Study of the OPTimum Duration of Acoustic Pulse ThromboLYSis ProcEdure in the Treatment of Acute Submassive Pulmonary Embolism

OPTALYSE PE – UK Extension – Revision UK Version 7

Statistical Analysis Plan

Primary and Long Term Follow Up

Protocol Number: EKOS – 12

Clinicaltrials.gov: NCT02396758

Version 1; 08 November 2019 – UK Extension

Sponsor:

EKOS Corporation, a BTG International Group Company

11911 North Creek Parkway S

Bothell, WA 98011

A. PROTOCOL SYNOPSIS

Title:	Study of the OPtimum Duration and Dose of r-tPA of Acoustic Pulse ThromboLYSis ProcEdure in the Treatment of Submassive Pulmonary Embolism OPTALYSE PE – UK Extension – Revision UK Version 7
Design:	A randomized, parallel, multi-arm, multi-center study
Brief Device Description:	The EkoSonic® Endovascular System (EKOS) employs high frequency (2-3MHz), low power ultrasound to facilitate the delivery of thrombolytic agents to the intravascular treatment site in the pulmonary arteries. The Acoustic Pulse Thrombolysis (APT) Procedure means the clinical use of EKOS in combination with r-tPA administration
Purpose:	The objective of this study is to determine the optimum dose of thrombolytic and duration of the ultrasound procedure (together are defined as the APT Procedure) as a treatment for acute submassive PE.
Primary Efficacy Endpoint:	Change in the ratio of the measurement of the Right Ventricular to Left Ventricular diameter ratio (RV/LV) as measured by CTA from baseline to 48 hours after the start of the APT Procedure.

Secondary Efficacy Endpoints:	1. Change from Screening/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 4 hours after the end of the APT Procedure, 24 and 48 hours after the start of the APT Procedure, and 30 days, 90 days and 365 days after the end of the APT Procedure 2. Change from Screening/Baseline in thrombus burden by modified Miller score as assessed by CTA at 48 hrs. after the start of the APT Procedure 3. Freedom from major harm occurring between enrolment and 30 days and assessed by the Safety Monitor using the following criteria: a. Mortality – all cause and PE related b. CV collapse: Defined as one or more of the following: i. >40mmHg drop in SBP (for >15 minutes from documented blood pressure as an in-patient) despite IV fluid challenge and absence of new atrial arrhythmia. ii. Requirement for emergency systemic thrombolysis iii. Requirement for emergency surgical embolectomy iv. Requirement for vasopressors v. Intubation/Ventilation c. Major bleeding per ISTH d. Recurrent PE (confirmed by imaging) e. Surgical correction of device related complication 4. Change in 6 minute walk (6MW) distance with BORG score and requirement for oxygen therapy at all post-hospitalization subject visits 5. Change in Quality of life (QOL) as measured by Pulmonary Embolism Quality of Life (PEmb-QOL) and EuroQual - 5 Dimensions – 5 Levels (EQ-5D-5L) at all post-hospitalization subject visits and phone contacts. 6. Healthcare resource utilisation during hospitalisation: a. Time from hospital admission to diagnosis of PE b. Time from diagnostic CT scan to initiation of treatment for PE c. Time in each Level of Care (Level 0 and 1; Level 2; and/or Level 3) through discharge. Levels are defined according to National Framework Document. d. Team managing the pt – specialties involved 7. Healthcare resource utilisation after hospitalisation and during 12 month follow-up: a. Team managing the pt - specialties b. HCP visits for VTE c. Hospital re-admission frequency and duration

A. PROTOCOL SYNOPSIS

<table>
<tr><td>Primary Safety Endpoint:</td><td>Major bleeding within 72 hours after initiating the APT Procedure</td></tr>
<tr><td>Population:</td><td>Subjects with acute symptomatic submassive PE with embolus located in at least one main or proximal lobar pulmonary artery and an end-diastole diameter RV/LV ratio ≥ 0.9 and at least one elevated biomarker. Subjects must be ≥ 18 to ≤75 years of age, have had PE symptoms for ≤14 days, and be able to be treated with APT Procedure within 48 hours of diagnostic CTA scan.</td></tr>
<tr><td>Treatment Arms:</td><td>
<table>
<tr><th>Treatment Group</th><th>Treatment Duration (hrs.)</th><th>Total dose r-tPA (one/two catheters (mg)</th><th>r-tPA infusion Rate</th></tr>
<tr><td>1</td><td>2</td><td>4/8</td><td>2 mg/hr/catheter</td></tr>
<tr><td>2</td><td>4</td><td>4/8</td><td>1 mg/hr/catheter</td></tr>
<tr><td>3</td><td>6</td><td>6/12</td><td>1 mg/hr/catheter</td></tr>
</table>
Please note that there are two doses of r-tPA in each treatment group and the dose is determined by the number of catheters placed. All data will be summarized by total r-tPA dose administered, i.e. six groups; however, the primary analysis will be based on patients who have bilateral catheters placed.</td></tr>
<tr><td>Post-APT procedure Follow-up:</td><td>Within four hours of completion of the APT Procedure, the subject will be assessed for signs and symptoms of PE including a Pulmonary Embolism Severity Index (PESI/sPESI) and have an echocardiogram obtained. Additional echocardiograms will be obtained at 24 and 48 hours in addition to a CTA at 72 hiours. The subject will return to the clinic at 30, 90 and 365 days for echocardiogram and QOL assessments.</td></tr>
<tr><td>Enrollment:</td><td><u>OPTALYSE PE</u>
101 subjects were randomized and 100 treated in the OPTALYSE PE study and were followed for one year.

