Protocol Number:	BTG-001653-01
Protocol Short Title:	KNOCOUT PE
Protocol Name:	Retrospective and prospective international E**K**oSo**N**ic® registry **O**f the treatment and **C**linical **OUT**comes of patients with **P**ulmonary **E**mbolism
Sponsor:	EKOS Corporation, a BTG International group company 11911 North Creek Parkway S. Bothell, WA 98011, USA
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Investigational Product (IP)	EkoSonic® Endovascular System (EKOS)
Clinicaltrials.gov identifier	NCT03426124
EudraCT Number	2018-001235-46

VERSION NUMBER	APPROVAL DATE	BRIEF DESCRIPTION OF CHANGES
1.0	22-Nov-2017	Initial Release.
1.1	1-Dec-2017	Protocol amended to increase number of sites from 50 to 100.
1.2	4-Jan-2018	Protocol amended to include electronic patient reported outcomes.
2.0	9-May-2018	Protocol amended to modify eligibility criteria, clarify assessments, and time points for follow up. Added details of planned analysis.
2.0.EMEA	27-Aug-2018	Removal of appendices; addition of OPTALYSE PE manuscript reference; consistency in device name; more inclusive regulatory focus.
2.1.EMEA	19-Oct-2017	Removal of r-tPA; change to physician-specified fluid to bring in alignment with IFU.

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PROTOCOL APPROVAL & RELEASE SIGNATURE PAGE

Protocol Number:	BTG-001653-01
Protocol Short Title:	KNOCOUT PE
Protocol Name:	Retrospective and prospective international E**K**oSo**N**ic® registry study **O**f the treatment and **C**linical **OUT**comes of patients with **P**ulmonary **E**mbolism
Protocol Version:	2.1.EMEA
Protocol Approval Date:	19-Oct-2018

The above-referenced protocol was reviewed and approved for release by the following:

Approver	Signature	Date (DD/MMM/YYYY)
Coordinating Principal Investigator		
Sponsor: VP, Clinical Development		
Sponsor: Study Manager		
Sponsor: Project Physician		
Sponsor: Statistician		

INVESTIGATOR PROTOCOL REVIEW STATEMENT

Protocol Number:	BTG-001653-01
Protocol Short Title:	KNOCOUT PE
Protocol Name:	Retrospective and prospective international E**K**oSo**N**ic® registry study **O**f the treatment and **C**linical **OUT**comes of patients with **P**ulmonary **E**mbolism
Protocol Version:	2.1.EMEA
Protocol Approval Date:	19-Oct-2018

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

The undersigned confirms that the registry will be conducted and documented in accordance with the Declaration of Helsinki, this protocol, standards of Good Clinical Practice, applicable laws and regulatory requirements specified in the protocol, and the stipulations of the Clinical Trial Agreement.

By written consent to this protocol, the Principal Investigator agrees to the above and to fully cooperate with all monitoring and audits in relation to this registry by allowing direct access to all documentation, including source data, by authorized individuals representing EKOS Corporation, BTG International, the relevant institutional review board/ethics committee (IRB/EC) and/or by regulatory authorities.

Investigator Name (please print): _____

Investigator Signature: _____

Date (DD/MMM/YYYY): _____

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1. TERMS, ACRONYMS, ABREVIATIONS

The following abbreviations and specialist terms are used in this protocol.

AE	Adverse event
APT	Acoustic Pulse Thrombolysis
aPTT	Activated partial thromboplastin time
BNP	Brain natriuretic peptide
CE	European Conformity
CFR	Code of Federal Regulation
CRA	Clinical research associate
CTA	Computed tomography angiography
CTEPH	Chronic thromboembolic pulmonary hypertension
CV	Curriculum vitae
DM	Data management
DMP	Data management plan
DVT	Deep vein thrombosis
eCRF	Electronic case report form
EDC	Electronic data capture
EP	Efficacy population
ePRO	Electronic Patient Reported Outcomes
EQ-5D-5L	Euroqol five dimension five level questionnaire
FDA	Food and Drug Administration
FPI	Full prescribing information
GCP	Good clinical practice
Hct	Hematocrit
Hgb	Hemoglobin
HIPAA	Health Information Portability and Accountability Act
ICF	Informed consent form
ICH	Intracranial hemorrhage
ICU	Intensive care unit
ID	Identification
IDDC	Intelligent Drug Delivery Catheter
IFU	Instructions for Use
INR	International normalized ratio
IP	Investigational product
IRB/EC	Institutional review board/ethics committee
IVC	Inferior vena cava
LV	Left ventricular
MHz	Megahertz
MSD	MicroSonic device
PE	Pulmonary embolism
PEmb-QOL	Pulmonary Embolism Quality of Life
PHI	Protected health information
PT	Partial thromboplastin time
Pts	Patients
QOL	Quality of Life
r-tPA	Recombinant tissue plasminogen activator

