

**Title:** Standard-dose Apixaban AFtEr Very Low-dose ThromboLYSis for Acute Intermediate-high Risk Acute Pulmonary Embolism

**Short Title:** SAFE-LYSE

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## STUDY SYNOPSIS

Funding Provided by	BMS/Pfizer Alliance
Protocol Title	<b>Standard-dose Apixaban After Very Low-dose Thrombolysis for Acute Intermediate-high Risk Acute Pulmonary Embolism (SAFE-LYSE)</b>
Background	<p>Pulmonary embolism (PE) is a major cause of mortality in the United States, with an estimated 100,000 deaths annually and up to 30% of patients dying within the first month of diagnosis. Recent guidelines now risk-stratify intermediate-risk PE patients to intermediate-low and intermediate-high risk categories, but consensus on treatment for those patients are controversial, as compared to that of high or low-risk patients.</p> <p>Because of an increased risk of major, non-major, and intracranial bleeding and an uncertain effect on survival and post-thrombotic complications, thrombolysis is not routinely recommended in the guidelines for intermediate-risk patients. However, studies have evaluated half-dose (50 mg dose) tissue plasminogen activator (tPA) and this appears to be effective for treating PE with a reduced yet still significant risk of bleeding. Catheter-directed thrombolysis studies have used even lower dose tPA (24mg) with significant reduction in clot burden, right ventricle to left ventricle ratios, and less bleeding; however, catheter-directed therapy requires a procedure which is time consuming, costly, center dependent, and introduces other potential complications. Based on our extensive clinical experience in treating acute PE, we believe that even lower doses of systemic (intravenous) tPA may be effective and safe, as well as simpler and more accessible than any form of catheter-directed thrombolysis (CDT). In addition, usage of the direct oral anticoagulant (DOAC), apixaban, after completion of anticoagulation therapy for PE has been shown to be effective in preventing recurrent VTE in patients while having a very low risk of major bleeding.</p> <p>To understand ways to improve PE patient outcomes while reducing risk of major bleeding, our proposed trial will compare a baseline CTA to a 24 hour CTA after administration of a 24 mg dose of systemic, (intravenous) tPA (treatment A) for intermediate-high risk PE patients. As a secondary endpoint we will compare treatment A to conventional anticoagulant therapy (treatment B). Patients with a low risk of bleeding will then receive standard dose apixaban. In addition to our primary endpoint analysis, we will follow patients after discharge to evaluate long-term efficacy and safety of the thrombolytic therapy on endpoints such as right ventricular (RV) function, residual clot burden, and long-term mortality.</p>
Diagnosis and Main Criterion for Inclusion	Adult individuals with intermediate-high risk (submassive) PE.
Primary Study Objective	To determine whether very low 24 mg dose systemic thrombolytic therapy is effective and safe in treating intermediate-high risk PE compared to anticoagulation alone.

Primary Endpoint	Mean change in percentage of Refined Modified Miller Score (RMMS) (measurement of extent of clot lysis) between baseline CTA and 24 hour CTA after 24 mg of systemic (intravenous; IV) tPA.
Primary Hypothesis	Very low-dose intravenous tissue-type plasminogen activator (24 mg) + standard anticoagulation therapy (intravenous heparin) for treatment of acute PE in intermediate risk patients will have clot lysis of at least 15% by chest CTA at $24 \pm 6$ hours post infusion compared with baseline CTA. All patients will be treated with oral apixaban at the approved dose of 10 mg twice-daily starting at least 24 hours after completion of the IV study drug for seven days followed by 5 mg twice-daily for at least 6 months, with the potentiality of decreasing the apixaban dose again to 2.5 mg twice-daily after 6 months.
Study Design and Methodology	<p>This is a randomized, double-blinded, placebo-controlled, single-center study intended to investigate very low dose systemic (IV) tPA along with standard anticoagulation therapy as a treatment for intermediate-high risk (submassive) PE. The study is planned to evaluate the reduction in clot burden based on the obstruction index using the Refined Modified Miller Score (RMMS), improvement in right ventricular (RV) function, and overall safety in the two treatment groups. Subjects with intermediate-high risk PE (hemodynamically stable PE with significant clot burden a RV dysfunction an at least one elevated biomarkers, will be randomized to one of two treatment groups: 24mg of systemic (IV) tPA + IV unfractionated heparin versus saline placebo + IV unfractionated heparin.</p> <p>Approximately 40 subjects will be enrolled. These subjects will be randomized in a 1:1 ratio (approximately 20 per treatment arm) to receive 24 mg tPA [Activase (alteplase)] + standard anticoagulation therapy (intravenous heparin) vs placebo + standard anticoagulation (intravenous heparin) therapy.</p> <p>Upon enrollment, the standard of care labwork, chest contrast-enhanced computed tomographic angiogram (chest CTA), echocardiogram and duplex ultrasound of lower extremities will be reviewed The sPESI core will be calculated.</p> <p>After delivery of the systemic (IV) tPA/placebo, patients will continue IV unfractionated heparin therapy for at least 24 hours. If there is no evidence of active bleeding nor significant hemoglobin drop (i.e., <math>\geq 2</math> mg/dL), patients will be transitioned to standard dose apixaban, 10 mg twice-daily x one week followed by 5 mg twice-daily for at least 6 months. Some patients will require indefinite apixaban therapy based on patient-specific factors, including unprovoked nature of PE event, and/or persisting DVT/PE risk factors. Finally, consideration will be given for decreasing the apixaban dose to 2.5 mg twice-daily after 6 months. Apixaban was selected as the anticoagulant of choice due to its very favorable bleeding profile in large clinical trials, which is an important consideration when prescribing an anticoagulant following systemic thrombolysis.</p> <p>Within <math>24 \pm 8</math> hours post study drug infusion, a repeat chest CTA and echocardiogram will be performed. sPESI will also be calculated at this timepoint.</p>

	<p>At Day 30, 180 and 365, all subjects will have clinic visits which will include a physical exam, repeat echocardiogram (at Day 30 &amp; 180), 6 minute walk test (6MWT), quality of life questionnaires, assessment of adverse and bleeding events and a review of concomitant medications including compliance with apixaban. At Day 3, 7, 90 and 270, a remote health check will occur via telephone or email assessing adverse and bleeding events, alongside a review of concomitant medications (including an assessment of compliance with apixaban).</p> <p>If any subject experiences an adverse event (AE), the investigator may, at his or her discretion, decrease or discontinue the study drug or apixaban.</p> <p>The DMC will meet after 10 subjects are enrolled; bleeding and other complications will be reviewed. An interim analysis will occur after 20 subjects have completed Day 30. The DMC will meet again after 30 subjects have completed Day 30. Because it is a single-center study, the investigators and study coordinators will be acutely aware of all adverse events.</p> <p>The primary analyses will compare the clot lysis on CTA in treatment A at 24 hours post study drug infusion. See Section 7 for a complete discussion of the statistical analysis.</p>
Inclusion Criteria	<ul style="list-style-type: none"> <li>• Male or female 18-75 years in age</li> <li>• Chest CT angiogram evidence of proximal PE with a filling defect in at least one main pulmonary artery or lobar artery</li> <li>• PE symptom duration <math>\leq 14</math> days</li> <li>• Intermediate-high risk PE: significant clot burden with RV dysfunction, an elevation in troponin <math>&gt; 0.05</math> ng/mL and/or brain natriuretic peptide (BNP) <math>&gt; 100</math> pg/mL, and hemodynamically stable (systolic blood pressure <math>&gt; 90</math> mm Hg without the use of vasopressor support)</li> <li>• Randomization within 36 hours of anticoagulation</li> <li>• Signed and dated informed consent obtained from subject or legally authorized representative before initiation of any study procedures</li> </ul>
Exclusion Criteria	<ul style="list-style-type: none"> <li>• Stroke or transient ischemic attack (TIA), head trauma, or other active intracranial or intraspinal disease within one year</li> <li>• Recent (within one month) or active bleeding from a major organ</li> <li>• Major surgery within 14 days</li> <li>• Clinician deems the subject too high-risk for bleeding using HAS-BLED criteria.</li> <li>• History of any hematologic disease or coagulopathy</li> <li>• Cirrhosis (as determined by Child-Pugh B or C)</li> <li>• History of heparin-induced thrombocytopenia (HIT)</li> <li>• Hemodynamic instability defined as systolic blood pressure (SBP) less than 90 mm Hg and/or use of vasopressors for greater than 15 minutes</li> <li>• Severe hypertension as defined as systolic blood pressure (SBP) greater than 180 mm Hg</li> <li>• Cardiac arrest or active cardiopulmonary resuscitation (CPR)</li> <li>• Receiving neuraxial anesthesia or undergoing spinal puncture</li> </ul>

	<ul style="list-style-type: none"> <li>• Patient with prosthetic heart valves</li> <li>• Evidence of irreversible neurological compromise</li> <li>• Evidence of poor functional status</li> <li>• History of major gastrointestinal bleed within the last month</li> <li>• Active gastric or duodenal ulcers</li> <li>• Use of thrombolytics or glycoprotein IIb/IIIa antagonists within 3 days prior to diagnosis</li> <li>• Lovenox administration within 12 hours of randomization</li> <li>• Direct-acting oral anticoagulant use (dabigatran, rivaroxaban, apixaban, or edoxaban) with last known dose within 48 hours</li> <li>• Hemoglobin &lt; 10 g/dL</li> <li>• creatinine clearance &lt; 30 mL/min</li> <li>• platelets &lt; 100 thousand/<math>\mu</math>L</li> <li>• INR &gt; 1.4</li> <li>• Alanine transaminase (ALT) or aspartate transaminase (AST) <math>\geq</math> 2 times upper limit of normal (ULN)</li> <li>• Total bilirubin (TBL) <math>\geq</math> 1.5 times ULN (except due to confirmed Gilbert's syndrome)</li> <li>• Patient is pregnant (positive pregnancy test; women of childbearing capacity must be tested prior to enrollment) or breast feeding</li> <li>• Patient who is a prisoner, or if subject who becomes compulsory detained</li> <li>• Active cancer defined as diagnosis of cancer within six months before the study inclusion, or receiving treatment for cancer at the time of inclusion or any treatment for cancer during 6 months prior to randomization, or recurrent locally advanced or metastatic cancer.</li> <li>• Known allergy, hypersensitivity or thrombocytopenia from heparin, tPA, or apixaban or iodinated contrast except for mild-moderate contrast allergies for which steroid pre-medication can be administered within 12 hours prior to the CTA.</li> <li>• HIV/AIDS</li> <li>• Weight &gt;130 kg or &lt; 40 kg on day of randomization</li> </ul>
Sample Size	<p>In this trial, 40 subjects (20 per arm) will be randomized into two treatment arms, 1) 24 mg IV PA + standard anticoagulation therapy (IV heparin) vs 2) saline placebo + standard anticoagulation therapy (IV heparin), using a computer program at Cedars-Sinai Medical Center in Los Angeles, California. Additional subjects may be consented to compensate for screening failures and/or treated patients who lack sufficient data.</p> <p>Approximately 40 subjects will be enrolled into the study, with approximately 20 subjects in each arm. A subject will be deemed evaluable if he/she has valid CTA imaging evaluations at both baseline and <math>\leq 24\text{h} \pm 8</math> hours post-end of infusion and successfully completed administration of study drug infusion. Randomized subjects who do not complete blinded study drug administration (i.e., subjects who stop the IV infusion early due to AEs) will still be followed for safety through Day 30.</p>