<u>OPTALYSE PE – UK Extension (OPTALYSE UK)</u>
Up to 120 additional subjects were planned to be enrolled in the UK Extension study to obtain up to 75 efficacy evaluable subjects (25 efficacy evaluable subjects enrolled and randomized in each of 3 treatment arms.). Due to slow enrollment and the ability for sites to participate in the KNOCOUT study, the OPTALYSE UK sites were instructed to stop enrollment on May 1, 2019. 29 subjects were enrolled in OPTALYSE UK and sites were instructed to continue following subjects for one 1 year per the protocol.

Evaluable subjects are those who have RV/LV assessments within specified windows and scores available at baseline and at 48 hours from the start of treatment.</td></tr>
</table>

A. PROTOCOL SYNOPSIS

Clinical Sites:	**OPTALYSE PE** 19 centers within the United States and the United Kingdom enrolled into OPTALYSE PE. **OPTALYSE PE – UK Extension (OPTALYSE UK)** Up to 10 centers located in the United Kingdome were planned for OPTALYSE UK. At the time enrollment was stopped, 5 sites had enrolled subjects into OPTALYSE UK.
Time Course:	**OPTALYSE PE** Enrollment into OPTALYSE PE took place from June 2015 through November 2016 with 1 year follow-up. **OPTALYSE PE – UK Extension (OPTALYSE UK)** Enrollment into OPTALYSE UK took place from October 2017 through March 2019with 1 year follow-up.

B. SCHEDULE OF ASSESSMENTS - OPTALYSE UK

	Screening/ Baseline[1]	Post APT Procedure				Follow-up - Clinic Visit			
	Day -2 within -48 Hrs. of APT start	Day 0 within 4 Hrs. of APT end	Day 1 24 Hrs. ±6 hrs of APT start	Day 2 48 Hrs. ±6 hrs of APT start	Day 3 72 Hrs. of APT start or D/C[10]	Day 30 ± 5 D	Day 90 ± 10 D	Day 365 ± 14D	Early Term[11]
Informed Consent	X								
Demographics	X								
Medical History, Physical Exam, & Risk Factors	X								
Vital Signs[2,3]	X	X	X	X		X	X	X	X
Electrocardiogram	X								
CTA	X			X					
Hemodynamics/SvO2[4]	Optional								
PESI/sPESI	X	X	X	X					
Echocardiogram[5,6]	X	X	X	X		X	X	X	X
Laboratory Tests[7]	X	X		X					
Biomarkers: Troponin, BNP/NT-proBNP, lactate/lactic acid, and D-dimer	X			X					
6 Minute Walk Test (6MW)						X	X	X	X
QOL Assessment: PEmb-QOL; EQ-5D-5L						X	X	X	X
Adverse/VTE/Bleeding Events		X	X	X	X	X	X	X	X
Anticoagulant medications[8]	X	X	X	X	X	X	X	X	X
Concomitant medications[9]	X	X	X	X	X	X	X	X	X

1. Screening/Baseline assessments to be completed within 48 hours prior to the start of APT Procedure unless otherwise noted (see Section 6.1 and 7).
2. Vital Signs are additionally required at the start and at the conclusion of the APT Procedure and at the time of obtaining an echocardiogram (see Section 7.4).
3. Select participating sites: Additional vital signs will be obtained at the start of the APT Procedure and at each 30 minute interval until 4 hours post procedure (see Section 7.8).
4. It is recommended to collect right heart pressures and SvO2 prior to start of APT Procedure (see Section 7.5).
5. Include RV/LV ratio, TAPSE, estimated RVSP, and collapse of the inferior vena cava (IVC) with respiration (see Section 7.7).
6. Select participating sites: an RV/LV ratio from a limited echocardiogram will be obtained hourly after the start of the APT Procedure through 4 hrs post procedure (see Section 7.8).
7. Hgb/Hct, Platelet count, BUN/Creatinine, aPTT, PTand INR. Pregnancy tests for females of childbearing age (see Section 6.1 and 7.10). At select participating sites, measures of thrombolytic actvitity such as r-tPA antigen, plasmin-antiplasmin, d-dimer, Plasminogen activator inhibitor – 1 (PAI-1), thrombin generation, prothrombin factor 1+2, and soluble S100A10 will also be collected.
8. Subject is excluded if thrombolytics or glycoprotein IIb/IIIa antagonists given **within 3 days prior** to start of APT Procedure.
9. Concomitant (non-anticoagulation) medications will be recorded from Screening/Baseline through 12 month follow-up for medications prescribed to treat a serious adverse event (SAE) only.
10. Adverse/VTE/Bleeding Events: Document at 72 hours after the start of the APT Procedure or at discharge whichever is earlier.
11. Early termination: obtain if subject withdraws early

1 STUDY OBJECTIVES AND ENDPOINTS

1.1 Objective

The objective is to determine the optimum dose of thrombolytic and duration of the ultrasound procedure (together defined as the APT Procedure) as a treatment for acute submassive PE. Symptomatic submassive PE are patients with acute (≤14 days) PE with normal systemic arterial blood pressure (>90 mmHg) and evidence of RV dysfunction (Right Ventricular to Left Ventricular diameter ratio, i.e., RV/LV ratio ≥0.9).

