENT, AND STUDY DISCONTINUATION

The bolus is given over 5-10 seconds. If patient has complaints within that timeframe or there is evidence of anaphylaxis, the clinical may attempt to discontinue the bolus, if time permits.

4.5.1 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:

1. Withdrawal of consent
2. Study termination or site closure

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented 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.

4.5.2 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:

1. The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
2. 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 anticoagulation 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 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.

5.1.1.1 Bleeding

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

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

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

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

Management of Bleeding

Patients will be excluded for the presence of conditions related to risks of bleeding (as outlined in Section 4.1.3 Exclusion Criteria).

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, may be lysed during tenecteplase therapy. In the event of serious bleeding (not controlled by local pressure) in a critical location (intracranial, gastrointestinal, retroperitoneal, or pericardial), study drug should be discontinued immediately, and any concomitant heparin or antiplatelet agents should be discontinued immediately and appropriate treatment initiated.

Guidelines for management of patients who develop bleeding are provided in Table 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 5.2.4) and should be reported and submitted to the Sponsor (Section 5.4).

5.1.1.2 Risk of Hypersensitivity

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

Management of Hypersensitivity

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

5.1.1.3 Thromboembolism

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

5.1.1.4 Cholesterol Embolization

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

infarction, spinal cord infarction, retinal artery occlusion, bowel infarction, and rhabdomyolysis.

5.1.1.5 Arrhythmias

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

5.1.1.6 Use with Percutaneous Coronary Intervention

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

5.1.1.7 Other Adverse Reactions

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

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

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Management Guidelines

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

Table 1: Guidelines for Management of Patients Who Experience Bleeding

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

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

5.2.1 Specification of Safety Variables

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.

5.2.2 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:

1. 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.
2. Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
3. If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

4. Preexisting 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.

5.2.3 Serious Adverse Events

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

1. It results in death (i.e., the AE actually causes or leads to death).
2. 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.).
3. It requires or prolongs inpatient hospitalization.
4. 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).
5. It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
6. 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).

5.2.4 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:

1. Any intracranial hemorrhage event (symptomatic and/or asymptomatic), if not already reported as an SAE
2. The non-drug specific AESIs:
    - Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.
3. 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

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

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

After initiation of study treatment, all adverse events will be reported until 30 days after study treatment.

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 and, if applicable, reappears upon re-challenge.

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 the tenecteplase dose).

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

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 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?"

5.4.2 Specific Instructions for Recording Adverse Events

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

5.4.2.1 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.

5.4.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.3.1), 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”.

5.4.2.3 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”).

5.4.2.4 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:

1. Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
2. 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:

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

5.4.2.5 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

Table 3: Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

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

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

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

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

5.4.3 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):

1. Temporal relationship of event onset to the initiation of study drug

2. Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (if applicable).
3. Known association of the event with the study drug or with similar treatments
4. Known association of the event with the disease under study
5. 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 4: Causal Attribution Guidance

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

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

5.4.3.1 Pregnancies

If a female patient becomes pregnant within 90±14 days after tenecteplase/placebo bolus, 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 tenecteplase/placebo should be reported to Genentech, Inc. as an SAE.

5.4.3.2 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/placebo 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.

5.4.3.3 Case Transmission Verification of Single Case Reports

The Investigator agrees to conduct Case transmission Verfication for the product to ensure that all single case reports have been adequately received by Genentech via the Investigator emailing Genentech a Quarterly line-listing documenting single case reports.

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 Investigator 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 Investigator 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 Investigator 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.

5.5 EXCHANGE OF SINGLE CASE REPORTS

Investigators are 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 reporting

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 call via:

PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

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.

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

All SAEs, AESIs, pregnancy reports other Special Situation Reports and Product Complaints (with or without an AE) where the patient has been exposed to the Genentech Product, shall be transmitted to Genentech/Roche on a MedWatch or CIOMS I or on Genentech approved SAE form within one (1) business day of the awareness date.

Serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports other Special Situation Reports and Product Complaints (with or without an AE) where the patient has been exposed to the Genentech Product, will be sent on a MedWatch form or CIOMS I form or on Genentech approved reporting forms to Genentech Drug Safety. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

1. SADRs

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

2. Other SAEs

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

3. Pregnancy Reports

While such reports are not serious AEs or ADRs per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to the Product, shall be transmitted to Roche 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.

4. 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.

5. Special Situation Reports

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:

1. Data related to product usage during breastfeeding
2. 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
3. Lack of therapeutic efficacy
4. Drug interaction
5. Use of a Medicinal Product in a Pediatric and Elderly population
6. 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.

5.5.1 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:

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

5.5.1.1 Follow-up Information

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

1. Adding to the original MedWatch 3500A report and submitting it as follow-up
2. Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
3. 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

5.5.2 Reporting to Regulatory Authorities, Ethics Committees and Investigators

The Sponsor of the Study, Dr. Victor Tapson, 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.

The Sponsor, Dr. Victor Tapson, will be responsible for the distribution of safety information to its own Investigators, where relevant.