	<p>The planned sample size is based on a two-sided two-sample equal-variance t-test. A previous study [19] showed that the mean and standard deviation of percentage change in RV/LV ratio from baseline to 48 hours are 26 and 22.7, respectively. Assuming these hold for our study, data from 17 patients per group (34 total) achieve 90% power to detect a mean difference of 26 percentage units between the two treatments with 5% significance level using a two-sided two-sample equal-variance t-test.</p>
Statistical Analyses	<p>The main objective is to determine the mean change in percentage clot lysis via chest CTA from baseline to 24 hours in treatment A (IV tPA + IV unfractionated heparin). Data will be presented as frequency (percentage, %) for categorical variables and mean (<math>\pm</math> SD, standard deviation) for continuous variables. Profile plots with mean Refined Modified Miller Score (RMMS) (<math>\pm</math> SE, standard error) at baseline and 24 hours will be displayed. The post-treatment RMMS score at 24 hours as an outcome variable will be modeled using a generalized additive model for location, scale and shape after adjusting for the treatment group and the baseline RMMS score [24] to examine if there is a difference in the change in RMMS from baseline to 24 hours in treatment group A. The underlying assumptions will be checked using residuals so that the most adequate response distribution and the regression functional form can be chosen. Statistical analyses will be conducted using R package version 3.4.1 with two-sided tests and a significance level of 0.05.</p>
Safety	<p>All recorded AEs will be listed and summarized. Vital signs and clinical laboratory tests will be listed and summarized by treatment. Any significant physical examination findings and results of clinical laboratory tests will be listed. Recurrent DVT and PE at 30 days, 60 days, 6 months, and 1 year compared with placebo. Since all patients will be on apixaban, we will compare DVT and PE recurrence rates with historic controls. The Data Monitoring Committee (DMC) will meet and review safety data after the first 10 subjects are enrolled and Day 30 assessments have been completed. A maximum of 3 additional subjects may be enrolled before the DMC approves study continuation.</p>

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# 1. INTRODUCTION AND STUDY RATIONALE

## 1.1. BACKGROUND AND RATIONALE

Venous thromboembolic (VTE) disease is a common condition with over a million cases in the United States per year [1]. Pulmonary embolism (PE) is a potentially deadly consequence of deep vein thrombosis with an estimated 100,000 deaths annually in the United States and up to 30% dying within the first month of diagnosis [2].

The detrimental effects of an acute PE are understood through the pathophysiologic increase in pulmonary vascular resistance (PVR). The emboli directly obstruct the pulmonary capillary bed but also indirectly induce hypoxic/acidotic vasoconstriction through the release of vasoactive mediators thus increasing the overall PVR. The acute increase in PVR causes an elevation in pulmonary artery pressures, which overwhelms the thin walled RV leading to RV dilation and decreased contractility and function. The dilated RV also causes septal bowing into the left ventricle. The net result is compromised left ventricular filling, decreased cardiac output, hemodynamic instability, cardiogenic shock, and ultimately death [3].

### **Risk stratification of acute pulmonary embolism**

The clinical classification of the severity of acute PE is generally based on the estimated early mortality risk defined by in-hospital or 30-day mortality. High-risk (massive) PE is defined by the presence of shock or persistent arterial hypotension. Patients with high-risk PE represent less than 5% of all patients with acute PE [4]. This is a life-threatening situation in which prompt reperfusion treatment (often systemic thrombolysis) is recommended to increase the chances of survival [5].

More than 95% of patients with acute PE do not present with hypotension or cardiogenic shock and are thus not considered to be at high risk. Within this group, prediction scores derived from clinical variables reliably select patients with a low 30-day mortality. Both the Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI) have a high negative predictive value for ruling out an adverse early outcome [6]. Thus, a substantial proportion of all patients with acute PE can be classified as being at low risk based on a PESI risk class of I or II, or a sPESI of 0. These patients generally have small embolic burdens and are not severely tachypneic, tachycardic or hypoxemic, unless they have other underlying concomitant pulmonary or cardiovascular comorbidities affecting their reserve. Such patients are treated with anticoagulation alone.

Clinically stable patients not classified into the low-risk category are classified as intermediate-risk. The most recent European Society of Cardiology (ESC) guidelines have further risk-stratified these patients into intermediate-low and intermediate high-risk categories. Intermediate-low-risk patients are defined by a sPESI score > 0 with either right ventricular (RV) dysfunction *or* elevated cardiac biomarkers (troponin or BNP). The patients with sPESI score > 0 and both RV dysfunction *and* elevated cardiac biomarkers are classified in the intermediate-high risk category [5]. Therapy for these patients has been much more controversial than therapy for high or low-risk patients.

### **Systemic thrombolysis at standard doses for acute PE**

Thrombolytic treatment achieves a faster improvement in hemodynamic parameters in acute PE than IV unfractionated heparin with a significant decrease in the mean pulmonary artery pressure and a significant increase in the cardiac index observed two hours after the start of the infusion whereas no difference is observed with heparin alone [7]. Thus, in PE patients for whom the risk of deterioration or mortality is higher, more aggressive therapy such as systemic thrombolysis is often considered.

In the most important therapeutic clinical trial involving intermediate-risk acute PE patients to date, the PEITHO trial [8], tenecteplase plus heparin was compared with placebo plus heparin. The trial was a randomized, double-blind trial, and eligible patients had RV dysfunction on echocardiography or chest computed tomographic angiography (chest CTA), as well as myocardial injury as indicated by positive troponin test (i.e., intermediate-high risk patients). The primary outcome was death or hemodynamic decompensation (or collapse) within 7 days after randomization. The main safety outcomes were major extracranial bleeding and ischemic or hemorrhagic stroke within 7 days after randomization. In the PEITHO trial, it was demonstrated for the first time that thrombolysis not only improves pulmonary vascular obstruction and right heart function, but also improves clinical end-points in intermediate-risk patients with PE [8].

However, in these intermediate-risk PE patients, thrombolytic therapy increased the risk of major hemorrhage and stroke; 6.3% and 1.2% of patients had major extracranial bleeding in the tenecteplase and placebo groups, respectively ( $P < 0.001$ ). Stroke occurred in 12 patients (2.4%) in the tenecteplase group and was hemorrhagic in 10 patients; 1 patient (0.2%) in the placebo group had a stroke, which was hemorrhagic ( $P = 0.003$ ) [8]. This increase in the risk of bleeding was confirmed in a recent meta-analysis, showing that in the subset of studies including patients with intermediate-risk PE, thrombolysis was associated with an odds ratio (OR) for major bleeding of 3.19 (95% CI: 2.07-4.92) [9].

In the PEITHO trial, no difference was observed in the risk of death; by day 30, a total of 12 patients (2.4%) in the tenecteplase group and 16 patients (3.2%) in the placebo group had died ( $P = 0.42$ ) [8]. It is important to realize that while there was no overall difference in mortality, it is likely that the population was not sufficiently enriched based on severity to demonstrate a difference.

Two meta-analyses have reported conflicting results. In one, a prespecified analysis performed of 8 trials enrolling patients who were hemodynamically stable with objective assessments of RV function, thrombolysis was associated with a lower mortality (odds ratio, 0.48; 95% CI: 0.25-0.92) [9]. In the other meta-analysis, the reduction in the risk of death for intermediate-risk PE patients receiving thrombolytic therapy was not significant (OR: 0.42; 95% CI: 0.17–1.03) [10].

The uncertain effect of thrombolytic therapy on survival and the increased risk of major and intracranial bleeding observed with the use of thrombolytic therapy in patients with intermediate-risk PE [11] prompted the recent guidelines issued by the ESC and the American College of Chest Physician to recommend against the use of thrombolysis in these patients [5, 11].

### **Lower (half)-dose systemic thrombolysis**

A newer approach has been to consider lower doses of thrombolytic therapy in hopes of improving outcomes with a low risk of major bleeding including intracranial hemorrhage (ICH). In patients with PE, three small randomized trials compared a reduced dose of systemic (IV) tPA administered to 162 patients with the conventional 100 mg dose given over 2 hours in 99 patients [12-14]. The reduced dose was similar in the different studies: in one trial, 50 mg given over two hours, and in the other two trials, 0.6mg/kg up to 50 mg given over 15 minutes [12-14]. No significant difference was observed in either trial regarding the different efficacy end-points including pulmonary artery pressure, cardiac index, residual vascular obstruction at 24h or recurrent PE [12-14]. However, the low-dose regimen was associated with a significant reduction in the risk of major bleeding (OR: 0.33; 95% CI: 0.12 to 0.91) [15]. Thus, lower dose therapy appears effective, but also safer than conventional dose systemic (IV) tPA. The improved safety of this regimen has also been demonstrated in patients with ischemic stroke with a significant 50% relative reduction in the risk of major symptomatic ICH as compared to the standard dose (1.0% in the low-dose group vs 2.1% in the standard-dose group;  $P = 0.01$ ) [16]. In

patients with PE, the efficacy of the reduced dose regimen is further supported by two studies comparing tPA given as a 0.6 mg/kg or 0.5 mg/kg and heparin in patients with PE, showing a larger improvement of vascular obstruction with tPA in one study [17] and a reduction in the combined end-point of persistent pulmonary hypertension or recurrent PE in the second study [18]. Based on our extensive clinical experience in acute PE, we believe even lower doses of systemic (IV) tPA are effective and even safer.

### **Catheter-directed thrombolysis (CDT)**

Catheter-directed thrombolysis (CDT) has been studied in intermediate-risk patients. Localizing the systemic (IV) tPA infusion directly into the pulmonary artery, and using lower doses of tPA, may improve the risk/benefit ratio. Doses of tPA have ranged from 8 to 24 mg total. Improvement in RV/LV ratio has been demonstrated, with more substantial improvement in clot burden using doses in the higher range [20-22]. However, there is only one randomized trial evaluating CDT to date, and while it demonstrated improvement in RV/LV ratio at 24 hours with a low risk of major bleeding, it was too small to (and did not intend to) demonstrate a difference in mortality [19]. Furthermore, CDT is not available at most smaller hospitals and the precise patients who benefit the most is not clear. Specialists in interventional cardiology or radiology must be available. Many hospitals around the U.S. and the world simply do not have access to CDT, and this practice has still not proven superior to (IV) tPA at similar doses. Thus, our approach is much simpler and more accessible than any form of CDT.