1.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in the ratio of the measurement of the RV/LV as measured by computed tomographic angiography (CTA) from baseline to 48 ± 6 hours after the start of the APT Procedure.

1.3 Secondary Efficacy Endpoints

1. Change from Screening/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 4 hours after the end of the APT Procedure, 24 and 48 hours after the start of the APT Procedure, and at 30 days, 90 days and 365 days after the end of the APT Procedure.
2. Change from Screening/Baseline in thrombus burden by modified Miller score as assessed by CTA at 48 hrs. after the start of the APT Procedure.
3. Freedom from major harm occurring between enrolment and 30 days and assessed by the Safety Monitor using the following criteria:
    a. Mortality – all cause and PE related
    b. CV collapse: Defined as one or more of the following:
        i. >40mmHg drop in SBP (for >15 minutes from documented blood pressure as an in-patient) despite IV fluid challenge and absence of new atrial arrhythmia.
        ii. Requirement for emergency systemic thrombolysis
        iii. Requirement for emergency surgical embolectomy
        iv. Requirement for vasopressors
        v. Intubation/Ventilation
    c. Major bleeding per ISTH
    d. Recurrent PE (confirmed by imaging)
    e. Surgical correction of device related complication

4. Change over time in 6 minute walk (6MW) distance with BORG score and requirement for oxygen therapy at all post-hospitalication subject visits

5. Change in Quality of life (QOL) as measured by the Pulmonary Embolism Quality of Life (PEmb-QOL) and EuroQual - 5 Dimensions – 5 Levels (EQ-5D-5L) at all post-hospitalization subject visits and phone contacts.
6. Healthcare resource utilisation during hospitalisation:
    a. Time from hospital admission to diagnosis of PE
    b. Time from diagnostic CT scan to initiation of treatment for PE
    c. Time in each Level of Care (Level 0 and 1; Level 2; and/or Level 3) through discharge. Levels are defined according to National Framework Document.
    d. Team managing the pt – specialties involved

7. Healthcare resource utilisation after hospitalisation and during 12 month follow-up:
    a. Team managing the pt - specialties
    b. HCP visits for VTE
    c. Hospital re-admission frequency and duration

1.4 Safety Endpoints

1.4.1 Primary Safety Outcome

The primary safety outcome is frequency of major bleeding within 72 hours after initiating the APT Procedure. Evaluation of clinically overt bleeding will depend upon the suspected bleeding site and clinician's judgment. Major bleeding events will be defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria for major bleeding as assessed by the Medical Monitor

1. Fatal bleeding and/or

2. Symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome) and/or

3. Bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red blood cells

1.4.2 Secondary Safety Outcomes

1.4.2.1 Technical procedural complications

Technical complications associated with the use of the EkoSonic® device will be recorded during catheter placement in the pulmonary artery and during the infusion procedure. Any significant dissection or perforation of the pulmonary arteries will be visible on the follow-up CTA.

1.4.2.2 Symptomatic recurrent PE

For the diagnosis of symptomatic recurrent PE throughout the study, documentation of clinical symptoms and/or signs suggesting recurrent PE is required in combination with objective confirmation with CTA, ventilation-perfusion lung scanning, or invasive contrast PAgram. Specifically, symptomatic recurrent PE will be diagnosed if a new filling defect (compared with the baseline CTA) is demonstrated on CTA or invasive contrast PAgram.

1.4.2.3 Mortality

All-cause mortality throughout the study will be recorded. Cause of death will be classified as related to cancer, myocardial infarction, PE, or other disease state based on MedDRA preferred terms for SAE with outcome of death.

2 STATISTICAL ANALYSIS

2.1 Analysis Subject Sets and Missing Data Handling Convention

The **Intent-to-Treat (ITT) Subject Set** includes all randomized subjects; analyses will be performed for all primary and secondary efficacy endpoints for the ITT Subject Set. Unless otherwise specified, all available data will be used for ITT analyses regardless of whether the assessment timing is within the specified window.

The **Efficacy Evaluable (EE) Subject Set** includes randomized subjects who received the APT Procedure with EKOS treatment and for whom a CTA calculated RV/LV ratio is available at both baseline and 48 ± 6 hours from the beginning of the APT procedure. For the primary endpoint of CTA RV/LV ratio change from baseline to 48 ± 6 hours only, a subset analysis will be performed for EE patients in the ITT Subject Set. These analyses will only include data obtained in the pre-specified windows of (a) within 48 hours before APT start for baseline and (b) within ± 6 hours for 48 hours from APT start.

Safety Evaluable Subjects are defined as enrolled subjects for whom the APT Procedure was initiated, i.e. venous access attempted for EkoSonic catheter introduction, as indicated in database by a non-mising start time for EkoSonic placement (EXSTTM in the interventional procedure (EX) dataset) . The **Safety Subject Set** (SSS) includes all safety evaluable subjects and will be used for all safety analyses.