5.5.2.1 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 tenectaplase. An unexpected adverse event is one that is not already described in the tenectaplase 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 site IRB:

Antonina Caudill, Study Coordinator, antonina.caudill@cshs.org will communicate with IRB.

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

Tel: (888) 835-2555

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

5.6 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

DEVELOPMENT SAFETY UPDATE REPORT

Dr. Victor Tapson will forward a copy of the Final Study Report to Genentech upon completion of the Study and any publications generated from the study.

Dr. Victor Tapson, as the Sponsor of the Study, will be responsible for the preparation of their own Development Safety Update Report (DSUR) for the Study and for the submission of the report to the regulatory authorities and Ethics Committees of the concerned Member States, where applicable. Dr. Tapson agrees to share a copy of their own DSUR with Genentech as soon as reasonably possible after completion. Genentech agrees to forward to Dr. Victor Tapson an executive summary of the Genentech DSUR upon request. Furthermore, Genentech agrees that Dr. Victor Tapson may cross-reference the executive summary of the Genentech DSUR, as applicable.

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

5.7 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 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

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

QUERIES

Queries related to the Study will be answered by Dr. Victor Tapson; 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. Dr. Victor Tapson agrees that he 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.

SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech shall have the final say and control over safety crisis management issues relating to the Product. Dr. Victor Tapson agrees that he shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech.

6. STATISTICAL CONSIDERATIONS

6.1 DETERMINATION OF SAMPLE SIZE

Our primary endpoint is shock index (heart rate / systolic blood pressure) 6 hours after administration of intravenous TNK or matching placebo. We will utilize a 2:1 randomization scheme, TNK:placebo. As shock index is a continuous measure, data will be summarized as numbers, mean, standard deviation (SD), and median, minimum, and maximum. We will use the independent samples T-test to compare the two arms with a two-sided 0.05 (5%) significance level. Power and sample size are based on the percent change in shock index from baseline to 6 hours. We assume that a clinically important difference between arms in mean percent shock index is 10% and that the SD of the changes is 12%. A total sample size of 45 (30 TNK / 15 placebo) provides 73% power to detect a 10% difference in the mean change in shock index from baseline to 6 hours. We seek to show that the TNK therapy is promising, not to demonstrate a significant difference in shock index.

6.2 PLANNED EFFICACY EVALUATIONS

The analysis population for the efficacy analyses will consist of all enrolled patients, with patients grouped according to their assigned treatment.

DATA COLLECTED

The above data used to determine primary and secondary efficacy and safety endpoints will be collected. Lab testing will be performed as well. Trends in Hgb and platelets will be followed daily as per standard of care (SOC). D-dimer, ferritin, C-reactive protein (CRP), IL-6 levels, and coagulation parameters will be performed as is now considered SOC in COVID-19 infected patients. Thromboelastography (TEG) will be performed after enrollment and before TNK / placebo administration. Patients will be evaluated for acute DVT and PE when suspected based on the standard of care. Oxygen saturation values and O2 requirements will be followed. The use of mechanical ventilation, ECMO, and vasopressors will be determined. The 7-point ordinal score will be determined daily. (SEE SCHEDULE OF ASSESSMENTS).

6.3 PRIMARY EFFICACY VARIABLES

The primary efficacy variable is percentage change in shock index from baseline at 6 hours after TNK/placebo.

6.4 SECONDARY EFFICACY VARIABLES

The secondary efficacy variables are as follows:

1. Clinical status at 24 hours after administration of TNK/placebo based upon 7-point ordinal scale
2. Clinical status at Day 7 after administration of TNK/placebo based upon 7-point ordinal scale
3. Clinical status at Day 28 after administration of TNK/placebo based upon 7-point ordinal scale
4. O2 sat / FIO2 ratio 6 hours and 24 hours after administration of TNK/placebo
5. Percentage change in shock index 24 hours after TNK/placebo
6. Percentage change in RV.LV ratio 24 hours after TNK/placebo
7. Post-enrollment days with O2 requirement < 4L/min at Day 7
8. Post-enrollment days with no O2 requirement at Day 7
9. Change in D-dimer level 24 hours after enrollment
10. Change in D-dimer level at Day 7 (if obtained)
11. Change in ferritin, C-reactive protein (CRP), IL-6 levels 24 hours after TNK/ placebo
12. Post-enrollment documented new clinical thrombotic events at Day 7
13. All-cause mortality at day 7 and day 30

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received study drug, with patients grouped according to treatment received.

6.6 EXPLORATORY ENDPOINTS

1. We will examine characteristics of patients prior to enrollment by measuring static measurements of hemostasis including D-dimer, PT, aPTT, INR, fibrinogen level, fibrin degradation products, FVIII, antithrombin. In addition, thromboelastography (TEG) will be performed (TEG 6S or 5000, depending on site's availability).

2. TEG will be performed immediately prior to, 10 min (+5min) after, and ideally at 24 (+/- 6) hours after TNK/placebo administration.