### **Trials evaluating the use of a DOAC after thrombolysis for acute PE**

This trial will compare *systemic* (IV) tPA at a lower dose than has ever been previously studied and the use of apixaban after thrombolysis. There are almost no data evaluating the use of apixaban after thrombolysis, despite the obvious logic of utilizing a short-acting oral anticoagulant with excellent safety data. One trial evaluated 98 consecutive patients with symptomatic PE over a 12-month period [23]. These patients were treated with a combination of systemic thrombolysis at a lower dose than traditionally prescribed, followed by rivaroxaban. The tPA was given over 2 hours. Heparin was administered for a total of 24 hours and rivaroxaban then started at the standard therapeutic dose. However, *no randomized trials* have examined thrombolysis followed by a DOAC. A number of PE systemic thrombolysis trials have been conducted in which anticoagulation has followed thrombolytic therapy, thus offering historical controls for comparison (7-10). Furthermore, the catheter-directed thrombolysis trials which have been conducted also offer potential control data [20-22]. We chose transitioning to apixaban based on the low risk of bleeding with apixaban in prior trials [24-25]. Apixaban was shown to be effective for the prevention of recurrent VTE in patients who had completed 6 to 12 months of anticoagulation for acute DVT or PE, with rates of major bleeding similar to placebo [24].

Furthermore, in the AMPLIFY trial [25], among patients who had PE at enrollment, the primary efficacy outcome occurred in only 21 of 900 patients (2.3%) in the apixaban group compared with 23 of 886 (2.6%) in the conventional-therapy group (relative risk, 0.90; 95% CI, 0.50 to 1.61; difference in risk, -0.3 percentage points; 95% CI, -1.7 to 1.2). Even more impressive, for all randomized patients with VTE (i.e. PE and/or DVT), major bleeding occurred in only 15 of 2676 patients (0.6%) in the apixaban group compared with 49 of 2689 (1.8%) in the conventional-therapy group, for a relative risk of 0.31 (95% CI: 0.17 to 0.55;  $P < 0.001$  for superiority) [25].

### **Very-low dose systemic thrombolysis followed by apixaban— our proposal**

This trial is comparing an even lower dose of *systemic* (IV) tPA than has previously been studied. We hypothesize that this dose of 24 mg will be effective at decreasing clot burden as measured on chest CTA by Refined Modified Miller Score (RMMS), as well as significantly improving RV function as

measured by RV/LV ratio. We also expect a very low risk of major bleeding, particularly when followed at 24 hours by apixaban which has been associated with a very low risk of major bleeding [24-25].

While even lower doses of systemic (IV) tPA have proven effective for acute PE when delivered by CDT [22], we are concerned that doses in the range of 8 to 12 mg, when delivered systemically, might be too low to confer benefit.

Patients with chest CTA-documented acute intermediate-high-risk PE (abnormal RV function by echocardiogram combined with an elevated troponin or BNP), who have no evidence of significant bleeding risk will receive systemic (IV) tPA (24 mg) combined with IV unfractionated heparin, or saline placebo and IV unfractionated heparin. After delivery of the systemic (IV) tPA, patients will continue IV unfractionated heparin therapy for 24 hours, and if the bleeding risk remains low, all patients will be subsequently transitioned to standard dose apixaban, 10 mg twice-daily x one week followed by 5 mg twice-daily at least 6 months (some patients will require indefinite apixaban therapy based on patient-specific factors, including unprovoked nature of PE event, and/or persisting DVT/PE risk factors). Finally, consideration will be given for decreasing the apixaban dose to 2.5 mg twice-daily after 6 months if bleeding suggests that a shorter acting anticoagulant (IV unfractionated heparin) should be continued longer, then it will be. Importantly, andexanet has now been FDA-approved for reversal of bleeding caused by apixaban, and will be available when our study is initiated [26]. After discharge, patients will be seen and followed in the Cedars-Sinai Pulmonary Embolism Response Team clinic.

We have specifically chosen to transition to apixaban based upon the very low risk of major bleeding seen in large randomized clinical trials [24-25]. Finally, we will obtain long-term efficacy data including the effects of thrombolysis followed by apixaban on RV dysfunction, dyspnea and long-term mortality. Safety will be assessed by examining major and minor bleeding rates in all patients at 30 days, 60 days, and 6 and 12 months. Thus, will have data on apixaban in PE patients treated with thrombolysis.

## 1.2. OBJECTIVES

The **OVERALL OBJECTIVE** of this investigation is to determine whether very low-dose intravenous tissue-type plasminogen activator (24 mg) + standard anticoagulation therapy (intravenous heparin) for treatment of acute PE in intermediate-high risk patients will have superior clot lysis by chest CTA at  $24 \pm 6$  hours post infusion compared to standard of care treatment alone. Acute intermediate-high risk PE patients are those with acute symptoms (<14 days), simplified Pulmonary Embolism Severity Index (sPESI) > 0, normal systemic arterial blood pressure (>90 mmHg) without vasopressor support, elevated biomarkers (troponin or BNP), and evidence of RV dysfunction (right ventricular to left ventricular ratio  $\geq 0.9$ ).

### 1.2.1. PRIMARY ENDPOINT

Change in percentage of clot lysis by chest computed tomographic angiography (chest CTA) (Refined Modified Miller Score; RMMS) after 24 mg of systemic (intravenous; IV) tPA compared with baseline CTA RMMS.

### 1.2.2. SECONDARY ENDPOINTS

- Change in percentage of clot lysis by chest computed tomographic angiography (chest CTA) (Refined Modified Miller Score; RMMS) from baseline to 24 hours for treatment A compared with treatment B.
- Change in right ventricular to left ventricular diameter ratio (RV/LV) as measured by chest CTA from baseline to  $24 \pm 8$  hours after the infusion of very low dose systemic (IV) tPA in patients with acute intermediate-high risk (submassive) PE compared with placebo.

- Change from baseline in echocardiographic parameters including RV/LV ratio, tricuspid annular plane systolic excursion (TAPSE), estimated right ventricular systolic pressure (RVSP), and collapse of the inferior vena cava (IVC) with respiration within 24 hours  $\pm$  8 hours and at 30  $\pm$  5 days after the end of the systemic (IV) tPA infusion compared with placebo.
- 6 Minute Walk Test (6MWT) distance with the Borg Dyspnea Scale score (Borg score) and requirement for oxygen therapy at Day 30, 180 and Day 365 clinic follow-up compared with placebo.
- Quality of life (QOL) as measured by the PROMIS PF-6 and Pulmonary Embolism Quality of Life (PEmb-QOL) at Day 30, 180, and 365 clinic follow-up compared with placebo.
- Recurrent DVT and PE at Day 30, 180 and 365 compared with placebo. Since all patients will be on apixaban, we will compare DVT and PE recurrence rates with historic controls.

### 1.2.3 SAFETY ENDPOINTS

#### Primary Safety Endpoints

The primary safety endpoint is major bleeding within 72 hours after initiating systemic tPA infusion. Major bleeding events will be defined by Global Use of Strategies to Open Occluded Arteries (GUSTO) criteria for severe or life threatening bleed. This includes:

- Intracerebral hemorrhage
- Resulting in a substantial hemodynamic compromise requiring treatment

#### Secondary Safety Endpoints

- GUSTO severe or life threatening bleeding within 30, 180 and 365 days
- Need for rescue therapies such as full dose systemic thrombolysis, catheter-directed thrombolysis, catheter directed embolectomies, or surgical embolectomy within 30 days
- Ischemic or hemorrhagic stroke within 30 days
- All-cause mortality at Day 365
- Symptomatic PE recurrence: The patient must have signs and symptoms of recurrent PE in addition to objective confirmation such as a new filling defect on chest CTA or pulmonary arteriogram at Day 365
- Hemodynamic decompensation within 30 days as defined as a systolic blood pressure  $<90$ mmHg and/or need for vasopressor support.

## 2. ETHICAL CONSIDERATIONS

This protocol and the template informed consent forms will be reviewed and approved by the Office of Research Compliance and Quality Assurance with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, site-specific informed consent forms, subject education and recruitment materials, and other requested documents — and any subsequent modifications — will also be reviewed and approved by the Cedars-Sinai IRB Board.

The Investigators will make safety and progress reports to the IRB at least annually and within three months of study termination or completion. These reports will include the total number of subjects enrolled and summaries of each DMC review of safety and/or efficacy.

### 2.1 GOOD CLINICAL PRACTICES

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonisation (ICH) consolidated

Guideline E6 for Good Clinical Practices (CPMP/ICH/135/95) and the United States Code of Federal Regulations (CFR), Title 21, Part 50 (21CFR50).

The study and any future amendments, the informed consent forms, HIPAA authorization and all recruitment materials will be submitted to the Cedars-Sinai Medical Center Institutional Review Board and will be approved by the IRB before the study or amendment is initiated. All study personnel have been trained in Human Subject's Protection, Good Clinical Practices and HIPAA.

Study tasks will be delegated by either Co-PI. No study personnel for whom sanctions have been invoked or where there has been scientific misconduct or fraud will be utilized in this study. The Investigators will assure that all staff are qualified by education, training, and experience to perform their respective tasks delegated to them.

All study records will be made available to the BMS/Pfizer Alliance and the FDA.

## 2.2. INSTITUTIONAL REVIEW BOARD

Before study initiation, we will obtain a written and dated approval letter from the Cedars-Sinai Medical Center IRB for the protocol, consent form, HIPAA Authorization form and all recruitment materials. The investigator will provide the IRB approval letter, stamped approved consents and recruitment materials to the BMS/Pfizer Alliance.

The investigator will provide the BMS/Pfizer Alliance and Cedars-Sinai Medical Center IRB with Serious Adverse Events (SAEs), protocol deviations and Data Safety Monitoring Board correspondences.

## 2.3. INFORMED CONSENT

The Investigators will:

- a) Provide a copy of the IRB approved consent form, HIPAA form and recruitment materials written in an easily understood language.
- b) Obtain an interpreter to help facilitate the informed consent discussion for non-English speaking patients.
- c) Emphasize that the study is voluntary and the potential subjects care will not be affected by declining participation.
- d) Explain the study in detail including purpose of the study, study procedures, potential risks, benefits, and alternatives to study participation.
- e) Allow the potential subject/legal representative to ask questions.
- f) Allow the potential subject/legal representative time to consider the study.
- g) Obtain an informed consent signed and personally dated by the participant or the subject's legally acceptable representative, and by the person who conducted the informed consent discussion before any study procedures are initiated.
- h) For non-English speaking subjects, obtain the English informed consent with the signatures mentioned above, along with the interpreter's signature as witness and obtain the short form consent in the subject's native language.
- i) If the informed consent is initially given by a legal representative and the subject becomes capable of providing their own consent, the informed consent process will take place again with the subject to assure they still wish to proceed with the study.
- j) Write a note in the medical record detailing the informed consent process.

## 2.4. *PROTOCOL AMENDMENTS*

Any modifications to the protocol which may impact the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the BMS/Pfizer Alliance and approved by the IRB prior to implementation.