Missing data will not be imputed for the efficacy and safety analyses.

2.2 General Methodology

All analyses will be performed separately for each of the treatment arms. Continuous measures will be summarized as n, mean, standard deviation, median, minimum and maximum. Categorical data will be summarized as frequency and percentage for each data category.

Where possible and indicated in Appendix 1 List of Tables , a pooled analysis will be performed with the OPTALYSE PE and OPTALYSE UK extension data combined. In each case, the same Analysis Subject Set for each population will be used.

2.3 Efficacy Analyses

2.3.1 Primary Efficacy Analysis

The primary efficacy outcome is the change in the RV diameter-to-LV diameter ratio, from Screening/Baseline to 48 ± 6 hours after the start of the APT procedure, as determined by CTA. For each treatment arm, the mean RV/LV ratio change will be compared to the historical control value of a 0.20 reduction for the heparin arm[1]. For this study, a 1-sided $p<0.15$ by t test rejecting a ≤ 0.20 reduction will regarded as a positive sign for further investigating a treatment regimen. As an example, should the standard deviation be 0.41 as observed in the SEATTLE II study, with 25 evaluable subjects the 1-sided p value would be <0.15 if the mean RV/LV ratio reduction is 0.29 or higher. To limit the 3-arm total false positive error rate to 0.15, the Hochberg procedure[2] will be used for statistical testing.

The main primary endpoint analyses will be performed for the ITT Subject Set and the Evaluable Subjects subset.

To explore a potential increasing trend in RV/LV ratio reduction for treatment Groups 1 through 3 as defined in Protocol Synopsis, i.e. Group 1 having the least reduction and Group 3 having the most reduction, an exploratory regression analysis will be performed on both absolute change and percent change data from all 3 groups. The independent variables will include baseline RV/LV ratio value, the unilateral vs. bilateral PE indicator, and treatment groups 1 through 3 coded ordinally as 1, 2, and 3. This exploratory analysis will only be performed on the ITT Subject Set.

2.3.2 Secondary Efficacy Analyses

Secondary efficacy outcomes are the following:

1. Change from baseline in echocardiographic parameters including RV/LV ratio, TAPSE, estimated RVSP, and collapse of the IVC with respiration within 4 hours of the end of the APT procedure,

24 and 48 hours after start of the APT procedure, 30 days, 90 days and 365 days after the APT procedure (procedure start date = Day 0)

2. Change from baseline in thrombus burden by modified Miller score as assessed by CTA at 48 hours after the start of the APT procedure
3. Freedom from major harm occurring between enrolment and 30 days and assessed by the Safety Monitor using the following criteria:
    a. Mortality – all cause and PE related
    b. CV collapse: Defined as one or more of the following:
        i. >40mmHg drop in SBP (for >15 minutes from documented blood pressure as an in-patient) despite IV fluid challenge and absence of new atrial arrhythmia.
        ii. Requirement for emergency systemic thrombolysis
        iii. Requirement for emergency surgical embolectomy
        iv. Requirement for vasopressors
        v. Intubation/Ventilation
    c. Major bleeding per ISTH
    d. Recurrent PE (confirmed by imaging)
    e. Surgical correction of device related complication

4. 6 minute walk (6MW) distance with BORG score and requirement for oxygen therapy at 30 days, 90 days and 365 days, and changes from 30 days
5. Quality of life (QOL) as measured by the Pulmonary Embolism Quality of Life (PEmb-QOL) and EuroQual - 5 Dimensions – 5 Levels (EQ-5D-5L) at all post-hospitalization subject visits and phone contacts.
6. Healthcare resource utilisation during hospitalisation:
    a. Time from hospital admission to diagnosis of PE
    b. Time from diagnostic CT scan to initiation of treatment for PE
    c. Time in each Level of Care (Level 0 and 1; Level 2; and/or Level 3) through discharge. Levels are defined according to National Framework Document.
    d. Team managing the pt – specialties involved
7. Healthcare resource utilisation after hospitalisation and during first 12 months:
    a. Team managing the pt - specialties
    b. HCP visits for VTE
    c. Hospital re-admission frequency and duration

For continuous efficacy endpoints, n, mean, standard deviaton, median, minimum, and maximum will be provided at baseline and all appropriate follow-up timepoints. Changes from baseline (absolute change and percent change) will be similarly summarized at all follow-up time points with 95% confidence intervals for mean changes. Statistical significance for changes from baseline will be assessed by t-test. In addition,

combining data over 4 hours, 24 hours, 48 hours, 30 days, 90 days and 365 days post APT procedure, mixed model repeated measures (MMRM) analyses will be performed for all echocardiogram absolute and percent changes from baseline measures (RV/LV ratio, TAPSE, and RVSP). The baseline value, unilateral vs. bilateral PE indicator, and time point indicators will be included in the model as covariates in all cases.

For IVC collapse (with respiration) changes from baseline, the data will be summarized as 2 × 2 tables for paired binary data at each follow-up time point. The statistical significance will be assessed by the exact McNemar's test.

The above secondary analyses will be performed for the ITT Subject Set.