RV	Right ventricular
RVSP	Right ventricular systolic pressure
SAE	Serious adverse event
SAP	Statistical analysis plan
SoC	Standard of care
SP	Safety population
sPESI	Simplified pulmonary embolism severity index
SpO_2	Peripheral capillary oxygen saturation
SvO2	Mixed venous oxygen saturation
TAPSE	Tricuspid annular plane systolic excursion
U.K.	United Kingdom
U.S.	United States
VTE	Venous thromboembolism

2. PROTOCOL SYNOPSIS

Protocol Number	BTG-001163-01
Protocol Short Title	KNOCOUT PE
Protocol Title	Retrospective and prospective international E**K**oSo**N**ic® registry study **O**f the treatment and **C**linical **OUT**comes of patients with **P**ulmonary **E**mbolism
Intervention	Device: EkoSonic® Endovascular System (EKOS) employs high frequency (2-3 MHz), low power ultrasound to facilitate the delivery of physician-specified fluids, including thrombolytics, in the pulmonary arteries. Acoustic Pulse Thrombolysis (APT) Procedure: The clinical use of the EKOS device in combination with physician-specified fluids.
Type of Protocol	International Registry
Trial Objectives	• To understand the APT treatment protocol used as SoC across institutions and document changes in practice following the OPTALYSE PE study results • To describe the effects of varied APT protocols on long-term patient outcomes
Outcome Measures	1. Change in the ratio of the measurement of the right ventricular to left ventricular diameters (RV/LV) as measured on echocardiogram or computed tomography angiography (CTA) from baseline to between 24 – 48 hours (hr) after the start of the APT procedure (matched pairs as available). 2. Diagnosis of pulmonary hypertension defined as mean pulmonary artery pressure greater than 25mm Hg by echocardiogram that persists at least 3 months after PE diagnosis 3. Frequency and safety outcomes of adjunctive therapies post APT procedure during hospitalization 4. Number of patients with non or partial response to other interventional procedures prior to APT procedure for index PE 5. Frequency and severity of serious adverse experiences (SAE) related to EKOS or procedure, major bleeding, or venous thromboembolic disease (VTE) during index hospitalization and during first 12 months post-APT procedure 6. All-cause mortality during first 12 months post-APT procedure 7. Recurrent symptomatic PE, PE related death, hemodynamic collapse at 30 days (composite measure) 8. Healthcare utilization during hospitalization: a. Time from hospital admission to ICU discharge b. Time from hospital admission to discharge

	9. Quality of life (QOL) as measured by the Pulmonary Embolism Quality of Life (PEmb-QOL) and EuroQol five dimension five level questionnaire (EQ-5D-5L) at 3 month and 12 month post-hospitalization follow-up visits 10. IVC filter placement (measured by number of occurrences)
Trial Duration	RETROSPECTIVE Data collection is expected to occur over a 6 month period at each site PROSPECTIVE Enrollment will take place over approximately a 24 month period. For each subject, their participation in the registry lasts 12 months.
Trial Design	A multi-center retrospective and prospective registry of the APT treatment of patients (pts) with submassive (Intermediate-High Risk) and massive (High Risk) PE. The retrospective portion of the registry will consist of consecutive patients treated with APT between January 1, 2014 and one year prior to date of site activation. The prospective portion of the registry will collect data for pts diagnosed and risk-stratified and treated with APT procedure. Pts will be followed for 12 months. Intermediate-High Risk PE will be defined by evidence of RV dysfunction (RV/LV $\geq$ 1.0), hemodynamic stability (normal systemic arterial blood pressure >90 mmHg), and troponin elevation. High Risk PE will be defined with hemodynamic instability (normal systemic arterial blood pressure <90 mm Hg and/or use of vasopressors)
Number of Patients	RETROSPECTIVE Up to 1000 evaluable cases PROSPECTIVE Up to 550 consented patients to yield 500 evaluable patients
Number & Location of Sites	Up to 100 sites geographically distributed throughout North America, Europe, and Asia
Eligibility Criteria	RETROSPECTIVE Inclusion Criteria 1. Treated with APT procedure between January 1, 2014 and one year prior to date of site activation 2. RV/LV $\geq$ 1.0 from diagnostic CTA or echocardiogram 3. PE symptom duration $\leq$ 14 days