## 2.5. *CONFIDENTIALITY*

All study-related data will be stored securely at study sites. The data will be coded with a unique study-specific identifier. Data will be stored on secured server, behind CSMC's firewall and only accessible to select study investigators.

# 3. *INVESTIGATIONAL PLAN*

## 3.1. *STUDY SETTING*

Cedars-Sinai is a full-service, acute tertiary care hospital and the largest nonprofit academic medical center in the Western United States. The Medical Center is located on a 24-acre site, which includes a 1.6 million square foot main complex and 12 other structures, for a total of more than 4.1 million sq. ft. This tertiary care facility contains over 800 beds for Internal Medicine, Obstetrics, Gynecology, Pediatrics and Surgery; a 28-bed rehabilitation and outpatient surgery unit; a 29-bed Skilled Nursing and Assessment Unit; the 150-bed Saperstein Critical Care Tower; and the new Advanced Health Sciences Pavilion. CSMC is a major teaching facility of the David Geffen School of Medicine at UCLA, with over 250 full-time faculty members in ten different departments. As a part of the DGSOM, most of the full-time staff hold full academic titles at UCLA, are active in the governance and committee structure of UCLA Academic Senate (graduate and undergraduate schools alike), and participate in the training of medical students, interns, residents and fellows. Cedars-Sinai marked its transition to a degree-granting institution June 11, 2013 by awarding doctorates to seven students in its own Graduate Program in Biomedical Sciences and Translational Medicine. At present, a total of 32 students have been awarded their doctorates. CSMC boasts a world-renowned faculty and over 60 highly competitive graduate medical education programs for more than 350 residents and fellows. Biomedical research is an integral function of the Medical Center's commitment to developing excellent patient care. Translational and clinical research at CSMC falls under the purview and oversight of the Burns and Allen Research Institute, ranked among the top ten non-university biomedical research institutions in the nation in terms of funding from the National Institutes of Health. The scope of research conducted at CSMC encompasses a broad spectrum of disease-related investigations, ranging from molecular genetics, biochemical analysis, comparative animal research to clinical investigation, therapeutic trials, and patient care outcomes research. Over 1,888 projects involve more than 341 principal investigators. New federal funding for research at CSMC has increased by more than 74.3% from FY 16. As of June 2017, there were 1,398 IRB-approved studies conducted by more than 341 unique PIs and 450 new studies approved with 128 unique PIs. Federal support as of June 2017 at CSMC for 425 federal projects reached a total of 65 million/yr that produce an average of approximately one peer-reviewed publication per working day. There is over 440,000 square feet of laboratory and laboratory support space, including the seven-story, 218,000 square foot, Barbara and Marvin Davis Research Building, adjacent to the main hospital, and the new state of the art Advanced Health Sciences Pavilion (AHSP) which opened in May 2013. Cedars-Sinai has a multi-disciplinary and comprehensive PE response team (PERT) program consisting of both acute care as well as long term follow-up. More than 600 acute PE patients are seen and evaluated at Cedars-Sinai, each year.

### **Scientific Environment: Cedars-Sinai Medical Center**

As the largest non-profit academic medical center in the Western United States and the largest teaching hospital affiliated with the David Geffen School of Medicine at UCLA, CSMC boasts a world-renowned faculty and over 60 highly competitive graduate medical education programs for more than 350 residents and fellows. A major expansion of research infrastructure has recently increased existing wet lab space to 400,000 sq. ft. with the completion of the new Advanced Health Sciences Pavilion (AHSP). The AHSP houses clinical programs, research laboratories, and expanded vivarium space, and is specifically intended to stimulate translational medicine by providing an environment that fosters interaction between translational scientists and clinicians. In addition, intensive recruitment efforts during the last five years have added over two dozen outstanding faculty investigators.

The scope of research conducted at CSMC encompasses a broad spectrum of disease-related investigations ranging from molecular genetics, biochemical analysis, comparative animal research to clinical investigation, therapeutic trials, and patient care outcomes research. Over 1,280 projects involve more than 310 principal investigators.

**Victor Tapson, MD:** In the field of venous thromboembolism, Dr. Tapson has served on the ACCP Consensus Statement for Venous Thromboembolism a number of times. He served as Chairman for the ATS Consensus Statement and Clinical Practice Guidelines for the Diagnostic Approach to Acute Venous Thromboembolism. He has cared for thousands of patients with acute PE. He has served as world-wide principal investigator (PI) or co-PI for several venous thromboembolism registries including DVT-FREE, IMPROVE, NABOR, ENDORSE. He is currently PI for the OPTALYSE PE study, the BiO2 IVCF study, and is co-PI for the world-wide TAFIa clinical trial in acute PE, as well as for the FLARE clot-extraction study. In 2014, he left Duke for an outstanding opportunity at Cedars-Sinai Medical Center where he continues this work.

**Aaron Weinberg, MD, MPhil:** Dr. Weinberg is a triple board certified (Internal Medicine, Pulmonary Disease, Critical Care) Pulmonologist at Cedars-Sinai Medical Center, specializing in the treatment and prevention of venous thromboembolic disease. He is a founding member of the Pulmonary Embolism Response Team (PERT) at Cedars-Sinai, and on a global scale, serves as the Communications Co-Chairman of the national PERT consortium. Dr. Weinberg is actively involved as Co- or Principal Investigator on over nine research studies. He is also a member of the teaching faculty for the Pulmonary and Critical Care Fellowship at Cedars-Sinai.

### **3.2 STUDY DESIGN**

This is a randomized, double-blinded, placebo-controlled, single-center study intended to investigate very low dose systemic (IV) tPA along with standard anticoagulation therapy followed by standard dose oral apixaban as a treatment for intermediate-high risk (submassive) PE. To date, studies have demonstrated that full dose (100 mg) and half-dose (50mg) systemic (IV) tPA are effective for lysing clot; however, at the expense of clinically significant bleeding. Catheter-directed trials have shown that 24mg of tPA can be administered through a pulmonary artery catheter with clinical improvement in obstructive index and RV/LV ratio without an increased risk of bleeding. However, such procedures are time consuming, expensive, and there is the concern for clinical decompensation during the intervention. To date, no study has tested whether the same low dose (24mg) of systemic (IV) tPA could be delivered systemically with equally favorable results.

In this trial, 40 patients (20 per arm) will be randomly assigned using a computer program at Cedars-Sinai Medical Center in Los Angeles, California. Additional subjects may be consented to compensate for screening failures and/or treated patients who lack sufficient data.



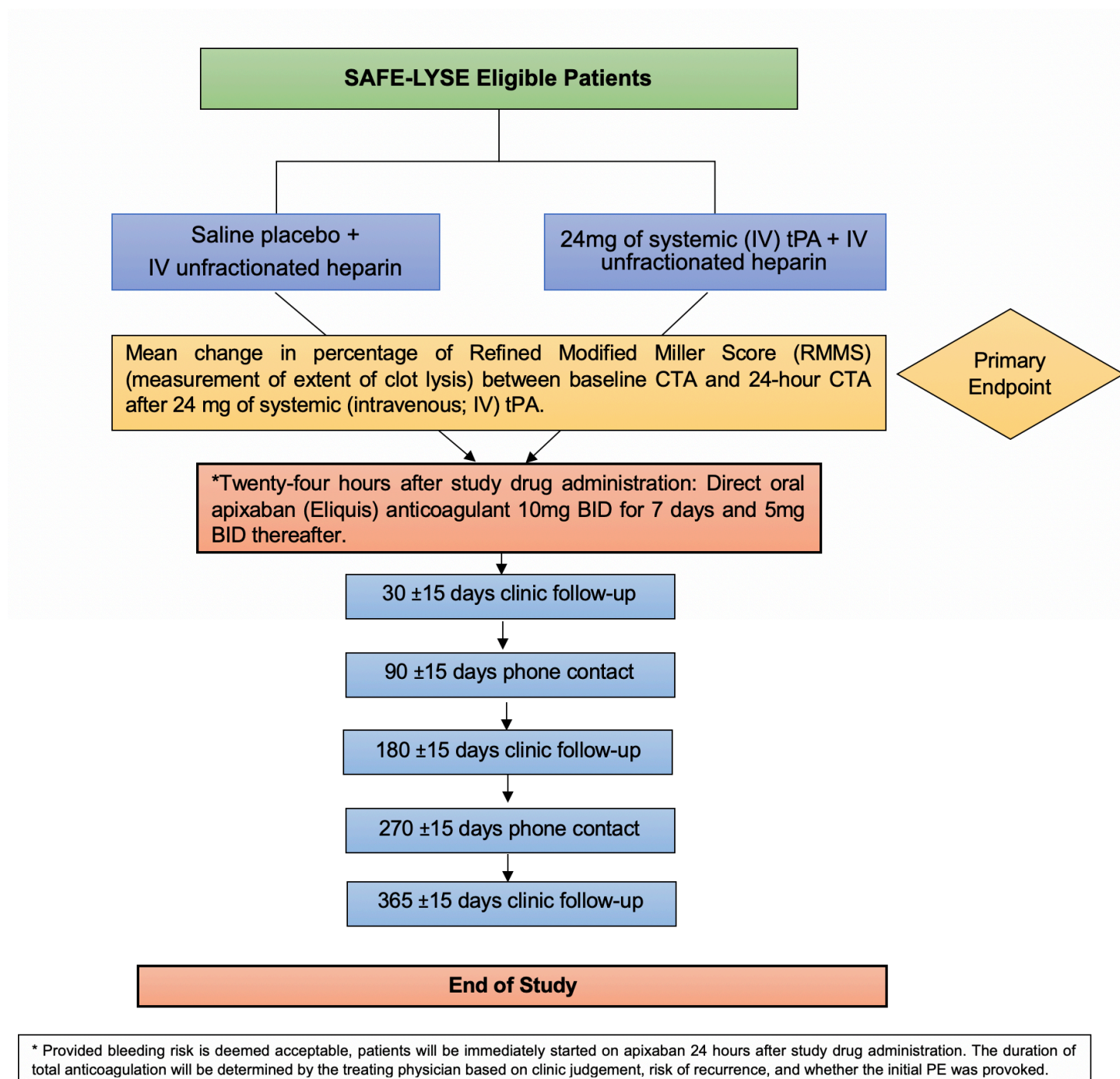
The study is planned to evaluate the reduction in clot burden (obstruction index using the Refined Modified Miller Score), improvement in RV dysfunction, and overall safety in the two treatment groups. Subjects with intermediate-high risk PE (hemodynamically stable PE with a RV dysfunction and an elevation in Troponin and/or BNP) will be randomized to one of two treatment groups: 24mg of systemic (IV) tPA + IV unfractionated heparin followed by the oral anticoagulant, apixaban, versus saline placebo + IV unfractionated heparin followed by oral apixaban.

Apixaban was chosen as the anticoagulant of choice due to its favorable bleeding profile in initial studies, which is an important consideration when using an anticoagulant following systemic thrombolysis.