Lastly, as for the primary endpoint of RV/LV ratio decrease from baseline, an increasing benefit trend from treatment groups 1 through 3 will be explored for echocardiogram endpoints (RV/LV ratio, TAPSE, and RVSP at all six timepoints), and modified Miller score (at 48 hours) for changes from baseline. The analyses will be the same as that for the primary RV/LV ratio analysis and will be performed for the ITT Subject Set.

2.4 Safety Analysis

Safety analyses will be performed for the **Safety Subject Set**.

For the primary safety analysis, the number and percentage of subjects with major bleeding events within 72 hours of start of APT procedure will be reported with a 95% Wilson confidence interval.

Secondarily, the frequencies and proportions of subjects with technical procedural complications, symptomatic recurrent PE, and all cause mortality through the 365 day follow-up period will be reported with 95% Wilson score confidence intervals.

In addition, adverse events experienced through 30 days and SAEs through 365 days will be mapped to standard terms and summarized. For a given event, the frequency and proportion of subjects reporting it will be tabulated according to the worst severity experienced. Two separate tables will be constructed for each a) all reported events, b) events related to interventional procedure (not EKOS system), c) events related to EKOS system, d) events related to thrombolytic drug, e) events related to anticoagulant drug, f) bleeding events (3rd table will be constructed through 72 hours), and g) SAEs.

2.5 Sample Size And Power Estimation

The primary efficacy endpoint for the study is the 48-hour decrease in RV/LV ratio. The Fasullo[1] study's heparin arm indicated a mean RV/LV ratio decrease of 0.20. Based on these results, we propose a mean

48-hour RV/LV ratio (absolute) decrease ≤ 0.20 as the null hypothesis for this study. Rejecting the null hypothesis with a 1-sided $p<0.15$ by t test will be regarded as a positive sign for further investigating a treatment regimen. For submassive PE subjects in the SEATTLE II study, a mean RV/LV ratio reduction of 0.43 was observed with a standard deviation of 0.41. Should these results be true for a regimen in the current study, with 25 evaluable subjects, the power to detect a positive signal is approximately 0.96.

The simultaneous power for the three treatment groups at the planned sample size of with n=25 evaluable per arm is approximately 0.88 by the Hochberg procedure[2].

Appendix 1: List of Tables (All summaries and analyses will be by treatment arm for the UK Extension portion of the study unless otherwise specified. Except for RV/LV ratio analyses, all p values are 2-sided. Analyses that will be conducted for the combined portions of the study (OPTALYSE PE plus UK Extension) as well as for the UK Extension alone and are indicated by an asterisk.)

Subject Set = ITT for (1) – (20) Unless Otherwise Specified

1) Enrollment by Site

2) Demographics
   a) Age
   b) Weight
   c) BMI
   d) Gender
   e) Ethnicity (Hispanic vs. not Hispanic)
   f) Race

3) Clinical History and Risk Factors
   (a) – (v) on Clinical History and Risk Factors CRF.
   a) Hypercholesterolemia
   b) Congestive Heart Failure
   c) Hepatic Insufficiency
   d) Renal Insufficiency
   e) TIA or Stroke
   f) Active Cancer
   g) Diabetes
   h) Hypertension
   i) Tobacco use
   j) BMI ≥ 30.0
   k) COPD
   l) History of Cancer in Remission
   m) Family History of VTE
   n) Chronic Inflammatory Disorders
   o) Acute Infectious Illness within 30 Days of signing ICF
   p) Atherosclerotic Cardiovascular Disease
   q) Currently taking a Hormonal Contraceptive or Replacement Therapy
   r) Osteoarthritis of Either Hip or Knee
   s) All co-morbid conditions under A25 of Clinical History and Risk Factors eCRF, i.e. Cerebrovascular Disease, Recent GI or GU Bleeding, Currently receiving oral anticoagulants, Recent (within 2 weeks) major surgery, Recent trauma (within 2 weeks), High Liklihood of Left Heart Thrombus, Acute Pericarditis, Subacute Bacterial Endocarditis, Hemostatic Defects, Significant Hepatic Dysfunction, Diabetic Hemorrhagic Retinopathy or Other Hemorrhagic Opthalmic Conditions, Septic Thrombophlebitis or Occluded AV Cannula at Seriously Infected Site, Any other Condition in which Bleeding Constitutes a Significant Hazard
   t) All hypercoagulables under A26 of Clinical History and Risk Factors eCRF, i.e. Anticardiolipin Antibodies, Antiphospholipid Antibody Syndrome, Lupus Anticoagulant, Activated Protein C

Resistance, Factor V Leiden Mutation, Prothrombin Gene Mutation (20210a), other *(make a listing for other hyperanticoagullables by arm)*

u) All presenting signs and symptoms A30 of Clinical History and Risk Factors eCRF, i.e. Dyspnea, Tachycardia, Hypoxemia, Transient Hypo-or Hypertension (treated by medications), Prolonged hypotension (> 15 minutes) requiring pressors to maintain adequate systolic pressure (exclude patient), Cardiogenic shock that has since resolved, Dizziness/lightheadedness, Syncope (fainting), Chest pain, Cyanosis, Tachypnea, Swollen upper extremity, Swollen lower extremity, Limb edema, Leg pain, Difficulty walking, Deep vein thrombosis confirmed by ultrasound scanning, Other *(make a listing for other presenting signs/symptoms by arm)*
v) Inferior Vena Cava Filter Currently Present
w) Platelet count <100,000 (Baseline labs)
x) Heparin-induced thrombocytopenia (Inclusion/Exclusion B6)
y) Pharmacomechanical treatment within 3 days (Inclusion/Exclusion B7)
z) Venous Thromboembolism History (*Venous Thromboembolism History CRF)*
    a) Type

