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

OPTALYSE PE

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Investigator Signature Page

Study Title: Study of the OPTimum Duration of Acoustic Pulse ThromboLYSis ProcEdure in the Treatment of Acute Submassive Pulmonary Embolism OPTALYSE PE

Device: EkoSonic® Endovascular System

Protocol Number: EKOS – 12

Version and Date: UK Version 8; October 15, 2019

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If I decide not to participate in the study, or if requested by EKOS, I will return all study materials to EKOS.

The Principal Investigator (undersigned) hereby declares that he/she has read this protocol and agrees to its contents.

The undersigned confirms that the trial will be conducted and documented in accordance with the Declaration of Helsinki, the protocol, standards of International Conference on Harmonisation (ICH) Good Clinical Practice, applicable laws and regulatory requirements specified in the protocol, and the stipulations of the clinical trial agreement.

Principal Investigator Signature

PRINT NAME	TITLE
SIGNATURE	DATE

Table of Contents

1 INTRODUCTION 14
1.1 Background 14
1.2 Study Rationale 15
2 EKOSONIC® ENDOVASCULAR DEVICE and r-tPA 17
2.1 EKOSONIC® ENDOVASCULAR DEVICE 17
2.2 Recombinant Tissue Plasminogen Activator (r-tPA) 18
3 STUDY OBJECTIVES AND ENDPOINTS 19
3.1 Objective 19
3.2 Primary Efficacy Endpoint 19
3.3 Secondary Efficacy Endpoints 19
3.4 Safety Endpoints 20
4 CLINICAL PLAN SUMMARY 21
5 STUDY POPULATION 23
5.1 Inclusion Criteria 23
5.2 Exclusion Criteria 23
6 STUDY PROCEDURES 24
6.1 Screening Procedures 24
6.2 Randomization to Study Treatment 26
6.3 Acoustic Pulse Thrombolysis Procedure, Treatments and Timing 26
6.4 Immediately and Within Four-hours Post-APT Procedure 28
6.5 Rescue Treatment in Case of Hemodynamic or Ventilatory Collapse 28
6.6 24, 48 And 72 Hours After the Start of the APT Procedure 29
6.7 Follow-up Clinic Visits and Subject Contact 30
6.8 Prohibited Medications 31
6.9 Anticoagulation and Concomitant Medications 31
6.10 Subject Withdrawal and Early Termination 31
7 INDIVIDUAL ASSESSMENTS 31
7.1 Pregnancy Test 31
7.2 Physical Exam and Patient Information 31
7.3 Electrocardiogram 32
7.4 Vital Signs 32

7.5 Right Heart Hemodynamic and SvO2 Measurements (Optional) 32
7.6 Computed Tomography Pulmonary Angiography (CTA) 32
7.7 Echocardiogram 32
7.8 Integrated Bedside Assessment (Select Participating Sites Only) 32
7.9 Pulmonary Embolism Severity Index and Simplified Pulmonary Embolism Severity Index 33
7.10 Laboratory Tests and Biomarkers 33
7.11 Anticoagulation and Concomitant Medications 35
7.12 6 Minute Walk Test (6MW) 35
7.13 Quality of Life (QOL) Assessments: PEmb-QOL and EQ-5D-5L 35
8 SAFETY REPORTING 35
8.1 Adverse Events 35
8.2 Serious Adverse Events (SAE) 35
8.3 Unexpected Adverse Events 36
8.4 Pre-Existing Medical Conditions 36
8.5 Device Deficiency, Device Failures and Malfunctions 36
8.6 Documentation Of Adverse Events 37
8.7 Reporting And Duration Of AE Reporting Period 37
8.8 Adverse Events Related To r-tPA And Definition Of Major Bleeding 37
8.9 Specific Reporting Guidelines 38
8.10 Pregnancy 39
8.11 Categorization Of Adverse Events 40
8.12 Expedited Reporting Of Serious Adverse Events 41
8.13 Safety Monitor 42
9 DATA COLLECTION 42
10 STATISTICAL ANALYSIS 42
10.1 Analysis Subject Sets, Evaluable Subjects and Missing Data Handling Convention 42
10.2 General Methodology 43
10.3 Efficacy Analyses 43
10.4 Safety Analysis 45
10.5 Sample Size And Power Estimation 45
11 RISK ANALYSIS 46
11.1 Description And Analysis Of Risks 46

11.2 Anticipated Risks Of APT Procedure 46
12 ETHICAL CONSIDERATIONS 49
13 RECORD RETENTION 49
14 INVESTIGATOR RESPONSIBILITES 50
14.1 General 50
14.2 Source Documentation 50
14.3 Study Deviations 51
14.4 Publication Policies 51
15 REFERENCES 52

APPENDICES

Appendix A EkoSonic® Instructions for Use A1
Appendix B Pulmonary Embolism Severity Index A52
Appendix C Placement and Removal of the EkoSonic® Endovascular System A64
Appendix D 6-Minute Walk Test A74
Appendix E Quality of Life Assessments: PEmb-QOL and EQ-5D-5L A82

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B. 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
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 Screening/Baseline to 48 hours after the start of the APT Procedure.

B. PROTOCOL SYNOPSIS

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. 6 minute walk test (6MW) distance with BORG score and requirement for oxygen therapy 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 follow-up visits. 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

B. 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. See Schedule of Assessments Table for further details on all testing required following completion of the APT Procedure. 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>100 subjects have been randomized and treated in the study and are currently being followed for one year. Up to 120 additional subjects will be enrolled in the study to obtain up to 75 efficacy evaluable subjects (25 efficacy evaluable subjects enrolled and randomized in each of 3 treatment arms.). Enrollment at all centres will cease when 25 efficacy evaluable subjects have been obtained in each arm.</td></tr>
<tr><td>Clinical Sites:</td><td>Up to 35 centers within the United States and the United Kingdom.</td></tr>
<tr><td>Time Course:</td><td>100 subjects treated in the study are currently being followed for 1 year.
UK Version 6: Up to 120 additional subjects will have an enrollment period of up to 2 years with 1 year follow-up.</td></tr>
</table>

C. SCHEDULE OF ASSESSMENTS

	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

D. ACRONYMS AND ABBREVIATIONS

6MW	6 minute walk test
AE	Adverse event
APT	Acoustic Pulse Thrombolysis
aPTT	Activated partial thromboplastin time
BNP/NT-proBNP	B-type natriuretic peptide/N-terminal pro b-type natriuretic peptide
CBC	Complete blood count
CPR	Cardiopulmonary resuscitation
CTA	Computed tomography angiography
CTEPH	Chronic thromboembolic pulmonary hypertension
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EKOS	EkoSonic® Endovascular System
EQ-5D-5L	EuroQual - 5 Dimensions – 5 Levels Quality of Life Assessment
FDA	Food and Drug Administration
HCP	Healthcare Professional
HIT	Heparin-induced thrombocytopenia
ID	Identification
IEC/IRB	Independent Ethics Committee /Investigational Review Board
ICH	Intracranial Hemorrhage
ICH - GCP	International Conference for Harmonisation – E6 Guideline for Good Clinical Practice
IDDC	Intelligent Drug Delivery Catheter
IFU	Instructions for Use
INR	International normalized ratio
IVC	Inferior vena cava
MDR	Medical Device Reporting
MSD	MicroSonic Device
PAgram	Pulmonary Arteriography
PE	Pulmonary Embolism
PEmb-QOL	Pulmonary Embolism - Quality of Life
PESI/sPESI	Pulmonary Embolism Severity Index/simplified PESI
QOL	Quality of Life
RSVP	Right ventricular systolic pressure
r-tPA	Recombinant tissue plasminogen activator
RV	Right Ventricle
RV/LV	Right ventricular/left ventricular diameter ratio
SAE	Serious adverse event
SBP	Systolic blood pressure
SpO2	Oxygen saturation with pulse oximetry
SvO2	Mixed venous O2 saturation
TAPSE	Tricuspid Annular Plane Systolic Excursion
TIA	Transient ischemic attack
VTE	Venous thromboembolic

1 INTRODUCTION

1.1 Background

Venous thromboembolism (VTE), comprised of deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disorder in the United States after myocardial infarction and stroke[1]. The 2008 United States Surgeon General's Call to Action to Prevent DVT and PE estimates that 100,000 to 180,000 deaths occur annually from PE in the U.S. alone[2]. In the 2003 U.S. Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample database, 196,134 VTE-related events, including symptomatic DVT, symptomatic PE, and VTE-related deaths, were calculated to have occurred among acutely ill hospitalized Medical Service subjects, afflicting two out of every 100 of these subjects[3].