Bleeding, recurrent PE and serious adverse events will be collected and reported throughout the study. Specific reporting for the primary safety (major bleeding) events will occur during the first 72 hours. We will continue monitoring for bleeding (secondary safety endpoints) for up to 30 days.

All imaging studies will be sent to the Syntactx core imaging laboratory for evaluation. Procedures for transfer of images from study site to Syntactx will be provided and we will maintain patient HIPAA confidentiality. Results of the assessments will be blinded and entered into the clinical database. All data from the study will be blinded and exclude information regarding the drug administered. Subjects will return for follow-up clinic evaluations at Day 30, 180 and 365  $\pm$  15 days. It is anticipated that the clinical study duration will be up to 24 months including first subject enrolled through to last subject completed or until the study is formally terminated. An individual subject's participation will be approximately 1 year.

The figure below shows the schematic summary of the trial design:



### 3.3. STUDY POPULATION

#### 3.3.1. INCLUSION CRITERIA

Patients eligible for the trial must comply with the following at randomization:

- Male or female 18-75 years in age
- Chest CT angiogram evidence of proximal PE with a filling defect in at least one main pulmonary artery or lobar artery
- PE symptom duration ≤14 days

- Intermediate-high risk PE: defined as PE with significant clot burden, RV dysfunction elevation in either troponin and/or BNP. and hemodynamically stable (systolic blood pressure >90 mm Hg without the use of vasopressor support)
- Randomization within 36 hours of anticoagulation
- Signed and dated informed consent obtained from subject or Legally Authorized Representative before initiation of any study procedures

### 3.3.2. EXCLUSION CRITERIA

Patients with any one of the following will be excluded from participation in this clinical trial:

- Stroke or transient ischemic attack (TIA), head trauma, or other active intracranial or intraspinal disease within one year
- Recent (within one month) or active bleeding from a major organ
- Major surgery within seven days
- Clinician deems the subject too high-risk for bleeding using HAS-BLED criteria
- History of any hematologic disease or coagulopathy
- Cirrhosis (as determined by Child-Pugh B or C)
- History of heparin-induced thrombocytopenia (HIT)
- Hemodynamic instability defined as systolic blood pressure (SBP) less than 90 mm Hg and/or use of vasopressors for greater than 15 minutes
- Severe hypertension as define as systolic blood pressure (SBP) greater than 180 mm Hg
- Cardiac arrest or active cardiopulmonary resuscitation (CPR)
- Receiving neuraxial anesthesia or undergoing spinal puncture
- Patient with prosthetic heart valves
- Evidence of irreversible neurological compromise
- Evidence of poor functional status
- History of a major gastrointestinal bleed
- Active gastric or duodenal ulcers
- Use of thrombolytics or glycoprotein IIb/IIIa antagonists within 3 days prior to diagnosis
- Lovenox administration within 12 hours of randomization
- Direct-acting oral anticoagulant use (dabigatran, rivaroxaban, apixaban, or edoxaban) with last known dose within 48 hours.
- Hemoglobin < 10 g/dL
- platelets < 100 thousand/ $\mu$ L
- INR > 1.4
- Alanine transaminase (ALT) or aspartate transaminase (AST)  $\geq$  2 times upper limit of normal (ULN)
- Total bilirubin (TBL)  $\geq$  1.5 times ULN (except due to confirmed Gilbert's syndrome)
- creatinine clearance < 30 mL/min
- Patient is pregnant (positive pregnancy test; women of childbearing capacity must be tested prior to enrollment) or breast feeding
- Patient who is a prisoner, or if subject who becomes compulsory detained
- Active cancer defined as diagnosis of cancer within six months before the study inclusion, or receiving treatment for cancer at the time of inclusion or any treatment for cancer during 6 months prior to randomization, or recurrent locally advanced or metastatic cancer
- Known allergy, hypersensitivity or thrombocytopenia from heparin, tPA, apixaban, or iodinated contrast except for mild-moderate contrast allergies for which steroid pre-medication can be administered within 12 hours prior to the CTA.
- HIV/AIDS

- Weight >130 kg or < 40 kg on day of randomization

### 3.3.3 WOMEN OF CHILDBEARING POTENTIAL

Women of childbearing potential is defined as any female who has experienced menarche and who has not been surgically sterilized or is not postmenopausal. Menopause is as 12 months of amenorrhea in a woman over age 45 in the absence of other physiological causes. Serum beta human chorionic gonadotropin ( $\beta$ -hCG) pregnancy test will be performed at the Screening Visit on all women of childbearing potential.

During the duration of the study, women of childbearing potential must agree to use two effective birth control methods (for example: birth control pills, condoms, etc) at the same time, and be able to comply with effective contraception without interruption during the study therapy (including dose interruptions).

## 3.4. CONCOMITANT TREATMENTS

### 3.4.1 PROHIBITED AND/OR RESTRICTED TREATMENTS

The following systemic medications may increase the risk of bleeding and will not be concurrently administered during the study:

- Other antithrombotic agents such as vitamin K antagonists (i.e., warfarin)
- Other factor Xa inhibitor oral anticoagulants (e.g. rivaroxaban, edoxaban, or betrixaban)
- Fondaparinux or low molecular weight heparins
- direct thrombin inhibitors (dabigatran, argatroban, bivalirudin, lepirudin, etc.)
- glycoprotein IIb/IIIa antagonists during the thrombolytic infusion
- NSAIDS

### 3.4.2 OTHER RESTRICTIONS AND PRECAUTIONS

None

## 3.5. DISCONTINUATION OF SUBJECTS FROM TREATMENT

### **Discontinuation of alteplase**

If a subject develops the following adverse events the alteplase infusion will be permanently discontinued:

- SAE or other safety concern that is related to study drug treatment
- New onset of neurological symptoms
- New onset of severe headache
- Major life-threatening bleeding (per GUSTO criteria)
- Initiating or continuing study drug places the subject at undue hazard as determined by the Investigator

The subject will continue to be followed for the remainder of the study. The subject will be assessed immediately after the infusion and appropriate clinical treatment will be instituted.

One of the PIs will use his clinical judgment to determine the treatment needed and this may include imaging studies, blood transfusions and IVC filter placement. Once the subject is stabilized, if anticoagulant therapy is considered a clinical option, the subject will be started on apixaban per protocol.

### **Discontinuation of Apixaban**

If a subject must be discontinued from apixaban before the end of the study, this will not result in automatic withdrawal of the subject from the study, and the subject should continue to be followed for efficacy and safety outcomes.

A subject should be discontinued from apixaban if:

- The investigator believes that for safety reasons (ie, adverse event) it is in the best interest of the subject to stop apixaban.
- The subject develops any condition which requires anticoagulation or thromboprophylaxis (ie, atrial fibrillation, VTE).
- The subject becomes pregnant.
- The subject requests to discontinue apixaban permanently
- The subject has a major life-threatening bleed (per GUSTO criteria);

If the subject permanently discontinues apixaban before the 6-month visit, he/she should be instructed to complete an unscheduled visit and the remaining scheduled visits. The investigator will provide a narrative to describe any adverse events that occur up to apixaban discontinuation. The appropriate adverse event or serious adverse event sections of the eCRF are to be completed.

A subject should have apixaban administration interrupted if the following conditions occur:

- Bleeding that is significant that does not fit GUSTO criteria
- Alanine transaminase (ALT) or aspartate transaminase (AST)  $\geq 2$  times upper limit of normal (ULN)
- Total bilirubin (TBL)  $\geq 1.5$  times ULN (except due to confirmed Gilbert's syndrome)
- Subjects with a significant drop in hemoglobin
- *Consider* discontinuation / follow if Hgb  $< 10$

The PI will use clinical judgment to determine course of action (labs, imaging studies, etc.) and decide when and if the apixaban can be restarted.

### **Withdrawal from the Study**

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up (only after all means of all subsequent contact, including locator services where permitted by law) or,
- Withdrawal of consent (unless specifically refused by the subject. Subject contact will be made to obtain vital status and other outcomes at the 3, 6- and 12-month visit).

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

If a subject withdraws consent from study or is lost to follow-up, his or her vital status and other outcomes will be collected at the Day 30, 180 and 365 visits either by telephone or in person, or if applicable, by a review of the subject's medical or public records unless this contact is not allowed by local regulations.

### **Stopping rules at the interim analysis for the treatment (tPA) group would involve:**

- Severe bleeding in the first 72 hours:
  - One fatal intracranial hemorrhage (ICH)
  - Two ICH of any kind
  - Severe or life-threatening bleed rate of 15%; i.e., three patients (GUSTO criteria)

- Two cases of death from acute PE (in either group), if occurring during hospitalization (deterioration in a patient who survives will not be considered in stopping rules).
- Any other issue that the DMC believes merits discontinuing the trial.

## 4. TREATMENTS

### 4.1. STUDY TREATMENTS

#### 4.1.1. Investigational Product and Apixaban Administration

Tissue Plasminogen Activator (tPA) is a commercially available drug approved for fibrinolysis of PE by systemic infusion at the dose of 100mg. tPA [Activase (alteplase)] (24mg) or placebo will be prepared by the research pharmacy.

Apixaban is an oral anti-Xa anticoagulant approved by the FDA for the treatment and prevention of venous thromboembolic disease. Study subjects will take 10mg by mouth twice a day for 7 days and 5mg by mouth twice a day thereafter for 12 months.

#### 4.1.2.. HANDLING AND DISPENSING

##### **Systemic (IV) tPA**

Systemic (IV) tPA used in the study will be procured from the research pharmacy and prepared following pharmacy procedures and manufacturer instructions.

##### **IV unfractionated heparin (Standard of Care)**

Unfractionated heparin will be administered intravenously and is approved by the FDA for the treatment and prevention of venous thromboembolic disease. Unfractionated heparin will be procured from the main hospital pharmacy and prepared following pharmacy procedures and manufacturer instructions.

##### **Apixaban anticoagulant**

Apixaban will be provided by BMS for the duration of the study. It will be stored and dispensed by the research pharmacy. After completion of the study, the treating physician will determine if apixaban should be continued based on current guidelines and expert opinion. If the treating physician desires continuation of treatment, the subject will obtain this medication via usual channels.

### 4.2. METHOD OF ASSIGNING SUBJECT IDENTIFICATION

A subject who has signed informed consent and meets all eligibility criteria will be randomized by computer to receive either very low dose systemic (IV) tPA (24mg) + anticoagulation vs normal saline placebo (of same volume as systemic [IV] tPA) + anticoagulation. Subjects will be transitioned to apixaban 24 hours after study drug administration if subject has no evidence of active bleeding nor significant hemoglobin drop (i.e.  $\geq 2$  mg/dL).

### 4.3. BLINDING AND UNBLINDING

All study personnel except the research pharmacy team will be blinded to intervention groups. The treatment medication and placebo will be prepared in similar IV bags and volumes. Assessments regarding clinical recovery will be conducted by an assessor blind to treatment allocation.

To maintain the overall quality and legitimacy of the clinical trial, unblinding should occur only in exceptional circumstances when knowledge of the actual treatment is absolutely essential for further management of the patient.