4) Anticoagulation Medication by Visit

Make table by arm with (a) total N, (b) n/% subjects taking no anticoagulant meds, (c) n/% subjects taking any anticoagulant meds. Then under (c): n/% subjects taking each anticoagulant listed in A1 of the Anticoagulation Medication (acm) CRF

5) Baseline CT scan

a) Locations of PEs
b) Number of locations per patient with (a) any occlusion, partial or total, (b) partial occlusion, (c) total occlusion (n, mean, std, median, minimum, maximum)

6.1) Vital Signs

At screening/Baseline, start and end of the APT procedure, within 4 hours of end of APT procedure and 24 hours, 48 hours, 30 days, 90 days, and 365 days after the start of the APT procedure:

a) Systolic BP
b) Diastolic BP
c) Heart Rate
d) Respiratory Rate
e) SpO2
f) Oxygen Source

For each of (a) through (e), summarize as n, mean, standard deviation, median, minimum, maximum at each time point; construct box/whiskers plots for all 7 timepoints in the same graph and connect means and medians. For (f), summarize as frequency and percent in the order of room air, nasal prongs, mask and intubated at each time point

6.2) Laboratory Data

a) Hemoglobin
b) Hematocrit
c) Platelet
d) aPTT
e) PT

f) INR
g) Troponin
h) D-dimer
i) BNP/proBNP
j) Lactate/Lactic Acid

For each of (a) through (f), summarize as n, mean, standard deviation, median, minimum, maximum at baseline, post procedure 1 (within 4 hours post treatment) and post procedure 2 (48 hours).
For (g) through (j), summarize as n, mean, standard deviation, median, minimum, maximum at baseline and post procedure (48 hours).

6.3) PESI/sPESI

Summarize as n, mean, standard deviation, median, minimum, maximum at baseline, post procedure 1 (within 4 hours post treatment), post procedure 2 (24 hours) and post procedure 3 (48 hours).

7) Interventional Procedure

a) Access Site Location
b) Utrasound Imaging Used
c) Number of Attempts Required to Gain Access
d) Total r-tPA dose per patient

8) EkoSonic Device Information

a) Number of Devices Successfully Placed and Used for Treatment per Patient *(table entries are numbers of patients) (A footnote will be added with total # devices which were not "succesfully placed and used for treatment" with reasons.)*
b) EkoSonic Device Placement Site *(table entries are numbers of devices)*

9) Thrombolytic Infusion Details (by device used)

a) r-tPA concentration (mg/mL)
b) r-tPA infusion rate (mg/hr)
c) Duration of r-tPA infusion (hrs)
d) Reason for Infusion termination (completed per protocol, AE, or other)
e) Deviations from prescribed therapy and reason (Protocol Deviation CRF, include all deviations with “APT Procedure not Peformed as Prescribed by Protocol’ checked)

10) EkoSonic System Details

a) Duration of Ultrasound (hrs)
b) Reason for ultrasound termination
c) Deviations from prescribed therapy and reason

11) Core Lab RV/LV ratio from CTA: Baseline, 48 hours Post APT Start, absolute difference (Post-Procedure - Baseline) and percent change*****

Summarize as continuous data for all above, i.e. n, mean, SD, median, minimum, maximum; provide 95% CI's for mean absolute and percent changes; provide 1-sided and 2-sided p values testing reduction ≤ 0.20 by t test for mean absolute change from baseline; provide same p values testing reduction ≤ 0 by t test for mean percent change from baseline.

All analyses above for RV/LV ratio by CTA will be repeated for the efficacy evaluable patient subset for ITT patients.

Lastly, repeat the above analyses for ITT patients as 6 arms, i.e. unilateral vs. bilateral for each of the 3 randomization arms.

Using continuous data from all 3 arms, perform increasing benefit trend analysis as described in the last paragraph of Section 2.3.1 and provide the 2-sided p value. (ITT only)

12) Core lab echocardiogram: Baseline, within 4 hours of APT end, 24 and 48 hours post APT start, Day 30, Day 90, Day 365 (procedure start date = Day 0) and change from baseline at all post-baseline time points *(for continuous endpoints a-c below, besides summarizing as n, mean, SD, median, minimum and maximum at each of the 7 time points, also provide box-wisker plots for all time points on the same graph)***

a) RV/LV ratio *(perform same analysis at all time points as for the primary endpoint of RV/LV ratio as described in (11) above with the exceptions that testing a mean reduction of 0.20 applies to the 48 hours time point only and binary endpoint applies to ≤ baseline vs. > baseline only) (ITT)*

b) TAPSE *(perform same analysis at all time points as for the primary endpoint of RV/LV ratio as described in (11) above, except mean absolute changes from baseline are tested against 0 as opposed to 0.20 and all p values are 2-sided and binary endpoint applies to ≤ baseline vs. > baseline only) (ITT)*

c) Estimated RVSP *(perform same analysis at all time points as for the primary endpoint of RV/LV ratio as described in (11) above, except mean absolute changes from baseline are tested against 0 as opposed to 0.20 and all p values are 2-sided and binary endpoint applies to ≤ baseline vs. > baseline only) (ITT)*

d) IVC collapse with respiration *(summarize as frequency and proportion at each time point and 2 × 2 tables for changes from baseline, provide p values by McNemar's test) (ITT)*