The mortality rate for acute PE exceeds 15% in the first three months after diagnosis, surpassing that of myocardial infarction[4]. In nearly 25% of all subjects presenting with acute PE, the initial presentation is sudden death[5]. The majority of deaths from acute PE results from right ventricular (RV) pressure overload and subsequent RV failure[6]. Survivors of acute PE are at-risk for developing debilitating chronic thromboembolic pulmonary hypertension (CTEPH)[7]. Subjects with CTEPH typically experience a "honeymoon" period after acute PE, during which symptoms are absent despite the onset of pulmonary hypertension. Unfortunately, the condition is usually detected when pulmonary hypertension has worsened to the point that it causes dyspnea, hypoxemia, and RV failure.

Therapeutic anticoagulation with immediate parenteral anticoagulants followed by oral agents is the cornerstone of therapy for acute PE[8]. However, while the majority of acute PE subjects has a benign clinical course with standard therapeutic anticoagulation alone, subjects with massive and submassive PE remain at increased risk for adverse clinical events, including RV failure and hemodynamic collapse.

Advanced therapy for patients with acute PE is usually reserved for patients with either massive or submassive PE. Options for advanced therapy include peripherally-administered systemic fibrinolysis, surgical pulmonary embolectomy, catheter-assisted embolectomy, and inferior vena cava (IVC) filter insertion.

Combined ultrasound/fibrinolytic therapy was developed to accelerate thrombolysis and rapidly achieve complete clot lysis while reducing the risk of serious complications such as bleeding. High frequency, low power ultrasound accelerates thrombolysis both in vitro and in vivo. This idea was pioneered by Kudo[9] and confirmed by other investigators[10,11,12]. Ultrasound temporarily alters the local architecture of the fibrin clot, thereby enhancing its permeability by reducing the diameter of the fibrin strands and increasing the pore size of the fibrin mesh[13]. Ultrasound energy also provides an acoustic pressure gradient to enable transport of a greater quantity of thrombolytic drug into the clot itself. The resulting faster, more complete clot lysis is due to increased diffusion of the thrombolytic agent into the clot and not mechanical disruption.

The EkoSonic® Endovascular System (EKOS) is an FDA cleared[14] and CE Marked[15] drug delivery catheter that uses ultrasound delivered through the catheter core to speed the delivery of thrombolytic drug into the interstices of the clot and increase the speed of lysis. By making the clot more permeable and pushing the drug into the fibrin mesh, EKOS has the potential to reduce time to lysis, effect more complete lysis, reduce drug dose and, thereby, reduce the risk of bleeding complications.

The U.S. Food and Drug Administration (FDA) approved recombinant tissue plasminogen activator (r-tPA) 100 mg as a continuous intravenous infusion over two hours for fibrinolysis of acute PE in 1990. Market authorization for this product was first granted in 1988 and subsequently renewed in 2009. Use of this dose regimen has declined over the years. Numerous contraindications to fibrinolytic administration and concerns for major bleeding complications, particularly intracranial hemorrhage, contribute to low utilization of fibrinolysis for acute PE. An analysis of data from five clinical trials of fibrinolysis for acute PE reported a risk of intracranial hemorrhage (ICH) of 1.9%[16]. An analysis from the International Cooperative Pulmonary Embolism Registry (ICOPER) reported the risk of intracranial hemorrhage to be as high as 3%[17]. A study from the Brigham and Women's Hospital demonstrated that the overall major bleeding rate is approximately 20%[18]. Currently, this dose regimen is used primarily in massive PE which has a mortality rate of about 30%. Debate continues about the usefulness of thrombolytic therapy in submassive PE, which has a mortality rate approximately the same as the rate of ICH that can occur with systemic lysis. EKOS studies (ULTIMA and SEATTLE II) have shown lower doses of r-tPA delivered with an ultrasound catheter are effective and no ICH was reported[19,20].

EKOS Corporation investigated the effectiveness of thrombolytics delivered by ultrasound catheter in PE in two prospective, multi-center studies that provide evidence for the efficacy and safety of an Acoustic Pulse Thrombolysis (APT) Procedure in the treatment of PE. There are published data for 370 subjects treated with the APT Procedure. The studies include one randomized-controlled study (RCT; ULTIMA) involving 30 of 59 pts; one prospective study (SEATTLE II) involving 150 pts. In May 2014, the FDA cleared EkoSonic® Endovascular Device for the "ultrasound facilitated, controlled and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of PE" based on the results of the ULTIMA and SEATTLE II studies.

1.2 Study Rationale

ULTIMA and SEATTLE II have shown the current APT Procedure regimen to be safe and effective in the treatment of PE. The reduction in the r-tPA dose and the reduction in treatment time of the APT Procedure reduce bleeding events and costs associated with length of stay in the ICU and hospital.

Pharmacology studies demonstrate that clot lysis occurs rapidly after r-tPA intravenous treatment and is ~90% complete by 90 minutes. A rabbit study demonstrated that thrombolytic activity after r-tPA, whether

administered as an intravenous bolus dose or infusion is dose-dependent and the duration of action is dose-independent[21]. After a single dose (0.5 to 0.4 mg/kg), to 2.3-3 kg rabbits, r-tPA was rapidly inhibited, resulting in duration of action of 15 minutes. The maximum extent of lysis after the bolus was 54% for a 0.4 mg/kg dose. During a 4 hour infusion of r-tPA (0.625 to 1 mg/kg), 90% of the thrombolytic activity occurred within 2 hrs. The maximum extent of lysis after the infusion was 87% for a 0.5 mg/kg dose. After administration of either a bolus or infusion, continued lysis activity decreased exponentially with time and there remained an unlysable clot at the end of the measurement period.

Similarly, a pharmcodynamic study of r-tPA in man demonstrated that even though the initial half-life of r-tPA in the systemic circulation is 3-4 minutes, fibrinolysis after an intravenous infusion of 20 to 150 mg continues from 7 to 12 hours[22]. The prolonged duration of action demonstrates that plasmin bound to fibrin continues to be active after r-tPA is cleared from the circulation. As fibrin is lysed, r-tPA is released and is metabolized by the liver.

The ability of r-tPA to lyse clot is dependent upon binding with fibrin and plasminogen in a centric ternary complex to activate plasminogen to form plasmin which lyse fibrin into degradation products[23]. Clot lysis is diffusion dependent. By increasing permeation, lysis increases. Several in-vitro studies have demonstrated that ultrasound enhances both urokinase and r-tPA mediated lysis of plasmin and blood clots. Enhancement is seen at a range of frequencies, intensities and lytic concentrations[24]. This enhancement is seen in both static and flowing thrombolytic models. Animal studies report faster recanalization times for clots exposed to ultrasound during lytic treatment using r-tPA. These effects were seen at the frequencies produced by the EKOS catheter. The time of clot treatment in the studies was 30 minutes. From these studies, we postulate that r-tPA in the presence of ultrasound will produce significant fibrinolysis within 2 hours of receptor binding and may continue for another 7 to 12 hours after the APT Procedure is complete. Thus, thrombus burden may be significantly reduced within a few hours of the APT Procedure to restore pulmonary perfusion, reduce RV dilatation, and decrease pulmonary artery pressures.

The earliest study of APT Procedure in PE demonstrated that doses of approximately 22 mg r-tPA delivered with the APT Procedure over 25 hours were effective in treating PE in subjects suffering from massive PE[25]. Since that time, doses used in treating PE have ranged from 0.5 to 1 mg/hr/catheter delivered over an average of 18 hours, with no infusion duration being less than 12.9 hours (excluding one subject). Even though efficacy measurements have been made at 24 and 48 hours, clinicians have reported subjects often improve within a few hours of the start of treatment. These observations, along with the aforementioned pharmacology studies, provide evidence to support the scientific rationale for investigating the reduction in ultrasound - r-tPA treatment time.

The OPTALYSE PE study is designed to investigate the lowest r-tPA dose-ultrasound treatment time required to achieve the same reductions in thrombus burden and associated improvement in physiologic parameters demonstrated in ULTIMA and SEATTLE II. Results of this study are intended to inform the study design for further studies of the APT Procedure. Analysis of the first 100 evaluable subjects in the U.S. study suggested equipoise between Arms 1, 2 and 3 of the protocol and therefore the sample size has been extended and additional sites in the UK National Health Service included, with a view to adding to the findings of the OPTALYSE study from sites in the UK and increasing the number of patients treated by treatment protocol.

Following the initial hospitalization, subjects will be followed for 12 months. The purpose of this follow-up is to obtain information on recurrence of venous thromboembolic events (VTE) and chronic thromboembolic pulmonary hypertension (CTEPH).

2 EKOSONIC® ENDOVASCULAR DEVICE and r-tPA

2.1 EKOSONIC® ENDOVASCULAR DEVICE

2.1.1 Intended Use

EKOS employs ultrasound energy intended for the ultrasound facilitated, controlled, and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of PE.

2.1.2 Description

The following is a summary of EKOS that is included in the Instructions for Use (IFU; Appendix A) and is also provided with each system.