	4. Troponin elevation Exclusion Criteria 5. Enrollment into the OPTALYSE PE study PROSPECTIVE Inclusion Criteria 1. Male or female ≥ 18 years of age and ≤ 80 years of age 2. RV/LV ≥ 1.0 from diagnostic CTA or echocardiogram 3. PE symptom duration ≤ 14 days 4. Troponin elevation 5. Signed informed consent obtained from subject or legally authorized representative 6. Investigator has selected EKOS to treat patient with massive or submassive PE Exclusion Criteria 7. Clinician deems the subject high-risk for catastrophic bleeding 8. Life expectancy < one year
Sample Size Justification	The aim of the registry is to collect observational data on standard of care APT treatment. The sample size is calculated from the expected enrollment per site based on estimated cases per physician across total number of sites. For retrospective cases, up to 1000 cases will be collected to capture details of PE treatment with EKOS from the time it became commercially available to the time the site was activated. For prospective, up to 500 patients will be treated to collect data on current EKOS use at up to 100 sites.
Statistical Methods	Patients will be analyzed according to the APT treatment protocol they received (i.e. duration of treatment and dose, type of fluid received). Frequency of use of each of the APT treatment protocols before and after OPTALYSE PE results were made public will be summarized and compared using fisher's exact test. Each outcome measure will be summarized for the full registry population as well as separately by the different APT treatment protocols, including 95% confidence intervals. Additionally, outcome measures will be summarized by the following subgroups: submassive and massive PE, each region, and by the retrospective and prospective portions of the registry.
Registry Procedures	See section 3. SCHEDULE OF REGISTRY ASSESSMENTS – PROSPECTIVE below

Registry Follow-up Visits	For prospective subjects, patients should be followed per Investigator's standard of care (SoC). Data will be collected for any echocardiograms and CTAs completed throughout the 12 month follow-up period. At minimum, a health status check should be performed at 3 and 12 months. An on-site visit with echocardiogram is recommended at 3 months for patients with abnormal echocardiogram post-treatment for evaluation of chronic pulmonary hypertension, and at 12 months for all patients. Safety data should be reported through 12 months post-index procedure. For retrospective cases, long term health data will be collected as available for up to 12 months post-index treatment.
Treatment	Subjects scheduled for treatment with EKOS will be treated as prescribed by the Investigator SoC for treating PE and in accordance with the instructions for use (IFU). Post-procedure care should be performed and prescribed in accordance with Investigator's SoC and as specified in the protocol.
Data Collection	All data will be collected via an electronic data capture (EDC) system. The Investigator and Investigator's staff will enter registry data into the EDC through a web portal. Each Investigator and Investigator staff member is granted a unique login into the EDC platform.

3. SCHEDULE OF REGISTRY ASSESSMENTS – PROSPECTIVE

Assessments will be performed per Investigator's SoC and collected according to the schedule below. Assessments marked with an asterisk (*) pertain to an outcome measure or eligibility.

Assessment	Baseline	Procedure/Post Procedure	Follow-up	
	Day -1	Day 0 thru Discharge	3 Months (±14 Days) Post APT (Phone or Visit)	12 Months (±1 Month) Post APT (Phone or Visit)
Informed Consent	X*			
Demographics	X*			
Medical history, risk factors	X*			
Vital signs[1]	X*	X		
Physical Examination	X			
CTA	X*	X*[3] (if collected)		
sPESI	X			
APT Procedure		X		
Echocardiogram[2]	X*	X[3] (if collected)	X* (if collected)	X* (if collected)
Quality of life surveys[4]		X*	X*	X*
Laboratory tests[5]	X[6]	X		
Biomarkers[7]	X*	X		
Adverse/VTE/Bleeding Events		X*	X*	X*
Anticoagulation medications	X	X	X	X