In addition: Combining data over 4 hours, 24 hours, 48 hours, Day 30, Day 90 and Day 365, perform mixed model repeated measures (MMRM) analyses for RV/LV ratio, TAPSE, and RVSP for absolute and percent changes from baseline as described in Section 2.3.2 (top of page 9). Provide the overall effect size estimate, 95% CI and 2-sided p value comparing effect to 0.(ITT)

15) Core Lab Modified Miller Score: baseline, 48 hours post APT, absolute and percent changes from baseline *(CTA data, perform same analyses as for (14a) above) (ITT)***

16) QOL:

For QOL measures (PEmb-QOL total score, EQ-5D-5L Index value, EQ-5D-5L VAS), summarize as continuous endpoints by treatment arm for 30, 90, and 365 days. Include analysis of change over time for both assessments.

*PEmb-QOL***

The PEmb-QOL questionnaire score ranges from 0 to 100. To score: Q1, Q4, Q5, and Q9 are to be reversedly scored with a low score indicating a better quality of life. Two questions (Q2 'At what time of day are your lung symptoms most intense?' and Q3 'Compared to one year ago, how would you rate the condition of your lungs in general

now?') are not used for scoring. Item 4a will be considered missing if the answer was 'I do not work'. For a PEmb-QoL summary score, first transform each answered item score to a scale ranging from 0 to 100 (38 items total). Then average these transformed scores (except items Q2 and Q3) to obtain an overall summary score. No mimimum was specified for the number of answered items. (Ref: Rochat et al. Health and Quality of Life Outcomes 2014, 12:174)

*EQ-5D-5L**

The EQ-5D-5L is a self-administered questionnaire consisting of 5 questions pertaining to specific health dimensions (mobility, self-care, pain, usually activities and anxiety and depression), and health status rating scale (visual analogue scale [VAS]). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. If a patient has died, the last EQ-5D-5L dimension assessment prior to death will be imputed as extreme problems (coded as 5) and flagged in the listing.

The VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' (Score=100) and 'the worst health you can imagine' (Score = 0). This information can be used as a quantitative measure of health as judged by the individual respondents. If a patient has died, the last EQ-5D-5L VAS assessment prior to death will be imputed as 0 and flagged in the listing.

Each one digit number expressing the level selected for each dimension can be combined into a 5-digit number describing the respondent's health state. For example, the number 11111 represents the respondent not having any problems in all five dimensions. These 5-digit numbers are health states which can be converted to an index value, where 1 represents full health and 0 is equivalent to death. A health state could be considered worse than death and the index values for those states will be less than 0. The index value will be calculated as:

Index value = 1 – (Dimension 1 Estimate + Dimension 2 Estimate + Dimension 3

Estimate + Dimension 4 Estimate + Dimension 5 Estimate). Each dimension estimate is based on the levels chosen for each dimension as specified in Appendix 2 Derivations

17) 6MW at 30, 90 and 365 days*****
Summarize as n, mean, standard deviation, median, minimum, maximum at 30, 90 and 365 days. Also include analysis of change over time and between group comparisons.

18) Healthcare resource utilisation during hospitalisation:
    a. Time from hospital admission to diagnosis of PE
    b. Time from diagnostic CT scan to initiation of treatment for PE
    c. Time in each Level of Care (Level 0 and 1; Level 2; and/or Level 3) through discharge. Levels are defined according to National Framework Document.
    d. Team managing the pt – specialties involved

19) Healthcare resource utilisation after hospitalisation and during 12 month follow-up:
    a) Team managing the pt - specialties
    b) HCP visits for VTE
    c) Hospital re-admission frequency and duration
20) Rescue Therapies *(by patient listing sorted by arm with data for sub id, arm, and answers to items A1, A2, B1, B2, B3, B4, B5, B6, B7, C1, C2, C3 on the Rescue Therapy CRF)*

21) Protocol deviations

22) Integrated Bedside Assessment (IBA) – Only performed at one site with up to 13 subjects using dedicated eCRFs for data collection.

At select participating sites: In addition to the vital signs specified in Section 7.4, bedside vital signs including, systolic/diastolic blood pressure, heart rate, respiratory rate, capillary refill time and SpO2 will be recorded at the start of the APT Procedure, and at each 30 minute interval until 4 hours post-completion of the APT Procedure. Along with the echocardiograms specified in Section 7.7, limited echocardiograms performed at the bedside for RV/LV ratio measurements will be obtained hourly after the start of the APT Procedure through 4 hours post procedure.