The system generates ultrasound waves in the treatment zone of the catheter through the piezoelectric conversion of radiofrequency energy. The ultrasound emanates radially from the treatment zone to improve the dispersion of infused physician-specified fluids, including thrombolytics.

The EKOS Device consists of two main components:

1. Single-use sterile device, consisting of an
    a. Intelligent Drug Delivery Catheter (IDDC)
    b. MicroSonic Device (MSD)
2. EkoSonic® Control System (reusable)

The IDDC is 5.4 French with a 106 cm or 135 cm working length. It includes two luer ports for coolant fluid and thrombolytic delivery and an electrical connector for the thermocouples that monitor the catheter system

temperature. Radiopaque markers are located approximately 1 cm proximal and 1 cm distal to the treatment zone. The IDDC central lumen is compatible with a 0.035" guidewire, accepts the MSD and delivers coolant during operation. Each EkoSonic® Device requires its own infusion tubing and infusion pump with coolant of normal saline to run at 35 ml/hr/device.

The MSD locks to the luer connector on the central lumen of the IDDC aligning the ultrasound-generating segment to the treatment zone of the IDDC. The device uses multiple ultrasound transducers to emit ultrasound energy radially from the long axis of the catheter system.

The EkoSonic® Control System provides electrical power to the piezoelectric elements in the treatment zone of the Device and monitors operating parameters during operation. The Control System also provides the user interface through the front panel display and keypad.

2.1.3 Regulatory Status

The EKOS device has been cleared by the United States Food and Drug Administration (FDA) for the ultrasound facilitated, controlled and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of PE and is marketed throughout the United States. In Europe, EKOS has an EC Design-Examination Certificate (CE 567229). In this study, EKOS is being used in accordance with its cleared indications for use.

The EkoSonic® Endovascular Devices used for this study will be commercially available product. Therefore, no special labeling or tracking is required for study devices.

2.2 Recombinant Tissue Plasminogen Activator (r-tPA)

2.2.1 Description

The r-tPA used in this study is a commercially available drug marketed in the participating geographies under various brand names for fibrinolysis of pulmonary embolism by systemic peripheral infusion. In this study, r-tPA will be delivered through the EkoSonic® Endovascular System (ultrasonic infusion catheter) to the site of the clot rather than by systemic infusion. The drug will be administered using each investigational facility's standard infusion pumps. See section 4 for a description of the doses and duration of r-tPA administration for the study's treatment groups. Doses of r-tPA administered in this study are lower than those delivered systemically.

2.2.2 Regulatory Status

Recombinant tissue plasminogen activator is authorized for use by country-specific regulatory agencies in all participating geographies for fibrinolysis of pulmonary embolism.

2.2.3 Drug Preparation and Accountability

The r-tPA used in the study will be procured from standard pharmacy supplies and prepared following pharmacy procedures and the manufacturer's instructions. Pharmacies are experienced in reconstituting and diluting r-tPA for infusion procedures. No special labeling or tracking is required for r-tPA used in this study at US sites but may be required by local agencies for sites outside the US.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 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) [26].

3.2 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 Screening/Baseline to 48 ± 6 hours after the start of the APT Procedure.

3.3 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. 6 minute walk test (6MW) distance with BORG score and requirement for oxygen therapy

5. Quality of life (QOL) as measured by the Pulmonary Embolism Quality of Life (PEmb-QOL) and EQ-5D-5L at all post-hospitalization subject visits.

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

3.4 Safety Endpoints

3.4.1 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

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

Major bleeding events will be categorized as in-hospital and/or taking place within 72 hours from the start of the APT Procedure or at time of hospital discharge (whichever is earlier).

3.4.2 Secondary Safety Outcomes

3.4.2.1 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.

3.4.2.2 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 Screening/Baseline CTA) is demonstrated on CTA or invasive contrast PAgram.

3.4.2.3 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. Death will be attributed to PE if it is either unexplained or sudden or if there is evidence to support an association with PE.

4 CLINICAL PLAN SUMMARY

Up to 75 additional efficacy evaluable subjects (25 efficacy evaluable subjects per each of the 3 treatment arms) with submassive PE will be enrolled in the study at up to 20 clinical sites in the UK. Once a subject provides Informed Consent and receives treatment with EKOS, those data will be collected and analyzed. While all subjects who meet enrollment criteria will be treated, efficacy evaluable patients will include treatment with two catheters. (Note: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.) It is anticipated that 30 subjects per treatment group will be enrolled to achieve 25 bilaterally treated efficacy evaluable subjects.

Additional subjects may be consented to compensate for screen failures, patients who are treated with one catheter and/or treated patients who lack sufficient data to be evaluable. The total number of consented patients will not exceed 120.

This is a randomized, parallel, multi-arm, multi-center study extended to continue investigating the optimal dose of r-tPA together with the optimal duration of ultrasound utilizing the EKOS device as a treatment for submassive PE. The study is planned to evaluate the reduction of right ventricular dysfunction and overall safety in three APT treatment groups. Subjects with submassive PE (hemodynamically stable PE with a RV/LV ratio ≥ 0.9 and at least one elevated biomarker) will be randomized to one of three APT treatment groups: ultrasound of 2 hours with r-tPA 2 mg/hr/catheter and ultrasound 4 and 6 hours with r-tPA, 1 mg/hr/catheter.

Treatment Group	Treatment Duration (hrs.)	Total Dose r-tPA (one/two catheters (mg)	r-tPA Infusion Rate
1	2	4/8	2 mg/hr/catheter
2	4	4/8	1 mg/hr/catheter
3	6	6/12	1 mg/hr/catheter

Placement of the EKOS catheter will be guided by focused PAgram and/or CTA scan. Following successful placement of the EKOS catheter, the APT Procedure will be initiated with r-tPA and the ultrasound started simultaneously. Within four hours after the end of the APT Procedure, subjects will have an echocardiogram obtained. A repeat CTA will be obtained at 48 hours (±6 hours) after the start of the APT Procedure. Echocardiograms will be obtained at 24 hours (±6 hours) and at 48 hours (±6 hours) after the start of the APT Procedure. Vital signs and hemodynamic measurements will be recorded as specified in Sections 7.4 and 7.5.

Integrated bedside assessments will only be obtained at select participating institutions by collecting vital signs and limited echocardiograms (RV/LV ratio only) at frequent intervals from the start of the APT Procedure through 4 hours after its completion to evaluate the possibility of developing a non-invasive PE response evaluation tool for use at the bedside (see Section 7.8). This collection of vital signs and echocardiograms will be reviewed to determine if there is a correlation with the change in clinical parameters and the change in markers of RV strain. The collection of routine bedside vital signs and limited echocardiograms (RV/LV ratio only) do not increase the potential risk to the patients participating in the study. They are non-invasive measurements that will be collected at a higher frequency than normal.

Bleeding, recurrent PE and serious adverse events will be collected and reported throughout the study. Specific reporting for bleeding events will occur during the first 72 hours from the start of treatment or at the time of discharge from the hospital, whichever is earlier.

All imaging studies will be provided to the Core Imaging Laboratory. Procedures for transfer of images from study sites to the Laboratory will be provided in the Syntactx Manual of Operations. Results of the assessments will be entered into the clinical database by the Core Imaging Laboratory.

Subjects will return for follow-up clinic evaluations at 30 (±5 days), 90 (±10 days), and 365 (±14 days) days. It is imperative that contact with subjects be made at the designated times during the study and the status of all subjects is known at 365 days after the Procedure. Subjects will be asked to provide three different means of contact in order to insure an ability to learn the subject's status.

It is anticipated that the clinical study duration for these 75 additional efficacy evaluable subjects will be up to 36 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 12 months.

5 STUDY POPULATION

5.1 Inclusion Criteria

Subjects must meet the following criteria to be eligible for participation in this clinical trial:

1. Male or female ≥ 18 years of age and ≤ 75 years of age
2. CTA evidence of proximal PE (filling defect in at least one main or lobar pulmonary artery)
3. PE symptom duration ≤14 days
4. Submassive PE: RV/LV diameter ≥ 0.9 from CTA, hemodynamically stable and an elevated biomarker.
5. Treatment must be started within 48 hours of diagnosis of PE by CTA.
6. Signed Informed consent obtained from subject or Legally Authorized Representative.