The Investigator is encouraged to maintain the blind as far as possible. The actual allocation must NOT be disclosed to the patient and/or other study personnel including other site personnel, monitors, BMS/Pfizer Alliance or project office staff; nor should there be any written or verbal disclosure of the code in any of the corresponding patient documents.

#### 4.4. TREATMENT COMPLIANCE

The Investigator(s) or designee(s) is responsible for accounting for apixaban that is issued to and returned by the subject during the course of the study. Accurate recording of all apixaban administration (including dispensing and dosing) will be made in the appropriate section of the subject's CRF and source documents. Study personnel will review the instructions printed on the package with the study subjects prior to dispensing the study drug. The apixaban will be dispensed as noted in the Flowchart of Procedures. The subjects will be instructed to return the apixaban containers, including any unused apixaban, to the study site at each visit for tablet counts and reconciliation. Subjects will be asked whether they have taken their apixaban as instructed at each study visit. Any problems with apixaban compliance will be reviewed with the subject. If a subject misses 4 or more consecutive days of dosing, the investigator will decide whether dosing should resume or whether the subject should be terminated from the study drug and entered into the Posttreatment Observational Follow-up Phase.

Study drug compliance will be calculated at each visit as:

$$\text{Compliance (\%)} = \frac{\text{Number of tablets actually taken between visits}}{\text{Number of tablets that should have been taken between visits}} \times 100$$

#### 4.5. DESTRUCTION OF STUDY DRUG

The research pharmacy will follow the CSMC drug destruction institutional policies.

### 5. STUDY ASSESSMENTS AND PROCEDURES

#### 5.1. SCREENING PROCEDURES

All subjects presenting for evaluation and treatment of intermediate-high risk PE will be considered for the study. All subjects that meet the study's inclusion criteria and do not meet any exclusion criteria are eligible for randomization into the study.

Potential subjects will be referred to the Pulmonary Embolism Response Team (PERT) by their treating physician. We will also identify potential patients through the Deep 6 AI Cohort Builder. Deep 6 will be the primary method of screening. If this primary method is not successful, then the study team is requesting a waiver of consent and HIPAA in order to conduct an additional secondary review of the patients' medical records. For the potential subjects identified via these methods, an investigator will discuss the study with their treating physician and seek permission to discuss the study with his/her patient. For patients referred by their treating physician or for patients who were identified by chart review and physician approval was granted, the informed consent process discussed in section 2.3 will be followed.

##### 5.1.1. INFORMED CONSENT

The Cedars-Sinai Medical Center informed consent template will be used to create the SAFE-LYSE informed consent form. This template includes all elements required by ICH, GCP, and applicable regulatory requirements. The informed consent form will adhere to the ethical principles that have their origins in the Declaration of Helsinki. The consent will also include a statement that the Bristol-Myers Squibb Company will not continue to supply study drug to enrolled patients after conclusion of the

study. The study participant's treating physician will be responsible to ensure that they receive appropriate standard of care or other treatment for their condition.

The consent form, HIPAA Authorization and all recruitment materials will be approved by the Cedars-Sinai Medical Center Institutional Review Board (FWA 00000468). The informed consent form will be revised if new safety information becomes available or if there are any new additions to the protocol. Subjects currently enrolled in the study who may be affected by the new information will be re-consented.

## 5.2 ENROLLMENT

Subjects will be considered enrolled in the study at the time informed consent is obtained.

### 5.2.1. SCREENING ASSESSMENTS

The following assessments will be performed at Screening:

- Informed consent
- Medical history and demographics
- Inclusion/exclusion criteria
- Pregnancy test if the subject is female and of child-bearing potential.
- Vital signs and physical exam including blood pressure, respiratory rate, heart rate, and SpO<sub>2</sub>.
- Electrocardiogram (ECG; 12 lead)
- CT Angiogram to evaluate the anatomic location of PE (at least pulmonary or lobar artery involvement). The RV/LV ratio at end-diastole and the initial Refined Modified Miller obstruction index score will be determined from this image by a third party blinded radiologist.
- Echocardiogram to measure: RV dysfunction, RV/LV ratio, TAPSE, estimated RVSP, and collapse of the IVC with respiration.
- Laboratory testing including hemoglobin (Hgb), hematocrit (Hct), platelet count, blood urea nitrogen (BUN), creatinine, aPTT, PT and INR, liver function tests (ALP, ALT, AST), troponin I, and B-type natriuretic peptide and (BNP).
- Simplified Pulmonary Embolism Severity Index (sPESI) score calculation
- Lower extremity duplex ultrasound

### 5.3. RANDOMIZATION TO TREATMENT

A subject who has signed informed consent and meets all eligibility criteria will be randomized by computer to receive either very low dose systemic (IV) tPA (24mg) + anticoagulation vs normal saline placebo (of same volume as systemic [IV] tPA) + anticoagulation. Subjects will be transitioned to apixaban 24 hours after study drug administration if subjects have no evidence of active bleeding nor significant hemoglobin drop (i.e.  $\geq 2$  mg/dL).

All patients who give consent for participation and who fulfill the inclusion/exclusion criteria will be randomized. Randomization will be requested by the staff member responsible for recruitment from Randomize.net.

In return, Randomize.net will send an answer form to the research pharmacy, who are not involved in assessing outcome of the study. This form will include a randomization number. A closed envelope with printed randomization numbers on it are available on-site. For every randomization number, the corresponding code for the therapy group of the randomization list will be found inside the envelopes. The research pharmacy will open the envelope and will find the treatment condition to be conducted. Treatment medication will be prepped according to the randomization assignment. Staff responsible for recruitment and symptom ratings is not allowed to receive information about the group allocation.



### 5.3.1. SEQUENCE GENERATION

Subjects will be randomly assigned to either control or experimental group with a 1:1 allocation as per a computer generated randomization schedule using permuted blocks of random sizes. The block sizes will not be disclosed to ensure concealment.

### 5.3.2. CONCEALMENT MECHANISM

Subjects will be randomized using Randomize.net, which is an online, central randomization service. Allocation concealment will be ensured, as the service will not release the randomization code until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed.

### 5.4. STUDY INTERVENTIONS

Eligible patients will be randomized in equal proportions between very low dose systemic (IV) tPA (24mg) + IV unfractionated heparin or saline placebo + IV unfractionated heparin. Study drug will be infused as follows: 4mg bolus IV push over 1 minute followed by 20mg infused IV over 19 minutes.

The study drug will be purchased from Genentech in its commercially available recombinant form. The study drug and placebo will be relabelled by the Cedars-Sinai Medical Center Research Pharmacy according to MHRA (Medicines and Healthcare Regulatory Agency) guidelines.

Study drug will be administered within 36 hours of anticoagulant administration. Study drug or placebo will be administered to the patient by a study-trained nurse while the patient is in hospital. All personnel will be blinded to the identity of the IV bag contents.

#### 5.4.1. TREATMENTS AND TIMING

<b>SAFE-LYSE Flowchart of Procedures</b>											
<b>Procedures</b>	<b>Baseline up to 48 hours pre study medication</b>	<b>Day 0</b>	<b>Day 1</b>	<b>Day 2</b>	<b>Day 3 &amp; Day 7</b>	<b>Day 30 ±15 days (Clinic Visit)</b>	<b>Day 90 ±15 days (Phone contact)</b>	<b>Day 180 ±15 days (Clinic contact)</b>	<b>Day 270 ±15 days (Phone contact)</b>	<b>Day 365 ±15 days (Clinic Visit)</b>	<b>ET<sup>1</sup></b>
Informed consent	X										
Inclusion/Exclusion	X										
Randomization		X									
Heparin anticoagulation therapy <sup>2</sup>	X	X	X								
Pregnancy test (if applicable)	X										
Medical and demographic history	X										
Physical exam	X		X			X		X		X	X
Vital signs including pulse ox	X	X	X	X		X		X		X	X

**SAFE-LYSE Flowchart of Procedures**

Procedures	Baseline up to 48 hours pre study medication	Day 0	Day 1	Day 2	Day 3 & Day 7	Day 30 ±15 days (Clinic Visit)	Day 90 ±15 days (Phone contact)	Day 180 ±15 days (Clinic contact)	Day 270 ±15 days (Phone contact)	Day 365 ±15 days (Clinic Visit)	ET <sup>1</sup>
Chest contrast-enhanced computed tomographic angiogram (chest CTA)	X		X								
Echocardiogram	X		X			X		X			X
Ultrasound of lower extremities to rule out DVT	X										
ECG	X										
Hemoglobin, hematocrit, platelet count	X	X	X	X		X					
BUN, creatinine	X	X	✗			X					
Liver Function Tests	X		-			X					
aPTT, PT and INR	X	X	-								
Troponin I (or Troponin T)	X										
BNP	X										
sPESI	X		X								
Quality of life questionnaires						X		X		X	X
Administration of tPA/placebo		X									
Administration of apixaban <sup>3</sup>			X	X	X	X		X			
6 Minute Walk and Borg Dyspnea scale						X		X		X	X
Remote health checks (phone and email)							X		X		
Review of medications and adverse events, bleeding events and VTE events	X	X	X	X	X <sup>4</sup>	X	X	X	X	X	X

<sup>1</sup>Early Termination: Obtain if subject withdraws early<sup>2</sup>Heparin duration up to clinician discretion but patient must be on for at least 24 hours after infusion of study drug.<sup>3</sup>Could start as early as soon as 24 hours post treatment, contingent upon clinician discretion.<sup>4</sup>72-hour assessment of AE will be conducted either in person or if discharged via telephone call. Day 7 follow up will be telephone call.

## Anticoagulation

All subjects will receive unfractionated IV heparin per standard of care with a goal of aPTT of 1.5 - 2 times control which is approximately 50-70 seconds, upon established diagnosis of PE.

Twenty-four hours after study drug administration, when the bleeding risk is determined to be low by the treating physician (i.e. no active bleeding nor significant hemoglobin drop  $\geq 2$  mg/dL), post-intervention evaluations are complete, the patient is tolerating oral medications, and the patient's creatinine clearance is  $>30$  mL/min, the IV unfractionated heparin will be stopped. Provided bleeding risk is deemed acceptable, they will be immediately started on apixaban (Eliquis) 10 mg twice-daily x one week followed by 5 mg twice-daily for at least 6 months. Based on patient-specific factors, including unprovoked nature of PE event, and/or persisting DVT/PE risk factors, consideration will be given for decreasing the apixaban dose to 2.5 mg twice-daily after 6 months for the remainder of the study. The duration of total anticoagulation will be determined by the treating physician based on clinic judgement, risk of recurrence, and whether the initial PE was provoked. Apixaban will be dispensed on Day 1, 30, and 180.

## Timing of Thrombolytic Intervention

The subject will receive 24 mg of systemic (IV) tPA vs normal saline placebo within 24 hours of initiation of anticoagulation therapy.