1. Record heart rate, blood pressure, respiratory rate, oxygen saturation vital signs at admission, at start and end of treatment, and once at same time each day of hospitalization
2. Includes RV/LV ratio, TAPSE, estimated RVSP, and collapse of the inferior vena cava (IVC) with respiration
3. Collect 24 – 48 hours after the start of the APT procedure
4. PEmb-QOL and EQ-5D-5L
5. Hemoglobin (Hgb), hematocrit (Hct), platelet count, creatinine, activated partial thromboplastin time (aPTT), partial thromboplastin time (PT), and international normalized ratio (INR)
6. Record if collected within 48 hours prior to the start of APT procedure
7. Troponin, brain natriuretic peptide (BNP)/NT-proBNP, lactate/lactic acid, and D-dimer

4. BACKGROUND

4.1 Pulmonary Embolism (PE)

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 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.

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

physician-specified fluids, including thrombolytics, 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.

EKOS Corporation investigated the effectiveness of thrombolytics delivered by ultrasound catheter in acute PE (symptoms ≤ 14 days) located in at least one main or proximal lobar pulmonary artery and with a RV/LV of ≥ 0.9 on chest CTA or echocardiogram in three prospective, multi-center studies that provide evidence for the efficacy and safety of the 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 ULTIMA involving 30 of 59 patients (pts); and two prospective studies: SEATTLE II involving 150 pts and OPTALYSE PE involving 100 pts.

4.2 EkoSonic® Endovascular System (EKOS) Product Description

4.2.1 EKOS Intended Use

EKOS is intended for the treatment of pulmonary embolism patients with ≥ 50% clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressures (mean pulmonary artery pressure ≥ 25 mmHg) or echocardiographic evaluation.

4.2.2 EKOS Description

The EkoSonic® Endovascular System (EKOS) 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.

EKOS consists of two main components:

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

The IDDC is 5.4 French with a 106 cm or 135 cm working length. It includes two luer ports for coolant and fluid 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. Fluid and coolant flow through distal side holes for delivery in the treatment zone. Each IDDC requires its own set of infusion tubing and infusion pump for fluid and coolant.

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

4.2.3 EKOS Regulatory Status

In Europe, EKOS has an EC Design-Examination Certificate (CE 567229) for the treatment of pulmonary embolism with a ≥ 50% clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressures (mean pulmonary artery pressure ≥ 25 mmHg) . In this registry study, EKOS is commercially-available and being used in accordance with its cleared indications for use. Therefore, no special labeling or tracking is required for devices.

4.3 EKOS Clinical Summary in Pulmonary Embolism

ULTIMA, SEATTLE II, and OPTALYSE PE have shown various APT regimens using recombinant tissue plasminogen activator (r-tPA) for thrombolysis to be safe and effective in the treatment of PE. Low dose r-tPA and reduction in treatment time of the APT procedure appear to 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[16]. 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 hours. 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 undissolved clot at the end of the measurement period

Similarly, a pharmacodynamics 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[17]. 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[18]. 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[19]. 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 the 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[20]. 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 was 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 the OPTALYSE PE study were 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 each study arm and therefore a sample size was extended to additional sites in the U.K. Improvement in the RV/LV diameters by core laboratory-assessed echocardiographic reads were -0.17, -0.17, -0.12, and -0.29 at 4 hours and -0.22, -0.25, -0.18, and -0.32 at 48 hours in patients randomized to 8 mg/2 hrs, 8 mg/4 hrs, 12 mg/6 hrs, and 24 mg/6 hrs, respectively.[21] Improvement in modified Miller score was also seen in all groups[22].

5. REGISTRY OBJECTIVE AND PURPOSE

5.1 Objectives

The objectives of this registry are:

- To understand the APT treatment protocol used as SoC across institutions and document changes in practice following the OPTALYSE PE study results
- To describe the effects of varied APT protocols on long-term patient outcomes

5.2 Design

This multicenter, international registry is designed to retrospectively and prospectively collect treatment and outcome data related to pts with submassive (Intermediate-High Risk) or massive (High Risk) PE undergoing the APT treatment. Subjects are treated per Investigator's SoC and in accordance with the IFU.

Intermediate-High Risk PE will be defined by evidence of RV dysfunction (RV/LV ≥ 1.0), hemodynamic stability (normal systemic arterial blood pressure >90 mmHg), and Troponin elevation.

High Risk PE will be defined by hemodynamic instability (normal systemic arterial blood pressure <90 mm Hg and/or use of vasopressors).[23]

Retrospective case data will consist of treatment and health outcomes of consecutive patients treated with APT between January 1, 2014 and one year prior to date of site activation.