5.2 Exclusion Criteria

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

1. Stroke or transient ischemic attack (TIA), head trauma, or other active intracranial or intraspinal disease within one year
2. Recent (within one month) or active bleeding from a major organ
3. Major surgery within seven days of screening for study enrollment
4. Clinician deems the subject high-risk for catastrophic bleeding

5. History of any hematologic disease potentially involving abnormal platelet number or function
6. History of heparin-induced thrombocytopenia (HIT)
7. Catheter-based pharmacomechanical treatment for PE within 3 days of study enrollment
8. Systolic blood pressure (SBP) less than 90 mm Hg and/or use of vasopressors
9. Cardiac arrest (including pulseless electrical activity and asystole) requiring active cardiopulmonary resuscitation (CPR)
10. Evidence of irreversible neurological compromise
11. Life expectancy < one year or enrollment in hospice care
12. Use of thrombolytics or glycoprotein IIb/IIIa antagonists within 3 days prior to APT procedure
13. Out-of-Range Laboratory Values: Hematocrit < 30%, Platelets < 100 thousand/μL, INR > 3,
14. Creatinine outside the normal range for the treating institution
15. Subject is pregnant (positive pregnancy test; women of childbearing capacity must be tested) or breast feeding
16. Active cancer (metastatic, progressive, or treated within the last 6 months). Exception: subjects with non-melanoma primary skin cancers are eligible to participate in the study
17. Known allergy, hypersensitivity, or thrombocytopenia from heparin, r-tPA, or iodinated contrast except for mild-moderate contrast allergies for which steroid pre-medication can be used

6 STUDY PROCEDURES

6.1 Screening Procedures

All subjects presenting for evaluation and treatment of submassive PE will be considered for the study. A consented subject who was screened but was not eligible for the trial will be entered on the eCRF as a screen failure.

All subjects that meet the study's inclusion criteria and do not meet any exclusion criteria are eligible for this study.

Informed Consent (IC) will be obtained from a subject with the capacity for medical decision-making and/or the subject's legally authorized representative prior to performing study related procedures. Subjects are not to be placed at additional risk caused by delays in treatment because of difficulties in obtaining legally effective informed consent for the research.

If the subject's condition deteriorates at any time during the screening process such that immediate start of life-saving therapy (such as CPR) becomes necessary, further attempts to complete screening procedures will be abandoned, and the subject will be treated immediately as deemed appropriate by the responsible clinician. The subject will be considered a screen failure.

The following assessments will be performed at Screening within 48 hours of the APT Procedure, unless otherwise noted.

1. Informed Consent
2. Medical History & Demographics
3. Inclusion/Exclusion Criteria
4. Pregnancy test if the subject is female and of child-bearing potential
5. Physical Exam including blood pressure, respiratory rate, heart rate and SpO2
6. Electrocardiogram (ECG; 12 lead)
7. CTA to evaluate the anatomic location of PE and the degree of RV enlargement (in the majority of subjects CTA will have been performed as part of the initial diagnosis of PE and does not need to be repeated as part of the Screening/Baseline data acquisition process). The RV/LV ratio at end-diastole will be determined from this image.
8. Echocardiogram to measure: RV/LV ratio, TAPSE, estimated RVSP, and collapse of the IVC with respiration
9. Laboratory testing including hemoglobin (Hgb), hematocrit (Hct), platelet count, blood urea nitrogen (BUN), creatinine, aPTT, PT and INR, troponin, B-type natriuretic peptide (BNP)/NT-proBNP, D-Dimer and lactate/lactic acid
10. Pulmonary Embolism Severity Index (PESI/sPESI)

It is recommended all patients get ultrasound of lower extremity to rule out deep vein thrombosis (DVT). If a DVT is present, the clinician should use standard of care procedures.

6.2 Randomization to Study Treatment

A subject who has signed informed consent and meets all eligibility criteria will be randomized to receive the APT Procedure. Basic subject identification information will be entered into the electronic case report form (eCRF) system to produce the randomization assignment and assign a subject study number appended to the site ID number. The system will assign a dose of r-tPA and duration of APT Procedure to be used for the subject. The treatment assignment for the subject will be one of the following:

1. APT Procedure duration of 2 hours and r-tPA of 2 mg/hour/catheter (total r-tPA dose of 4 or 8 mg)
2. APT Procedure duration of 4 hours and r-tPA of 1 mg/hour/catheter (total r-tPA dose of 4 or 8 mg)
3. APT Procedure duration of 6 hours and r-tPA of 1 mg/hour/catheter (total r-tPA dose of 6 or 12 mg)

6.3 Acoustic Pulse Thrombolysis Procedure, Treatments and Timing

6.3.1 Anticoagulation

All study subjects will continue on the anticoagulant medication initiated prior to enrollment in the trial. For those subjects receiving full dose anticoagulation with intravenous unfractionated heparin, their dose will be reduced to intermediate dose continuous infusion, target aPTT 40-60 seconds, during the APT Procedure. Subjects receiving anticoagulants other than unfractionated heparin (such as low molecular weight heparin, fondaparinux) prior to enrollment in the trial will not receive any additional intravenous heparin during the APT Procedure provided they received therapeutic doses of the anticoagulant.

Following the APT Procedure, subjects will be prescribed ongoing anticoagulation therapy of the physician's choice which will be recorded in the eCRF throughout the 12 month follow-up period.

6.3.2 Timing of APT Procedure

The subject will have treatment with the APT Procedure started within 48 hours from the Screening/Baseline CTA evaluation.

6.3.3 Recombinant tPA (r-tPA)

Any commercially available formulation of r-tPA may be used and all instructions for reconstitution provided in the package insert should be followed. r-tPA will not be specially labeled for the study. r-tPA will be infused at a rate designated by randomization procedure.

6.3.4 APT Procedure

The APT Procedure must be performed by an experienced interventional cardiologist, vascular, cardiac, or cardiothoracic surgeon, or radiologist in an angiographic suite with digital angiographic equipment. Placement of the EKOS will be guided by focused PAgram and/or CTA scan. If a PAgram is performed, limited quantity of contrast should be used (recommend using no more than 40 cc of contrast).

In the case of:

1. Unilateral filling defect in one main or proximal lobar pulmonary artery as detected by CTA, only one EkoSonic® catheter will be placed in the involved vessel; and

2. Bilateral filling defects in both main or proximal lobar pulmonary arteries by CTA, two EkoSonic® catheters will be placed; one in each of the involved main or proximal pulmonary arteries.

See Appendix C for an illustration of indications for the placement of one or two EkoSonic® devices by PAgram and/or CTA scan. Choice of venous access is at the discretion of the treating physician and in alignment with the hospital standard of care. However, multiple attempts at peripheral venous access are a predictor of bleeding complications in patients undergoing thrombolysis and therefore it is strongly recommended that venous access will be performed utilizing ultrasound guided puncture with use of a 4F or 5F micropuncture technique. Please refer to Appendix C for instructions for obtaining venous access, selecting the proper treatment zone length, and placing the EkoSonic® device(s). The length of the treatment zone of the EkoSonic® device used for each side of the pulmonary arterial tree will be recorded on the eCRF. Vital signs and oximetry will be obtained immediately before the APT Procedure begins. Baseline right-heart pressures including mean right atrial, right ventricular systolic and diastolic, and main pulmonary artery systolic, diastolic and mean pressures, as well as mixed venous O2 saturation (SvO2) will be obtained before the APT Procedure begins.

Please refer to Appendix A for the EkoSonic® Instructions for Use for detailed directions on proper preparation of the EKOS device. Infusion of r-tPA at the assigned dose and saline coolant at 35 ml/hour per catheter will be started. The MicroSonic Device will then be activated. If technical difficulties are encountered which interfere with proper operation of the system or infusion of either r-tPA or coolant, the Instructions for Use will be consulted to assist in resolution of the issue. If the issues cannot be resolved, the affected device will be exchanged for another EkoSonic® device. This exchange and serial numbers will be recorded in the eCRF. The device will be saved and returned to EKOS.

During placement of the EkoSonic® System and throughout the Procedure, the following events would require discontinuation of the Procedure:

1. Major vessel injury, such as pulmonary artery dissection or perforation
2. Major injury to the structures of the heart, such as disruption of the pulmonic or tricuspid valve or perforation of the right atrium or ventricle
3. Hemodynamic or respiratory deterioration requiring CPR
4. Acute neurological or mental status changes develop

The occurrence of any of these events will be recorded on the Adverse Event eCRF.

6.4 Immediately and Within Four-hours Post-APT Procedure

At the end of the assigned APT Procedure, ultrasound and r-tPA treatment will be stopped. Vital signs and oximetry will be obtained immediately after the APT Procedure.

Within four hours of discontinuing study treatment, the subject will be assessed for improvement in PE signs and symptoms including PESI score, vital signs and oximetry, and have an echocardiogram. Laboratory tests for Hgb, Hct, Platelet count, aPTT, PT and INR, BUN and creatinine will also be obtained.