## Systemic (IV) tPA

Commercially available formulation of systemic (IV) tPA (Genentech) may be used and all instructions for reconstitution provided in the package insert should be followed. tPA will be specially labeled for the study. The systemic (IV) tPA will be infused as follows: 4mg bolus followed by infusion at a rate of 20mg over 19 minutes for a total of 24mg.

## Normal Saline Placebo

The pharmacy will prepare a normal saline placebo packaged in the same fashion as the systemic (IV) tPA. The saline will be infused as follows: 4mg bolus followed by infusion at a rate of 20mg over 19 minutes for a total of 24mg.

## Day 0 Assessments: Pre-Infusion and Post-Infusion

- Vital signs including temperature, respiratory rate, heart rate, blood pressure, and oximetry will be obtained.
- Assessment of adverse events and bleeding events.

## Day 1 Assessments

- Vital signs including temperature, respiratory rate, heart rate, blood pressure, and oximetry will be obtained.
- Physical Examination will be completed.
- Within  $24 \pm 8$  hours of discontinuing treatment, the subject will be assessed for improvement in PE signs and symptoms including sPESI score, repeat CT angiogram for determination of thrombus burden as measured by a Refined Modified Miller Score and RV/LV ratio, and an echocardiogram.
- Laboratory tests for Hgb, Hct, platelet count, aPTT, PT and INR, BNP, troponin, BUN and creatinine will also be obtained.
- Adverse events, VTE recurrence, and bleeding events will be recorded.

## Day 2 Assessments

- Vital signs including temperature, respiratory rate, heart rate, blood pressure, and oximetry will be obtained.
- Laboratory tests for Hgb, Hct, platelet count, aPTT, PT and INR, BUN and creatinine will also be obtained.
- Adverse events, VTE recurrence, and bleeding events will be recorded.

## Follow-up Clinic Visits and Subject Contact

- The subjects will be followed until Day 365  $\pm$  15 days.
- A 72-hour follow-up assessment of Adverse Events will be conducted either in-person if the subject is still admitted at CSMC, or via telephone call if the subject is discharged.
- A Day 7 follow-up assessment of Adverse Events will be conducted via telephone call.
- The subject will return to the clinic Day 30, 180 and 365.
- The following assessments will be performed at follow-up clinic visits:
  - Echocardiogram at Day 30 and Day 180. Echocardiogram will be repeated at Day 365/EOT if last echocardiogram was abnormal.
  - Blood draw for laboratory tests, including hemoglobin, hematocrit, platelet count, BUN, creatinine, and liver function tests at Day 30.  
Physical exam and vital signs including respiratory rate, heart rate, blood pressure, temperature, and sPO<sub>2</sub>
  - 6MWT with Borg score and requirement for oxygen therapy
  - Quality of life (QOL) as measured by the PROMIS PF-6 and Pulmonary Embolism Quality of Life (PEmb-QOL)
  - Adverse Events through 1 year follow-up.
  - Signs or symptoms of recurrent VTE
  - Changes in anticoagulant medications
  - Evidence of chronic thromboembolic disease or chronic thromboembolic pulmonary hypertension
- Phone calls for remote health checks will be conducted at Day 7, Day 90  $\pm$  15 days and Day 270  $\pm$  15 days.

## 5.5. RESCUE TREATMENT

In the event of hemodynamic collapse, the following emergency supportive and therapeutic measures can be provided at the discretion of the investigator and responsible clinical team:

- Inotropic or vasopressor agents
- Additional rescue peripherally-administered systemic fibrinolytic therapy
- Surgical pulmonary embolectomy
- Catheter-assisted embolectomy including catheter directed thrombolysis and embolectomy
- IVC filters: The insertion of IVC filters is discouraged unless the subject develops a contraindication to therapeutic dose systemic anticoagulation or if the subject suffers recurrent PE despite therapeutic levels of anticoagulation.
- ECMO

## 5.6 SAFETY ASSESSMENTS

Adverse events/SAEs, vital signs, significant physical examination findings, and results of clinical laboratory tests will be assessed throughout the study. A local laboratory will perform the laboratory

analyses and will provide reference ranges for these tests. The following clinical laboratory tests will be performed:

### **Hematology**

Hemoglobin  
Hematocrit  
Platelet count

### **Liver Function Tests**

ALT  
AST  
Total Bili

### **Chemistry**

Creatinine

### **Other Analyses**

Pregnancy test (WOCBP only: screening)

## ***6. DATA COLLECTION, MANAGEMENT AND ANALYSIS***

### ***6.1. DATA COLLECTION METHODS***

After obtaining consent, all subjects are assigned a study-specific ID upon enrollment, which will be used in lieu of PHI to obtain patient data for SAFE-LYSE. The study-specific ID will be linked to the subject's medical record number. The information will be stored in a password protected file on a secure server, behind CSMC's firewall and only accessible to select study investigators.

When a physician refers patients to the SAFE-LYSE study, study staff will pre-screen the patient for eligibility. If the patient qualifies, the PI or sub-investigator will introduce the study and review the informed consent with the patient. If the patient agrees to participate, the consent form will be signed and the patient will be randomized. The research pharmacy is notified and will begin to prepare study drug or placebo as assigned. In the meantime, appropriate study staff will collect necessary labs, administer questionnaires, and complete case report forms at certain timepoints per protocol. All imaging will be de-identified and transferred to the Syntactx imaging core laboratory for evaluation. Upon discharge, study staff will coordinate attendance at Day 30, 180 and 365 follow-up visits. Study staff will also conduct interim phone calls to assess for AE's and administer questionnaires per protocol at Day 90 and 270.

#### ***6.1.2. WITHDRAWAL***

Subjects may withdraw from the study for any reason at any time. The investigator also may withdraw subjects from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Subjects also may be withdrawn if BMS/ Pfizer Alliance or government or regulatory authorities terminate the study prior to its planned end date.

All data collected prior to withdrawal will remain part of the study. Every effort will be made to have the subject return to the clinic to obtain final study assessments.

## 6.2. DATA MANAGEMENT

The Investigator will ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; CTA reports; and records kept at the pharmacy and the laboratories, as well as copies of CRFs.

### 6.2.1. DATA FORMS AND DATA ENTRY

Data will be collected via case report forms (CRF) and entered into a research database maintained in REDCap (Research Electronic Data Capture). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be flagged in REDCap and corrected by the study team. An audit trail within REDCap will track all changes made to the data.

CT and Echo DICOM images will be transmitted to the imaging core laboratory, Syntactx. A central reader will review the images and complete a case report form. Syntactx will read the images in bulk at the end of the study.

### 6.2.2 DATA TRANSMISSION AND EDITING

The data entry fields in REDCap will resemble the CRFs used to capture study data. Data integrity will be enforced through a variety of mechanisms. Referential data rules, valid values, range checks, and consistency checks against data already stored in the database will be supported. Checks will be applied at the time of data entry into a specific field and/or before the data is written into the database. Modifications to the data written to the database will be documented through either the data change system, an inquiry system, and/or the electronic audit trail created in REDCap for entries and changes. Data entered into the database will be retrievable for view in REDCap. The type of activity that an individual user may undertake is regulated by the privileges associated with his/her user identification code and password.

### 6.2.3 DATA DISCREPANCY INQUIRIES AND REPORTS TO CORE COORDINATING CENTERS

Additional errors will be detected by programs designed to detect missing data or specific errors in data. These errors will be summarized along with detailed descriptions for each specific problem in Data Query Reports. The research staff who receives the inquiry will respond by checking the original forms for inconsistency, checking other sources to determine the correction, and/or modifying the original form by entering a response to the query. The CDCC will be responsible for making appropriate corrections to the original paper forms whenever any data item is changed. Written documentation of changes will be available via electronic logs and audit trails.

### 6.2.4 SECURITY AND BACK-UP OF DATA

Study-related reports, documents and trackers will be stored on a HIPAA compliant secure server on a password-protected computer. The research team will ensure that records and documents pertaining to the conduct of the study are complete, accurate, filed and retained. A complete back-up of the primary database will be performed once per month.

## 6.3. DATA MONITORING

### 6.3.1. FORMAL COMMITTEE

A Data Monitoring Committee (DMC) will be assembled to assess safety endpoints. The Board will be comprised of 3 non-study personnel who are experts in the field of Pulmonary Medicine. The Board will

meet after the first 10 patients complete Day 30. The DMC will be independent from the CSMC, BMS and competing interests. A charter with further details will be available.

### 6.3.2. HARMs

A rigorous screening process will be utilized to verify eligibility. This will include reviewing the imaging diagnosis of PE (to ensure that subjects without acute PE are not inadvertently enrolled in the study), performing a detailed history and physical examination (to ensure that enrolled subjects truly fulfill all eligibility criteria), and carefully reviewing the results of laboratory testing (in particular, hematocrit, platelet count, INR, and creatinine clearance).

During study drug treatment period, the subject will be monitored during the infusion and the infusion will be stopped if bleeding occurs. To reduce the risks associated with the CTA, we will ascertain that the subject has no history of allergic reaction to the contrast and we will make sure their creatinine clearance is adequate.

During the follow-up period, changes in health status will be evaluated by the study doctor and reported as deemed appropriate.

### 6.3.3. AUDITING

Through the combination of our use of REDCap with its electronic error detection, QA/QC plan, and regular site monitoring, we will ensure the quality and completeness of data in this trial.

## 7. STATISTICAL CONSIDERATIONS

### 7.1. SAMPLE SIZE DETERMINATION

#### 7.1.1. EFFICACY

*The following information was prepared in collaboration with the Cedars-Sinai Biostatistics Department.* The *primary outcome* is mean change in percentage of clot lysis by RMMS from the 24 hour CTA after 24 mg of systemic (IV) tPA + standard anticoagulation therapy compared to the baseline CTA.

- *Statistical Analysis:* The main objective is to determine the mean change in clot lysis by RMMS from baseline to 24 hours in treatment A (systemic [IV] tPA + IV unfractionated heparin). Data will be presented as frequency (percentage, %) for categorical variables and mean ( $\pm$  SD, standard deviation) for continuous variables. Profile plots with mean RMMS ( $\pm$  SE, standard error) at baseline and 24 hours will be displayed. The post-treatment RMMS score at 24 hours as an outcome variable will be modeled using a generalized additive model for location, scale and shape [26, 27] after adjusting for the treatment group and the baseline RMMS score [28] to examine if there is a difference in the change in RMMS from baseline to 24 hours between two treatment groups. The underlying assumptions will be checked using residuals [29]. Statistical analyses will be conducted using R package version 3.4.1 [30] with two-sided tests and a significance level of 0.05.
- *Sample Size Justification:* Statistical power was estimated with a two-sided two-sample equal-variance t-test. A mean difference of at least 15 percentage units between baseline and post-treatment A will be clinically meaningful. According to a previous study [22], the baseline RMMS was 21.14 units, thus a decrease of 15% from the amounts is 3.171 units in RMMS. Using the standard deviation of the difference in RMMS to 48h post-procedure from the baseline of 2.7 units obtained from the same study, 17 patients per group (34 total) achieve 99.5% power, to detect a

difference of 15 percentage units (i.e., 3.171 units difference in RMMS) between the baseline CTA and 24 hour post-treatment CTA in treatment A with 5% significance level using a two-sided two-sample equal-variance t-test.