Prospective subject data will consist of treatment and health outcomes of treated subjects since the site was activated to participate in the registry. For each treated subject enrolled, participation in the registry lasts approximately 12 months. Subjects should be followed per Investigator's SoC. Data will be collected for any echocardiograms and CTAs completed. At minimum, a health status check should be performed at 3 and 12 months. For patients with an abnormal echocardiogram post-APT treatment, an on-site visit with echocardiogram should be performed at 3 months to assess for chronic pulmonary hypertension. An echocardiogram at 12 months is also requested for all patients. Safety data should be reported through 12 months post-index procedure.

5.3 Outcome Measures

1. Change in the ratio of the measurement of the RV/LV diameters as measured by echocardiogram or CTA from baseline to between 24 – 48 hours after the start of the APT procedure (matched pairs as available).
2. Diagnosis of pulmonary hypertension defined as mean pulmonary artery pressure greater than 25 mm Hg by echocardiogram that persists at least 3 months after PE diagnosis
3. Frequency and safety outcomes of adjunctive therapies post APT procedure during hospitalization
4. Number of patients with non or partial response to other interventional procedures prior to APT procedure for index PE
5. Frequency and severity of SAEs related to EKOS and procedure, major bleeding, or VTE during index hospitalization and during first 12 months post-APT procedure
6. All-cause mortality during first 12 months post-APT procedure
7. Recurrent symptomatic PE, PE related death, hemodynamic collapse at 30 days (composite measure)
8. Healthcare utilization during hospitalization:
    a. Time from hospital admission to ICU discharge
    b. Time from hospital admission to discharge
9. Quality of life (QOL) as measured by the PEmb-QOL and EQ-5D-5L at baseline and 3 month and 12 month post-hospitalization subject follow-up visits
10. IVC filter placement (measured by number of occurrences)

6. SUBJECT SELECTION

6.1 Registry Population

This registry is designed to collect data related to APT treatment in patients experiencing symptoms of submassive or massive PE with a baseline RV/LV ≥ 1.0.Data will be collected for up to 1000 retrospective cases and 550 prospective subjects selected by their physician to receive APT treatment for PE. Enrollment will occur at up to 100 investigational sites globally.

6.2 Subject Selection

6.2.1 Inclusion Criteria

Retrospective cases must meet all of the following inclusion criteria:

1. Treated with APT procedure between January 1, 2014 and one year prior to date of site activation
2. RV/LV ≥ 1.0 from diagnostic CTA or echocardiogram
3. PE symptom duration ≤ 14 days
4. Troponin elevation

Prospective subjects must meet all of the following inclusion criteria:

5. Male or female > 18 years of age and ≤ 80 years of age
6. RV/LV ≥ 1.0 from diagnostic CTA or echocardiogram
7. PE symptom duration ≤ 14 days
8. Troponin elevation
9. Signed informed consent obtained from subject or legally authorized representative
10. Investigator has selected EKOS to treat patient with massive or submassive PE

6.2.2 Exclusion Criteria

Retrospective cases must not meet the following exclusion criteria:

11. Enrollment into the OPTALYSE PE study

Prospective subjects must not meet any of the following exclusion criteria:

12. Clinician deems the subject high-risk for catastrophic bleeding
13. Life expectancy < one year

6.3 Subject Completion

A subject will be considered to have successfully finished the registry upon completion of their 12 month follow-up.

6.4 Withdrawal

For cases in which the subject does not complete all assessments and follow-up visits, the subjects will be classified as follows:

- Investigator withdrawal – Investigator can withdraw a subject from the registry for a safety concern or non-compliance. Reason for Investigator withdrawal of a subject and last date of contact for the registry will be documented in the EDC system.

- Subject withdrawal – Subjects may withdraw from participation at any time during the registry. All data collected prior to withdrawal shall remain part of the registry data. Reasonable effort should be made to encourage the subject to remain in the registry. If the subject declines further participation, the reason for withdrawal will be documented in the EDC system.
- Lost to follow-up – The site should collect three methods to contact a subject. A subject will be considered lost to follow-up if there are at least three documented attempts to contact the subject for their last expected follow-up without success. Last date of contact will be documented in the EDC system.