6.5 Rescue Treatment in Case of Hemodynamic or Ventilatory Collapse

Rescue medications and additional treatment in case of hemodynamic or ventilatory collapse

In the event of hemodynamic or ventilatory 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 at any dosage regarded necessary
- Rescue peripherally-administered systemic fibrinolytic therapy
- Surgical pulmonary embolectomy
- Catheter-assisted embolectomy including thrombus fragmentation or aspiration
- IVC filters

Of note, reperfusion techniques including rescue fibrinolytic therapy, emergency surgical pulmonary embolectomy, or emergency catheter-assisted embolectomy should not be performed unless the subject suffers hemodynamic collapse. The recommendation is consistent with current treatment guidelines which discourage the use of these advanced therapies for hemodynamically stable subjects with acute PE[27]. Rescue fibrinolysis, surgical pulmonary embolectomy, and catheter-assisted embolectomy should be recorded in the eCRF.

Inferior vena cava filter insertion

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. If an IVC filter is placed, the procedure should be noted in the appropriate section of the eCRF.

6.6 24, 48 And 72 Hours After the Start of the APT Procedure

At 24 hours (±6 hours) after the start of the APT procedure, the following assessments will be performed.

1. Vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate, and SpO2)
2. PESI score (sPESI will be calculated from PESI)
3. Adverse/VTE/Bleeding Events

At 48 hours (±6 hours) after the start of the APT procedure, the following assessments will be performed.

1. Vital signs
2. PESI score (sPESI will be calculated from PESI)
3. Prior to CTA: Laboratory Tests and biomarkers
    a. Hgb, Hct, BUN, creatinine and bleeding tests per Standard of Care based on anticoagulant therapy
    b. D-dimer, BNP/NT-proBNP, lactate/lactic acid and troponin
4. CTA to obtain RV/LV ratio and Modified Miller Score
5. Echocardiogram to measure: RV/LV ratio, TAPSE, estimated RVSP, and collapse of the IVC with respiration
6. Adverse/VTE/Bleeding events

At 72 hours after the start of APT Procedure or at discharge from hospital, whichever comes first, all Adverse/VTE/Bleeding Events that occurred from Screening/Baseline will be recorded in the eCRF. Any events recorded will be followed to resolution.

Data Collected for Hospital Stay

From Admission through Discharge, intervals will be collected including the following:

1. Time from hospital admission to diagnosis of PE

2. Time from diagnostic CTA to start of APT procedure

3. Time of each aspect of the procedure: beginning (start of APT procedure), end (conclusion of APT procedure), assessment times, rate of infusion and total dose of r-tPA. If the APT procedure is restarted, collect beginning and end of APT Procedure, rate of infusion and total dose of r-tPA.

4. 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.

6.7 Follow-up Clinic Visits and Subject Contact

The subject will be followed for 12 months. The subject will return to the clinic 30 ± 5 days, 90 ± 10 days, and 365 ± 14 days after treatment. It is recommended that the clinic staff collect at least three means of contacting the subject including a next of kin or close associate.

The following assessments will be performed at each follow-up clinic visit:

1. Echocardiogram

2. Six Minute Walk Test - 6MW (see Appendix D)

3. Quality of Life assessments (see Appendix E): PEmb-QOL and EQ-5D-5L

4. Adverse Events (non-serious) only through 30 day follow-up

5. Serious adverse events including recurrent VTE through 365 day follow-up

6. Changes in anticoagulant medications through 365 day follow-up

7. HCP visits for VTE

8. Hospital re-admission frequency and duration

9. Team managing the pt – specialties

6.7.1 Unscheduled Assessments For Clinical Events In Follow-Up

Subjects will be instructed to urgently contact medical personnel or to present to the Emergency Department if they develop symptoms compatible with recurrent PE, DVT, bleeding, or complications of the APT Procedure. Unscheduled assessment for clinical events will be documented on the eCRF when study staff learn of the event or at the next scheduled follow-up visit, whichever is earlier.

6.8 Prohibited Medications

The following systemic medications may increase the risk of bleeding and will not be concurrently administered during the APT Procedure: other anti-thrombotic agents such as vitamin K antagonists (warfarin, etc.), non-vitamin K oral anticoagulants (dabigatran, rivaroxaban, apixaban, or edoxaban), fondaparinux, direct thrombin inhibitors (argatroban, bivalirudin, lepirudin, etc.); and glycoprotein IIb/IIIa antagonists during the thrombolytic infusion.

6.9 Anticoagulation and Concomitant Medications

Anticoagulation medication history will be obtained at Screening/Baseline for the **3 days prior** to start of the APT procedure. (Note: Patient is excluded if thrombolytics or glycoprotein IIb/IIIa antagonists given **within 3 days prior** to start of APT Procedure.) Changes in anticoagulation medications will be recorded on the Anticoagulant eCRF throughout the 12-month follow-up period.

Other concomitant (non-anticoagulation) medications will be recorded on the Concomitant eCRF from Screening/Baseline through 12 month follow-up for medications prescribed to treat a serious adverse event only.

6.10 Subject Withdrawal and Early Termination

Subjects may withdraw from participation at any time during the clinical study. 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. If the subject declines, determine and document the reason for withdrawal.

7 INDIVIDUAL ASSESSMENTS

Unless otherwise noted, assessments for Baseline/Screening are to be performed within 48 hours prior to initiating the APT Procedure.

7.1 Pregnancy Test

A pregnancy test, blood or urine human chorionic gonadotropin (HCG) must be performed at Screening/Baseline prior to study enrollment for any women of child bearing potential. If pregnancy test has already been performed, a repeat test is not required.

7.2 Physical Exam and Patient Information

Data from routine physical examination of the patient will be documented at Screening/Baseline prior to study enrollment. The physical exam will include an assessment of all major body systems. Significant findings will be recorded in the subject's Medical History according to the Investigator's clinical judgment.

Patient demographics, medical history and VTE risk factors will be obtained and documented on the eCRF. If physical examination findings and/or patient information are available from initial admission notes, a repeat of these assessments is not required.

7.3 Electrocardiogram

A 12-lead ECG will be performed at Screening/Baseline. If an ECG has already been performed for this PE event, a repeat ECG is not required.

7.4 Vital Signs

Vital signs including, systolic/diastolic blood pressure, heart rate, respiratory rate, and SpO2 will be recorded at Screening/Baseline, at the start and at the conclusion of the APT procedure, within 4 hours Post-APT Procedure, at 24 (± 3) hours and 48 (± 6) hours after the start of the APT Procedure, and at all clinic visits. Temperature will be recorded for the purpose of completing the PESI/sPESI score at Screening/Baseline, within 4 hours, and at the 24 and 48 hour time points when the echocardiograms are performed

7.5 Right Heart Hemodynamic and SvO2 Measurements (Optional)

It is recommended that baseline right-heart pressures including mean right atrial, right ventricular systolic and diastolic, and main pulmonary artery systolic, diastolic and mean pressures, as well as mixed venous O2 saturation (SvO2) are obtained immediately prior to APT treatment.

7.6 Computed Tomography Pulmonary Angiography (CTA)

CTA will be performed at Baseline/Screening and at 48 (± 6) hours after the start of the APT Procedure to evaluate change in the RV/LV diameter ratio and thrombus burden (modified Miller Score).

7.7 Echocardiogram

An echocardiogram will be obtained at Screening/Baseline, within 4 hours Post-APT treatment, 24 (± 6) hours and 48 (± 6) hours after the start of the APT Procedure, and at 30 (± 5 d), 90 (± 10 d) and 365 (± 14 d) day clinic visits to evaluate RV/LV ratio, TAPSE, estimated RVSP, and collapse of the IVC with respiration.

7.8 Integrated Bedside Assessment (Select Participating Sites Only)

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.

The purpose for the collection of vital signs at 30 minutes and hourly focused echocardiography is to correlate change in clinical parameters (vital signs) with change in markers of RV strain (RV/LV ratio) documented in a non-invasive imaging method - echocardiography. There is preliminary evidence from the first 100 patients that the right heart recovers within a couple hours of treatment. Confirmation for this finding will be important in identifying the best treatment duration and dose of r-tPA required. The echocardiogram is the most sensitive non-invasive, real-time method outside of a CT scan to image both ventricles of the heart and quantify RV strain. The collection of routine bedside vital signs and limited echocardiograms (RV/LV ratio only) do not increase the potential risk to the patients participating in the study since they are non-invasive measurements that will be collected at the bedside with a limited number of sites during the conduct of the study.

7.9 Pulmonary Embolism Severity Index and Simplified Pulmonary Embolism Severity Index

PESI/sPESI will be calculated at Screening/Baseline, within 4 hours Post-APT treatment , at 24 (± 6) hours and at 48 (± 6) hours after the start of the APT Procedure. Refer to Appendix B for PESI/sPESI scoring information.

7.10 Laboratory Tests and Biomarkers

The following laboratory tests will be performed at Screening/Baseline, within 4 hours of the end of the APT procedure and at 48 (± 6) hours after the start of the APT Procedure.