A *secondary outcome* is mean change in percentage of clot lysis by RMMS from the 24 hour CTA after 24 mg of systemic (IV) tPA + standard anticoagulation therapy (treatment A) compared to that of the 24 hour CTA after standard anticoagulation therapy alone (treatment B).

- **Statistical Analysis:** We will also compare the RMMS at 24 hours for treatment A, with that of treatment B (saline placebo + IV unfractionated heparin) as a secondary outcome. Data will be analyzed and presented in the same way as the primary outcome.
- **Sample Size Justification:** Statistical power was estimated in the same way as the primary outcome. 17 patients per group achieve 91% power to detect a difference of 15 percentage units between 24 hour post-treatment CTAs of treatments A and B.

Another *secondary outcome* is change from baseline RV/LV ratio by chest CTA expressed as percentage change from baseline.

- **Statistical Analysis:** Statistical analysis for the secondary outcome will be similar to the primary outcome.
- **Sample Size Justification:** Statistical power was estimated with a two-sided two-sample equal-variance t-test. A previous study [22] showed that the mean and standard deviation of percentage change in RV/LV ratio from baseline to 48 hours are 26 and 22.7, respectively. Assuming these hold for our study, data from 17 patients per group (34 total) achieve 90% power to detect a mean difference of 26 percentage units between the two treatments with 5% significance level using a two-sided two-sample equal-variance t-test.

### 7.1.2. SAFETY

- **Sample Size Justification:** The main safety risk is bleeding in a critical site. The full list of primary and secondary safety endpoints is presented in Section 1.3.4. We expect that the incidence of bleeding will be 5% or less at Day 30. Table 1 shows two-sided exact confidence intervals (Clopper-Pearson) at 95% level for selected incidences of bleeding with a sample size of 17 patients.

<b>Table 1. 95% Exact Confidence Interval Width, Lower Limit, and Upper Limit for selected incidences of bleeding</b>			
<b>Incidences</b>	<b>Confidence Width</b>	<b>Lower Limit</b>	<b>Upper Limit</b>
0.01	0.212	0	0.212
0.02	0.229	0	0.229
0.03	0.244	0	0.245
0.04	0.259	0	0.26
0.05	0.274	0.001	0.274

### 7.1.3. ATTRITION

The determined sample size is 17 subjects per arm (34 total), but we will enroll 20 per arm (40 total) to allow for potential attrition.



## 8. ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered to be related to the investigational product.

A **non-serious adverse event** is an AE not classified as serious.

### 8.1. SERIOUS ADVERSE EVENTS

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization).
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy and potential drug-induced liver injury (DILI) are not always serious by regulatory definition, these events must be reported within the SAEs timeline.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event).
- elective surgery, planned prior to signing consent.
- admissions as per protocol for a planned medical/surgical procedure.
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.

- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).

#### 8.1.1. ADVERSE EVENT COLLECTION AND REPORTING INFORMATION:

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

An appropriate SAE form (e.g., ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS. If you prefer to use your own institutional form, it must be reviewed by the BMS Protocol Manager prior to study initiation to ensure that, at a minimum, all of the data elements on the CIOMS form are present. Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.

- The CIOMS form is available at: <http://www.cioms.ch/index.php/cioms-form-i>
- The MedWatch form is available at: [MedWatch 3500 Form](#)
- The Sponsor will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance ([Worldwide.Safety@bms.com](mailto:Worldwide.Safety@bms.com)).
  - The Investigator will request from BMS GPV&E, [aepbusinessprocess@bms.com](mailto:aepbusinessprocess@bms.com) the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary.
  - GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
  - The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS ([Worldwide.Safety@bms.com](mailto:Worldwide.Safety@bms.com)).
- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).
- In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.

- Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor or BMS decision to end or temporarily halt a clinical study for safety reasons.
- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS. BMS will perform due diligence follow-up using the BMS Pregnancy Form which the investigator must complete.

**SAE Email Address:** Worldwide.Safety@BMS.com

**SAE Facsimile Number:** +1 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization. The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

- **Related:** There is a reasonable causal relationship between study drug administration and the AE.
- **Not related:** There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs).

### **Non-serious Adverse Event**

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g., IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

### **Non-serious Adverse Event Collection and Reporting**

The collection of non-serious AE information should begin at initiation of study drug. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously through week 52 visit.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

### **Laboratory Test Abnormalities**

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

### **AEs of Special Interest**

In this study, the following adverse events are to be reported to BMS, regardless of whether these reports are classified as serious or unexpected:

Potential or suspected cases of liver injury including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis.

### **Pregnancy**

If following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant).

The investigator must immediately notify [Worldwide.Safety@bms.com](mailto:Worldwide.Safety@bms.com) of this event and complete one of the following forms within 24 hours of awareness of the event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch, BMS Pregnancy Surveillance Form, or approved site SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

### **Other Safety Considerations**

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

## **9. STUDY MANAGEMENT**

### **9.1 COMPLIANCE**

#### **9.1.1 COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS**

The study will be conducted as described in this approved protocol. All revisions to the protocol will be discussed with the BMS/Pfizer Alliance. The investigator will not implement any deviation or change to the protocol without review and documented approval from the CSMC IRB of the amendment, except where necessary to eliminate immediate danger to study subjects. If a deviation or change to a protocol is implemented to eliminate immediate danger before obtaining CSMC IRB approval, as soon as possible the deviation or change will be submitted to both CSMC IRB and BMS/Pfizer Alliance for review and approval.

Documentation of the IRB approval, consent form, HIPAA authorization and all recruitment materials will be sent to the sponsor. If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form will be revised and submitted to the CSMC IRB for review and approval; (2) participants will be re-consented with the new revised consent form and the re-consenting process will be documented in the subject's chart; and (3) the new approved cosent form will be used to obtain consent from new potential subjects before enrollment.

#### **9.1.2 MONITORING**

The study will be monitored internally. Monitoring will include the review of study records, source documents, a meeting with one of the investigators about the conduct of the study and a meeting with the research pharmacists as necessary.

#### **9.1.3 INVESTIGATIONAL SITE TRAINING**

All study staff will be trained by the investigators before initiation of the study. In addition to the GCP, HIPAA, human subjects and informed consent training discussed in Section 2 of the protocol, the staff will be trained on the protocol, study drug administration, AE reporting, entry into the REDCap EDC, and study documentation. All trainings will be documented in the regulatory binder.

### **9.2 RECORDS**

### 9.2.1 RECORDS RETENTION

Essential documents will be retained by the Investigator according to the period of time outlined in the Clinical Trial Agreement. The Investigator will retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, BMS/Pfizer Alliance, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- Apixaban accountability records;
- All other source documents (subject records, hospital records, laboratory records, etc);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator will notify BMS/Pfizer Alliance if he wishes to assign the essential documents to someone else or remove them to another location. The Investigator will obtain approval in writing from BMS/Pfizer Alliance prior to destruction of any records.

All study documents will be made available if required by relevant health authorities. The Investigator or Cedars-Sinai Medical Center will take measures to prevent accidental or premature destruction of these documents.

### 9.2.2 STUDY DRUG RECORDS

The investigator will ensure that a current disposition record of investigational product is maintained in the research pharmacy and in the CRF.

- Records or logs will comply with applicable regulations and guidelines and will include:
  - Amount received and placed in storage area in research pharmacy
  - Amount currently in storage area
  - Label identification number or batch number
  - Amount dispensed to and returned by each participant, including unique subject identifiers
  - Nonstudy disposition (e.g., wasted due to expiration)
  - Amount destroyed at study site
  - Amount returned to the BMS if applicable
  - Dates and initials of person responsible for investigational product dispensing/accountability, as per the Delegation of Authority Log

### 9.3. CLINICAL STUDY PUBLICATIONS

The data collected during this study are confidential and proprietary to the investigators. Any publications or abstracts arising from this study require approval by the BMS/Pfizer Alliance before publication or presentation and must adhere to the BMS/Pfizer Alliance's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the BMS/Pfizer Alliance at

the earliest practicable time for review, but at any event no less than 30 days before submission or presentation unless otherwise set forth in the CTA. The BMS/Pfizer Alliance shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

The results of the SAFE-LYSE study will be disseminated via peer-reviewed journal publications, presentations and scientific conferences, and educational lectures nationally and internationally. Co-investigators will have priority for publishing data.

#### *9.4. REVIEW PROCESS*

Each scientific manuscript or abstract must be submitted to all SAFE-LYSE investigators and BMS/Pfizer Alliance for review of its appropriateness and scientific merit prior to submission to a journal or conference. Recommended changes to the authors will be made and the manuscript will be modified accordingly. A final version will be agreed upon by the study team.

#### *9.5. ACCESS TO DATA*

Study investigators will only be given access to the coded data sets. Project data sets will be housed in REDCap and other password-protected access systems.

#### *9.6. ANCILLARY AND POST-TRIAL CARE*

A research-related injury or illness is a direct result of the Study Drug, or a procedure performed only as a part of the study and that is not part of your standard clinical medical treatment. Injury or illness related to an underlying medical condition or caused by non-research-related activities (such as treatment generally provided outside of the study) would not be considered research-related. The CSMC IRB Chair will determine whether the illness or injury is research-related. If the subject is being treated for a research-related injury or illness, they will not pay for the costs of the appropriate medical or emergency room care provided so long as the IRB has determined that the illness or injury is research-related. CSMC has no plans to pay for losses such as lost wages.

#### *9.7. CLOSE-OUT PROCEDURES*

SAFE-LYSE may terminate at the planned target of 2 years after the last subject has been randomized, or at an earlier or later date if the circumstances warrant. Regardless of the timing and circumstances of the end of the study, close-out will proceed in two stages:

- Interim period for analysis and documentation of study results
- Debriefing of subjects and dissemination of study results.

#### *9.8. INTERIM*

Every attempt will be made to reduce to an absolute minimum the interval between the completion of data collection and the release of the study results. We expect to take about 3 to 4 months to compile the final results paper for an appropriate journal.

#### *9.9. DATABASE LOCK*

Permissions to allow data entry to the study will be removed from all persons except the Data Manager when all of the following are complete:

- All requested information has been collected
- All applicable data has been entered into REDCap
- All data queries and discrepancies have been resolved

A series of meetings will be held with the data and trial management teams, including the PI, to review the status of matters that need to be resolved before the study can be finally locked. When all standing issues are rectified, the study database will be put into a state such that further additions and changes

to the data are not possible. Data extracted after the lock will be transferred, using standard practices, to the person responsible for data analysis.

#### *9.10. REPORTING OF STUDY RESULTS*

The study results will be released to the participating physicians, referring physicians, patients and the general medical community.



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