Scatterplots of RV/LV ratio (y-axis) vs vital sign measures (x-axis) and of change in RV/LV ratio vs changes in vital sign measures will be presented to assess the correlation of change in clinical parameters (vital signs) with change in markers of RV strain (RV/LV ratio), and associated Pearson or Spearman correlation coefficients, where applicable.

Subject Set = Safety Subject Set for (19 – 23)

21) Major Bleeding Events within 72 hours of initiation of APT*****

22) Technical Procedural Complications *(captured on the EkoSonic Device CRF as "Was this device successfully placed and used for treatment?"; make this a by-patient listing)*

23*)* Symptomatic Recurrent PE and Symptomatic Recurrent PE up to Day 365 (Confirmed by imaging)

24) All cause mortality up to Day 30 and all cause mortality up to Day 365 *(note: per AE and study exit CRFs)*

25) Adverse Events *(Run tables for AEs up to Day 30: AE start date ≤ Date of 30 Day Follow Up Visit per Follow-Up CRF)*

a) All reported events
b) Related to interventional procedure (not EKOS system)
c) Related to EKOS system
d) Related to thrombolytic drug
e) Related to anticoagulant drug
f) Bleeding events *(all site reported bleeding events, make tables for:*
-All reported bleeding events
-Those within 72 hours of APT start
-Those related to:
-interventional procedure (not EKOS system)
-EKOS system
-thrombolytic drug
-anticoagulant drug
g) SAEs

Also run analyses for (g) through Day 365, including those through 30 days.

26) Freedom from major harm occurring between enrolment and 30 days and assessed by the Safety Monitor using the following criteria:

a. Mortality – all cause and PE related
b. CV collapse: Defined as one or more of the following:
    i. >40mmHg drop in SBP (for >15 minutes from documented blood pressure as an in-patient) despite IV fluid challenge and absence of new atrial arrhythmia.
    ii. Requirement for emergency systemic thrombolysis
    iii. Requirement for emergency surgical embolectomy
    iv. Requirement for vasopressors
    v. Intubation/Ventilation
c. Major bleeding per ISTH
d. Recurrent PE (confirmed by imaging)
e. Surgical correction of device related complication

Appendix 2: Derivations

2.6 Imputation rules

2.6.1 AE date imputation

The following algorithm should be used to estimate start dates for which only partial information is known:

- Missing day and month
    - If the year is the same as the year of first study treatment, then the day and month of the start date of treatment will be assigned to the missing fields
    - If the year is prior to the year of first study treatment, then December 31 will be assigned to missing fields
    - If the year is after the year of first study treatment, then January 1 will be assigned to the missing fields
- Missing month only
    - Treat day as missing and replace both month and day accordingly to the procedure above
- Missing day only
    - If the month and year are the same as the year and month of first study treatment, then the start date of treatment will b assigned to the missing day
    - If the month and year are before the year and month of first study treatment, then the last day of the month will be assigned to the missing day
    - If the month and year are after the year and month of the first study treatment, then the first day of the month will be assigned to the missing day

If the imputed start date result is after the stop date (and the stop date is complete), the imputed start date will be reset to the stop date.

The following algorithm should be used to estimate stop dates for which only partial information is known:

- Missing year
    - Date left missing
- Missing month
    - Impute “December”
- Missing day

- Impute last day of that month

2.7 EQ-5D-5L Derivations[3]

Question	Text	Coded Value
Mobility	No problems/No pain/Not anxious	1
Self-Care	Slight problems/Slight pain/Slightly anxious	2
Usual Activities	Moderate problems/Moderate pain/Moderately anxious	3
Pain/Discomfort	Severe problems/Severe pain/Severely anxious	4
Anxiety/Depression	Unable/Extreme Pain/Extremely anxious	5

The following table will be used in calculating the index value from the 5-digit health state.

Index value *= 1 – (Dimension 1 Estimate + Dimension 2 Estimate + Dimension 3 Estimate + Dimension 4 Estimate + Dimension 5 Estimate)*

The dimension estimates will be taken from the table below. Each estimate corresponds to the level each respondent checked for each dimension. For example, if a patient has a health state of 23245, the following calculation will be used:

1 – (0.058+0.080+0.050+0.276+0.289) = 0.247

Constant		1.000
Mobility	None	0
	Slight	0.058
	Moderate	0.076
	Severe	0.207
	Unable	0.274
Self-care	None	0
	Slight	0.050
	Moderate	0.080
	Severe	0.164
	Unable	0.203
Usual Activities	None	0
	Slight	0.050
	Moderate	0.063
	Severe	0.162

	Unable	0.184
Pain/discomfort	None	0
	Slight	0.063
	Moderate	0.084
	Severe	0.276
	Unable	0.335
Anxiety/depression	None	0
	Slight	0.078
	Moderate	0.104
	Severe	0.285
	Unable	0.289

References

[1] Fasullo S, Scalzo S, Maringhini G, et al. Six-month echocardiographic study in patients with submassive pulmonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. Am J Med Sci. 2011;341: 33-39

[2] Hochberg, Y, A Sharper Bonferroni Procedure for Multiple Tests of Significance, Biometrika 75, 800 2, 1988

[3]Devlin N et al. Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. EuroQol Research Foundation. 2016.