- Hemoglobin, Hematocrit
- Platelet count
- Bleeding Times:
    - aPTT (seconds to form a blood clot in a sample of blood through measurement of the amount and function of coagulation factors);
    - PT and INR – prothrombin time (PT; time for clot to form in a sample of blood). Internationalized Normalized Ration (INR; adjusts for changes in the PT reagents)
- Kidney Tests: BUN (blood urea nitrogen), Creatinine

In addition, the following biomarker laboratory tests will be performed at Screening/Baseline, and 48 (± 6) hours after the start of the APT Procedure:

- Cardiac troponin : used to detect and evaluate mild to severe heart injury, and to distinguish chest pain that may be due to other causes. Elevations may indicate some degree of damage to the heart.

- BNP/NT-proBNP: produced primarily by the left ventricle of the heart. It is associated with blood volume and pressure and with the work of the heart. When the left ventricle of the heart is stretched, BNP concentrations increase.

- D-Dimer: a fibrin degradation product that reflects endogenous fibrinolysis.

- Lactate/Lactic acid: used to determine if lactic acidosis is present. Lactic acid is a product of cell metabolism that can accumulate when cells lack sufficient oxygen (hypoxia) and must turn to a less efficient means of energy production, or when a condition causes excess production or impaired clearance of lactate. For laboratories that do not measure lactate, lactic acid may be substituted.

At select participating sites, additional biomarker laboratory tests will be performed to assess thrombolytic activity at Screening/Baseline, at the end of the APT procedure, and at 48 (± 6) hours after the start of the APT Procedure. They include:

- Tissue plasminogen activator (t-PA) antigen to give the level of plasma t-PA

- Plasmin-antiplasmin levels- a marker of plasmin activation/turnover. Plasmin is the most powerful enzyme in the body and no free plasmin is found as any not bound to surface receptors binds to its inhibitor alpha-2 antiplasmin. Thus the quantity of plasmin-antiplasmin reflects how much plasmin is being generated.

- D-dimer ELISA (highly sensitive) – a marker of fibrinolytic turnover. This will provide a marker of turnover/amount of fibrinolysis

- Plasminogen activator inhibitor -1 (PAI-1) – a regulator of t-PA that binds to t-PA to inhibit it.

- Thrombin generation – a marker of thrombin activation which will demonstrate the ability of the coagulation system to work effectively and produce thrombin?

- Prothrombin factor 1+2 –a marker of thrombin activation, cleaved off from prothrombin when thrombin is generated

- Soluble S100A10. A receptor on the endothelium for plasminogen.

7.11 Anticoagulation and Concomitant Medications

Concomitant (non-anticoagulation) medications will be recorded on the Concomitant eCRF from Screening/Baseline through the 12 month follow-up period for medications prescribed to treat a serious adverse event only.

Anticoagulation history will be obtained at Screening/Baseline for the **3 days prior** to start of the APT procedure. Patient is excluded if thrombolytics or glycoprotein IIb/IIIa antagonists given **within 3 days prior** to start of APT Procedure. Changes in anticoagulation medications will be recorded on the Anticoagulant eCRF throughout the 12-month follow-up period.

7.12 6 Minute Walk Test (6MW)

Exercise testing will be performed at all follow-up clinic visits and in the event of early termination. Subjects will be evaluated with a 6MW and BORG Dyspnea scale (Appendix D).

7.13 Quality of Life (QOL) Assessments: PEmb-QOL and EQ-5D-5L

Two QOL Instruments will be used in this study and are included in Appendix E. The PEmb-QOL and EQ-5D-5L will be administered at follow-up during Days 30 (± 5 d), 90 (± 10 d), 365 (± 14 d), and Early Termination.

8 SAFETY REPORTING

8.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence observed in a subject that develops or worsens from Screening/Baseline, whether or not considered intervention related. An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an intervention and does not imply any judgment about causality.

8.2 Serious Adverse Events (SAE)

An AE is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

1. Death
2. Life-threatening (had the event occurred in a more severe form, might have caused death)
3. Inpatient hospitalization or prolongation of existing hospitalization

4. Permanent impairment of a body structure or body function; a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, for example, persistent or significant loss of function, disability, or incapacity

5. Congenital abnormality or birth defect if subject should become pregnant within 90 days of the treatment completion

6. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3 Unexpected Adverse Events

An AE is considered "unexpected" if it is not listed in the IFU or package insert or is not listed at the specificity or severity that has been observed.

8.4 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Pre-existing medical conditions should be reassessed during the trial and reported as an AE only if the frequency, severity, or character of the conditions worsens significantly or unexpectedly during the study. When reporting such adverse events, the description should convey that the pre-existing condition has changed by including applicable descriptors (for example, "more frequent" headaches). Scheduled hospitalizations required for diagnostic or elective surgical procedures for the management of unchanged pre-existing medical condition should not be considered AEs.

8.5 Device Deficiency, Device Failures and Malfunctions

Manufacturers must report device-related deaths, serious injuries and malfunctions to the country-specific regulatory agency whenever they become aware of information that reasonably suggests that the reportable event occurred (one of their devices has or may have caused or contributed to the event).

8.5.1 Definitions

A device failure is defined as the device is used in accordance with the IFU, but does not perform according to IFU and negatively impacts the treatment.

A device malfunction is defined as an unexpected change to the device that is contradictory to the IFU and may or may not affect device performance.

8.5.2 Reporting Requirements

All device failures and malfunctions will be documented on the eCRF within one working day after the designated study site personnel first learn of the event, and reported to the IEC/IRB (if required) within the IEC/IRB required timeframe. The Investigator will enter data into EDC within one working day and an automatically generated email notification will be sent to EKOS.

Device Malfunction

In the event of a device malfunction contact the BTG EKOS representative or EKOS Helpline for assistance. If the device cannot be restarted or is damaged in some way, if possible, the malfunctioning device will be replaced to continue ultrasound treatment for the desired length of time. If it is not possible to replace the device, thrombolytic infusion can be continued without the activation of ultrasound. The duration of the ultrasound will be recorded. The malfunctioning device will be retained for return to EKOS. When the malfunction is reported to EKOS, product return information will be provided.

Contact Information

For United States: [redacted]

For United Kingdom: [redacted]

8.6 Documentation Of Adverse Events

AEs will be reported when noted during the hospitalization for the initial treatment and in the subject's medical record through the 30 day follow-up period. Subjects will be encouraged to report AEs spontaneously or at follow-up visits in response to non-directed questioning by Investigator or Research Coordinator (for example, in response to the question "How has your health been since your last visit?"). If it is determined that an AE has occurred, the study staff member entering data into the eCRF will obtain all of the information necessary to complete the AE section.Serious adverse events including VTE events will be reported through the 365 day study. Subjects will be specifically asked about visits to a physician, hospitalizations and other events that meet the definition of serious.

8.7 Reporting And Duration Of AE Reporting Period

Because the EKOS is a commercial medical device, Investigators will comply with any hospital user reporting requirements. All observed or reported AEs including type of event, severity and relationship to the procedure, device use, thrombolytic and anticoagulant drug use will be recorded in the eCRF during hospitalization and through 30 day follow-up. At subsequent visits, SAEs and AEs related to venous thromboembolism, bleeding events or the EKOS treatment will be collected. Previously reported AEs will continue to be followed to resolution.

8.8 Adverse Events Related To r-tPA And Definition Of Major Bleeding

AEs related to r-tPA are well-described and consist mainly of bleeding complications, including intracranial hemorrhage. The incidence of these complications has been quantified in subjects receiving comparatively large systemic doses of r-tPA for acute myocardial infarction, stroke, and acute PE. Any bleeding that is attributable to r-tPA is most likely to occur within 24 hours of treatment and is very unlikely to occur after 72 hours. Therefore, all bleeding events without known cause that occur within 72 hours of the APT Procedure will be attributed to the use of r-tPA.

The following definition of major bleeding[12] (ISTH) will be used: As general principles, a definition of major bleeding will be based on objective criteria, and major bleeds are those that result in death, are life-threatening, cause chronic sequelae or consume major health-care resources. With this in mind, the Control of Anticoagulation Subcommittee recommends the following criteria for major bleeding in non-surgical subjects:

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ, such as 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 gL^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells

For this protocol, a fall in Hgb of 20 gL^{-1} or more with no objective evidence of bleeding or symptoms of bleeding will not be considered a major bleeding event.

8.9 Specific Reporting Guidelines

Study Investigators will adhere to the following guidelines to ensure the quality and precision of AE reporting:

1. Use recognized medical terms.
2. Avoid the use of colloquialisms and non-standard abbreviations
3. If known at the time of AE reporting, a diagnosis will be reported instead of individual symptoms and signs (for example, record only “pneumonia” rather than “productive cough” and “elevated white blood cell count”).
4. If the reported symptoms and signs cannot be medically characterized as a single diagnosis or syndrome at the time of AE reporting, the information that is available will be reported. If a diagnosis is subsequently established, it will be reported as follow-up information as described earlier.
5. A cascade of clinical events (such as sequelae of an adverse event) will be identified as the primary, causative event.