6.7 INTERIM ANALYSIS

An interim analysis will be performed after 18 patients are enrolled to evaluate patient safety. The study will be stopped if there are two critical site bleeds in the interventional (TNK) study arm, as adjudicated by the DSMB.

6.8 METHOD OF ANALYSIS

The primary and secondary endpoints will be summarized by treatment group using descriptive statistics. Continuous variables will be summarized by mean (standard deviation and/or median (range), as appropriate. Incidences will be summarized by count and percentages. The associated 95% confidence intervals will be provided as appropriate. Time to event endpoints will be analyzed by the Kaplan-Meier method with the median time to event estimated along with the associated 95% confidence interval. For the primary efficacy endpoint, improvement from baseline will be determined by the percentage change in shock index at 6 hours from baseline. A 10% improvement in the primary endpoint would be considered clinically significant.

6.9 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.

6.10 STUDY MEDICAL MONITORING REQUIREMENTS

This clinical research study will be monitored both internally by the PI and externally by the Cedars-Sinai Medical Center IRB. In terms of internal review, the PI will continuously monitor and tabulate AEs. Appropriate reporting to the Cedars-Sinai Medical Center and additional study site IRBs will be made. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

1. Interim analyses occur as scheduled,
2. Stopping rules for toxicity and/or response are met,
3. Risk/benefit ratio is not altered to the detriment of the patients,
4. Appropriate internal monitoring of AEs and outcomes is done,

5. Over-accrual does not occur,
6. Under-accrual is addressed with appropriate amendments or actions, and
7. 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.

6.11 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.

6.12 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 Cedars-Sinai Medical Center IRB.

7. ETHICAL CONSIDERATIONS

7.1 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.

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

7.2 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.).

7.3 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.

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APPENDIX 1: SCHEDULE OF ASSESSMENTS

Schedule of Assessments

Timepoint	**Screening**	**Study intervention period**			**Follow-Up[6]**		
Day/hour +/- window	**-3 or 1**	**Day 1 (pre-bolus)**	**Day 1 (post-bolus)**	**24 hours (+/- 6 hours)**	**Day 2-7 or until discharge**	**Day 14 (+/- 2 days)**	**Day 30 (+/- 4 days)**
Informed Consent	X						
Demographics and Medical History collection	X						
Complete physical exam (collected from medical record)	X						
Targeted exam (if applicable/indicated)					X	X	X
Review SARS-CoV-2 results	X						
Randomization		X					
Prophylactic anticoagulation[1]		X		X	X		
Administration of TNK / placebo		X					
Vital signs (including oxygen saturation)		X	X		X	X	X
Clinical data collection		X	X		X	X	X
Echocardiogram	X			X			
Targeted medication review		X			X	X	X
Adverse event evaluation		X	X		X	X	X
Safety Labs: CBC, Chemistry	X[2]	X			X	X	X
Other Labs: CRP, Ferritin, IL-6, Fibrinogen, D-dimer[3]		X		X	X		
Collection of lab results performed for standard of care (Liver Function Tests, PT/PTT, Troponin, Creatinine Kinase, INR)[4]		X			X		
Pregnancy testing for females of childbearing potential	X						
TEG (thromboelastography)[5]		X	X	X			
SARS-CoV-2-specific neutralizing antibody titer[7]							X

1. *All patients must be on prophylactic anticoagulation; enoxaparin 40 mg once-daily is preferred.*
2. *Screening and Day 30 Chemistry panel must include liver function tests. If screening labs are performed within 3 days of Day 1, they may be used as Day 1 labs as well.*
3. *The labs referenced are required Day 1 (pre-bolus) and 24 hours (+/- 6 hours after the bolus). For Day 1 (pre-bolus) labs, labs performed within 3 days of Day 1 may be used. On Days 2-7, data should be collected only if labs were performed as standard of care.*
4. *The labs referenced are required Day 1 (pre-bolus), but labs performed within 3 days of Day 1 may be used. On Days 2-7, data should be collected only if labs were performed as standard of care.*
5. *This test will only be obtained by sites that have the capacity to run TEG.TEG will be performed immediately prior to study drug administration and 10min(+5min) after the bolus. The 24 hour TEG is encouraged, but not mandatory. If the pre-bolus TEG is not performed, please do not obtain follow-up TEG samples.*
6. *In-person visits are preferred but recognizing quarantine and other factors may limit the subject's ability to return to the site for the visit. In this case, these visits may be conducted by phone / telemedicine and blood will not be collected. Labs at Day 30 are preferred but not mandatory. Any relevant exam finding (e.g., leg swelling, discoloration) will be noted by in-person exam or photo / telemedicine.*
7. *This test will only be obtained for persons under investigation (PUIs) who did not otherwise have a COVID positive PCR or public health assay prior to their Day 30 visit and have not had a positive C19 titer within the past 40 days.*

APPENDIX 2: SAFETY REPORTING FAX COVER SHEET

Genentech
A Member of the Roche Group

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)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

APPENDIX 3: FDA MEDWATCH 3500 FORM

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