6. Any AE potentially related to the study procedure that results in inpatient re-hospitalization or prolongs the index hospitalization will be reported as a SAE. If a subject is re-hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure (not the procedure itself) will be reported as the SAE. For example, if a subject is re-hospitalized to undergo exploratory surgery as a result of a major bleeding event, record the major bleeding event that necessitated surgery as the SAE.
7. All observed or reported serious bleeding events occurring through the 365 day follow-up period, must be recorded.
8. Previously scheduled hospitalizations required for diagnostic or elective surgical procedures for the management of unchanged pre-existing medical conditions will not be considered AEs.

8.10 Pregnancy

If a subject becomes pregnant within 90 days of receiving r-tPA and undergoing APT Procedure, follow-up will be obtained from the medical record to determine the outcome of the pregnancy (successful live-birth, etc.). Congenital abnormalities must be reported as a SAE.

8.11 Categorization Of Adverse Events

All AEs must be classified according to intensity or severity, relatedness, outcome, and treatment or action taken.

Intensity Or Severity

The following categories for intensity or severity of an AE will be used in reporting:

Mild	Awareness of a symptom or sign that does not interfere with the subject's usual activity or is transient and resolves without treatment and without sequelae
Moderate	Interferes with the subject's usual daily activities, but he or she is still able to function
Severe	Interrupts a subject's usual daily activities and generally requires medication, surgery, or other intervention for treatment

Relatedness

Each AE will be evaluated as to whether it was related to the study procedures, thrombolytic and anticoagulation drugs, or EKOS as follows:

Definite	An AE that has a causal relationship to the drug (r-tPA), anticoagulation medication, or EKOS
Probable	An AE that has a 'reasonable possibility' of a causal relationship to the use of r-tPA, anticoagulation medication, or EKOS; another etiology is significantly less likely
Not related	An AE is not related to the use of r-tPA, anticoagulation medication, or the APT® Endovascular System; there is no temporal relationship or a much more likely alternative etiology exists
Unknown	An AE where the relationship to the use of r-tPA, anticoagulation medication, or EKOS cannot be determined.

Outcome

The clinical course of all AEs will be followed until a medical outcome is determined (resolution, stabilization, or determination that it was unrelated to study participation). The clinical outcome of all AEs will be recorded as follows:

Death	Subject expired
Recovered	Subject returned to baseline health and functional status

Not yet recovered	Subject did not recover and symptoms or sequelae persist
Recovered with sequelae	Subject did recover but continues to experience clinical sequelae from the adverse event

Treatment or action taken

AEs and SAEs will be categorized by the actions taken in response to the event:

Intervention	Surgery or other invasive procedure
Non-surgical treatment	Drug start, interruption, dose reduction, dose increase, or discontinuation
None	No action was taken

8.12 Expedited Reporting Of Serious Adverse Events

Any AE that is considered serious must be reported to the device manufacturer, EKOS Corporation, within 24 hours of the site's knowledge of the event throughout the study. The Investigator will enter into EDC as much of the information listed below is available within 24 hours. An automatically generated email notification will be sent to EKOS when the event is classified as a Serious Adverse Event in EDC.

a. Subjects demographics

b. Pre-existing conditions

c. The adverse event's description

d. Date and time of AE onset

e. Severity

f. Treatment

g. Results of diagnostic testing

h. Duration of sequelae

i. Outcome (if known)

j. Information on suspected medications

When a device-related SAE is reported, the device must be retained and returned to EKOS (see above for address for return devices). The EKOS representative may contact the Investigator to collect additional information on EKOS.

When reporting a death, the primary event or condition that caused or contributed to the fatal outcome will be reported as the serious adverse event. Death would be reported as the outcome of the serious adverse event. If the cause of death is unknown at the time of reporting, record "unknown cause of death."

8.13 Safety Monitor

A safety monitor will review all AEs,adjudicate all SAEs and major bleeding events during the study, as well as assess freedom from major harm occurring between enrolment and 30 days for each subject. The safety monitor will determine if the AE meets the definition of serious and unexpected and will notify EKOS if the number or type of events is of concern.

9 DATA COLLECTION

All study data will be recorded in eCRFs. Images will be provided to the Core Imaging Laboratory as described in the operations manual provided to the sites. Instructions and training on data collection/entry will be provided to the Investigator and their staff during site start-up and will be available throughout the study for new personnel.

Data gathered during the course of the study will be entered into an eCRF as soon as possible and at least within 7 days of subject enrollment or follow-up visit. Data will be reviewed on a periodic basis and any incomplete or inconsistent data will be requested from the Investigator.

10 STATISTICAL ANALYSIS

10.1 Analysis Subject Sets, Evaluable Subjects and Missing Data Handling Convention

Intent-to-Treat (ITT) Subject Set includes all randomized subjects; analyses performed on the ITT Subject Set will be by randomization treatment assignment regardless of actual treatment's deviations from the assigned treatment protocol. Unless otherwise specified, all available data will be used for ITT analyses regardless of whether the assessment timing is within the pre-specified window.

Efficacy Evaluable Subject Set are defined as randomized subjects who met all eligibility criteria, received the randomization assigned APT Procedure with bilateral EkoSonic treatment, and for whom CTA imaging data are available and the assessments are within the pre-specified window at both Screening/Baseline (within 48 hours prior to APT start) and 48 ± 6 hours from the beginning of the APT procedure.

Safety Evaluable Subject Set are defined as randomized subjects for whom the APT Procedure was initiated, i.e. venous access attempted for EkoSonic catheter introduction. Safety analysis will be performed on the Safety Evaluable Subject Set according to the actual treatment received.

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

10.2 General Methodology

Unless otherwise specified, all analysis will be performed separately for each of the treatment arms and separately for unilateral and bilateral patients within each treatment arm . For Screening/Baseline demographics and subject or disease characteristics, continuous measures will be summarized as mean, standard deviation, median, minimum and maximum. Categorical data will be summarized as frequencies and percentages for each data category. For changes from Screening/Baseline to follow-up time points, continuous measures will be summarized as mean, standard deviation, median, minimum, and maximum. Categorical outcomes will be summarized in two-way tables. Statistical significance for changes from Screening/Baseline will be assessed by t-test or a nonparametric test as appropriate for continuous data; Fisher's exact test will be done for 2x2 tables and Friedman Halton exact test will be performed for tables with higher dimensions.

Further analysis details will be described in the Statistical Analysis Plan.

10.3 Efficacy Analyses

Efficacy analyses will be performed on both the **ITT Subject Set** and the **Efficacy Evaluable Subject Set**.

10.3.1 Primary Efficacy Analysis

The primary efficacy outcome is the change in the RV diameter-to-LV diameter ratio, from Screening/Baseline to 48 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[28]. For this study, a 1-sided $p<0.15$ 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[29] will be used for statistical testing.

10.3.2 Secondary Efficacy Analyses

Secondary efficacy outcomes are the following:

1. Change from Screening/Baseline in echocardiographic parameters including RV/LV ratio, TAPSE, estimated RVSP, and collapse of the 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 hours after the start of the APT Procedure

3. Freedom from major harm occurring between enrolment and 30 days as 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

5. Quality of Life (QOL) as measured by the PEmb-QOL and EQ-5D-5L at all post-hospitalization subject visits.

6. Healthcare resource utilisation during hospitalisation:
    a. Time from hospital admission to diagnosis of sPE
    b. Time from diagnostic CT scan to initiation of treatment for sPE
    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

Analyses for all secondary efficacy endpoints will be performed as described under 9.3 General Methodology.

10.4 Safety Analysis

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

For the primary safety analysis, the number and percentage of subjects with major bleeding 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 up to 365 days, and death during the 365 day follow-up period will be reported with 95% confidence intervals.

In addition, adverse events experienced 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. Separate tables will be constructed for (a) all reported events, (b) events judged as related to the study procedure/device/medications, and (c) SAEs.

10.5 Sample Size And Power Estimation

The primary efficacy endpoint for the study is the 48-hour decrease in RV/LV ratio. The Fasullo 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 sub-massive 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 0.95.

11 RISK ANALYSIS

11.1 Description And Analysis Of Risks

The risks that are associated with use of EKOS are expected to be the same as the risks associated with the placement of any catheter into the venous system including vessel injury such as dissection, perforation, or rupture and are listed in the EkoSonic IFU Appendix A. Potential risks associated with thrombolytic drugs are similar for all commercially available r-tPA products and are described in the manufacturer's prescribing information.

The effectiveness and safety of 24 mg r-tPA delivered over 12 or 24 hours via the EKOS system have previously been studied in 150 patients (SEATTLE II). This study requires delivery of 4-12 mg r-tPA over infusion times of 2-6 hours. The risks associated with use of the EKOS system are unchanged by the reduced infusion times. Because the maximum dose of drug allowed in this study is now ≤ 50% of the 24 mg delivered in SEATTLE II, no additional risks associated with r-tPA are anticipated in this study. Potential risks for subjects undergoing the procedure are listed in the following text.

11.2 Anticipated Risks Of APT Procedure

Anticipated risks of the APT Procedure are categorized as likely, less likely, and rare.

Likely

1. Anxiety related to undergoing the APT Procedure
2. Discomfort or bruising at sites for blood draws, intravenous line placement, or EkoSonic® catheter placement
3. Discomfort from mandatory immobility during the APT Procedure.

Less likely

1. Infection, pre-syncope, or syncope due to intravenous line or catheter placement or additional peripheral blood draws needed to monitor therapy
2. Hematoma at the venous access site
3. Major bleeding requiring transfusion of blood products
4. Nausea and vomiting
5. Adverse reaction to iodinated contrast or other medications

6. Local discomfort during placement of the EkoSonic® Device
7. Limiting the dose of r-tPA and infusion time could potentially result in ineffective treatment of the study subject.

Rare

1. Adverse drug reaction to r-tPA
2. Severe allergic reaction (such as anaphylaxis) to iodinated contrast or other medications
3. Anesthesia complications
4. Post-procedure wound complications
5. Renal failure requiring hemodialysis
6. Vascular complications (such as dissection, perforation, vasospasm, pseudo aneurysm, occlusion, and arteriovenous fistula)
7. Thromboembolism
8. Recurrent PE
9. Fatal, life-threatening, or intracranial hemorrhage or stroke
10. Severe internal bleeding (such as gastrointestinal or retroperitoneal) that requires surgical or interventional laboratory intervention
11. Device-related trauma to cardiac structures (such as heart valves)
12. Death
13. Other rare or unforeseen adverse effects

11.2.1 Protection Of Subjects Against The Risks Of Standard Therapy For Acute PE

Standard therapy for acute PE will be supervised by licensed physicians who are experienced in the management of anticoagulation. Complications of anticoagulation will be minimized by the use of widely accepted regimens for unfractionated heparin, and low-molecular weight heparin.

11.2.2 Protection Of Subjects Against The Risks Of Research Procedures

Before study enrollment

A rigorous screening process will be utilized to ensure that subjects who are not likely to benefit from APT Procedure or who are at particularly high risk for adverse outcomes (especially bleeding) are excluded from the study. This will include confirming 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 serum creatinine). If there is an intracranial or intraspinal lesion of any kind, the subject will not be enrolled in the study.

During APT Procedure

The APT Procedure will be performed by a licensed physician who has expertise in endovascular techniques, particularly with experience in placement of catheters into the pulmonary arteries. Analgesia during the procedures will be provided through the use of conscious sedation if required. The risks of conscious sedation will be minimized by continuous monitoring of heart rate, respiratory rate, blood pressure, oxygen saturation and cardiac rhythm.

Sterile technique will be utilized to minimize the risk for infection at the venous access site. Discomfort at the venous access site will be minimized by administration of local anesthesia into the overlying skin and adjacent tissues. Catheter access into the appropriate vein(s) will be performed using ultrasound-guided venipuncture as necessary to prevent inadvertent arterial puncture with subsequent bleeding. Real-time fluoroscopic monitoring of all catheter/wire manipulations will be used to prevent vascular injury.

To minimize bleeding risk, heparin will be infused at the intermediate intensity level to achieve a target aPTT between 40 to 60 seconds at the start of the APT Procedure.

The risk of significant iodinated contrast reaction will be minimized by exclusion of subjects with a serum creatinine outside normal limits, use of non-ionic contrast agents, and appropriate pre-procedure hydration. Device-related complications, primarily mechanical failure or vascular injury, will be minimized by meticulous angiographic technique. Bleeding risks will be minimized by limiting the total r-tPA dose to $\leq$ 12 mg and the thrombolytic infusion time to 6 hours or less.

During Follow-up

Changes in health status during the 12-month follow-up period will be evaluated by the investigator or designated research staff.

11.2.3 Protection Against Loss Of Confidentiality

Subject confidentiality will be protected by maintaining all paper records in locked file cabinets in locked offices and all electronic records in password-protected computer files. All study data will be de-identified for storage in the electronic data repository. In addition, any identifying information will be removed from images or other data used in publication or presentations. All database information will be stored on computer systems that are located behind an electronic firewall, which will only permit access to certified study personnel. Access to study data files will be password-protected.

12 ETHICAL CONSIDERATIONS

In this randomized, parallel, multi-arm, multi-center clinical study, we will be evaluating the impact of APT Procedure for acute submassive PE. The benefits versus risks of peripherally-administered systemic fibrinolysis remain unclear for both acute massive and submassive PE despite a number of randomized controlled trials that have been conducted. The risk of bleeding, especially intracranial hemorrhage, in the setting of systemic fibrinolysis represents a major limitation to its use in subjects with acute PE. The combination of local catheter-directed administration with a lower dose of fibrinolytic agent may be as effective as or even more efficacious than peripherally-administered systemic fibrinolysis with a lower risk of bleeding. However, it is also possible that peripherally-administered fibrinolysis is more efficacious than a local catheter-based approach because of the higher dose used and a more potent systemic effect that may dissolve residual DVT thereby preventing subsequent PE. Therefore, equipoise for such a clinical trial exists. A successful trial has the potential to provide clinicians and subjects with a wider variety of treatment options for acute submassive PE.

Written consent from all study subjects and IEC/IRB approval at all study sites. Study sites must obtain and submit proof of IEC/IRB approval prior to start of enrollment at the site.

13 RECORD RETENTION

All study records and reports will remain on file at the sites for a minimum of two years after completion date of the trial. Trial records are to be discarded or relocated only upon notification by EKOS. The Investigator or designee must contact EKOS before the destruction of any records and reports pertaining to the trial to ensure they no longer need to be retained.

14 INVESTIGATOR RESPONSIBILITES

14.1 General

Although this clinical study will monitor an approved device, the following responsibilities are required.

1. The Investigator will ensure that all work and services described herein, will be conducted in accordance with the highest standards of medical and clinical research and in compliance with ICH Good Clinical Practice (GCP) guidelines and this protocol, and all conditions of the Independent Ethics Committee (IEC)/Investigational Review Board (IRB).

2. The Investigator will ensure that the protocol has been provided to all Sub-Investigators and that site personnel responsible for the study have been trained. The Investigator will ensure that study personnel conduct the study to the protocol and study procedures.

3. The Investigator is responsible for protecting the rights, safety, and welfare of subjects under the Investigator's care.

4. The Investigator is responsible for ensuring that Informed Consent is obtained prior to any study procedures and maintained throughout the study.

5. Subjects must be informed that their medical records may be subject to review by BTG, its representatives, and government agencies.

6. Notify BTG if the investigator plans to leave the investigational site.

14.2 Source Documentation

International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice – E6 require that Investigators maintain information in the subjects medical records that corroborate data collected on the eCRF. In order to comply with these regulatory requirements, the following information will be maintained and made available as required by BTG and or its designees and/or regulatory authority inspectors.

1. Medical history/physical condition of the subject before involvement in the study sufficient to verify investigational plan entry criteria and evaluations or prior signs and symptoms

2. Medical record documenting the informed consent was obtained for the subject's participation in the trial

3. Description of device procedure (device used, drugs administered during the procedure, date, time, angiographic and clinical findings, etc.)

4. Notations on abnormal lab results and their clinical significant/resolution
5. Dated printouts or reports of special assessments
6. Description of AEs and follow-up of the AEs (at a minimum include the description, onset date, duration, relation to device, treatment and outcome)
7. Notes regarding adjunctive treatment and concomitant medications including start and stop dates.
8. Subject's condition upon completion or withdrawal from the study.

14.3 Study Deviations

A study deviation is defined as an event where the Investigator or study personnel did not conduct the trial according to the protocol, applicable laws or regulations, or the Clinical Trial Agreement. It is required that Investigators maintain accurate, complete and current records, including documentation of any deviations from the investigational plan including the date of and reason for the deviation. The deviations must also be reported to BTG. Subject specific deviations will be reported on the protocol deviations case report form.

14.4 Publication Policies

At the conclusion of the study, a multi-center manuscript may be prepared for publication in a reputable scientific journal. The publication of the principal results from any single site experience within the study is not allowed until the preparation and publication of the multicenter results. Exceptions to this rule require approval from the BTG Clinical Affairs Department. All publications of results from this study must be approved by the BTG Clinical Affairs Department.

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