7. CASE DATA COLLECTION – RETROSPECTIVE

7.1 Protected Health Information (PHI) Authorization Waiver

The sites participating in retrospective case data collection will apply for a PHI authorization waiver with the relevant IRB/EC to review, use, and submit specific case data to the Sponsor. The specific case data is outlined in the Measurements-Retrospective section of the Protocol and will be de-identified before being entered into the EDC system.

8. MEASUREMENTS – RETROSPECTIVE

8.1 Screening/Baseline

The following data will be collected for screening, as available. Record most recent assessments prior to beginning of APT procedure.

- Review and confirmation of eligibility to participate in the registry
- Demographic information, medical history, and clinical risk factors
- CTA to evaluate the anatomic location of PE and degree of RV enlargement (as part of the initial diagnosis of PE). The RV/LV ratio at end-diastole will be determined from this image.
- Echocardiogram to measure: RV/LV ratio, TAPSE, estimated RVSP, and the collapse of the IVC with respiration
- Laboratory tests
    - Hemoglobin (Hgb)
    - Hematocrit (Hct)
    - Platelet count
    - Bleeding Times: aPTT, PT, and INR
    - Biomarker measurements: Troponin (to confirm eligibility), BNP/NT-proBNP, lactate/lactic acid, and D-dimer
- Anticoagulation medications 72 hours leading up to the APT procedure

8.2 Procedure

The following data will be collected:

- Vital signs prior to initiation of procedure
- APT procedure treatment details

8.3 Post-Procedure

The following data will be collected as available:

- First set of vital signs after end of APT procedure
- Laboratory tests
    - Hemoglobin (Hgb)
    - Hematocrit (Hct)
    - Platelet count
    - Creatinine
    - Bleeding Times: aPTT, PT, and INR
    - Biomarker measurements: Troponin, BNP/NT-proBNP, lactate/lactic acid, and D-dimer
- Echocardiogram 24 – 48 hours after start of APT procedure: RV/LV ratio, TAPSE, estimated RVSP, and the collapse of the IVC with respiration
- CTA 24 – 48 hours after start of APT procedure: RV/LV ratio
- Vital signs once at same time each day of hospitalization through discharge
- Length of post-procedure hospitalization (date and time of hospital discharge)
- SAEs related to EKOS or procedure, bleeding events, or VTE events

8.4 Long Term Health Data

The following data will be collected as follow up data, up to 12 months post index APT procedure, as available:

- Occurrence of VTE or bleeding events,
- Changes in anticoagulation medications
- Echocardiograms: RV/LV ratio, TAPSE, estimated RVSP, and the collapse of the IVC with respiration
- Mortality, including cause

9. TREATMENT OF SUBJECTS - PROSPECTIVE

9.1 EkoSonic® Endovascular System (EKOS)

9.1.1 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. Proper placement of EKOS to treat PE will be performed using standard image guidance techniques associated with catheterization of the pulmonary artery. Choice of venous access is at the discretion of the treating physician and in alignment with the hospital standard of care[22].

Infusion of physician-specified fluids will be at the physician-prescribed dose. Infusion of fluid and saline coolant will be started. The MicroSonic Device will then be activated at start of infusion. If technical difficulties are encountered which interfere with proper operation of the system or infusion, 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 EKOS device. This exchange and serial numbers will be recorded in the EDC system. The affected device will be saved and returned to the Sponsor.

9.1.2 Post-treatment Management

Following treatment with EKOS, subjects should be treated with the Investigator's SoC. Anticoagulation medication should be prescribed according to physician's clinical judgement.

9.1.3 Duration of Treatment and Follow-up

Following the initial treatment with EKOS, each subject is followed per their Investigator's SoC follow up schedule. At minimum, a 3 and 12 month post-APT procedure phone call or visit should be made to record health status. During the follow-up period, subjects are followed for re-hospitalizations, recurrence of VTE, and other clinical outcomes. Any echocardiograms collected during follow-up should be recorded in the EDC system. The final health status of the subject will be reported in the EDC system. A final echocardiogram at 12 months is requested.

9.1.4 Adjunctive Interventions

Investigator may utilize any adjunctive interventions as deemed necessary according to their clinical judgement. Investigator will note any adjunctive interventions to the APT procedure for the treatment of PE including type, start date, and stop date in the EDC system.

10. MEASUREMENTS AND EVALUATIONS - PROSPECTIVE

10.1 Screening/Baseline (Day -1)

The screening phase begins when the ICF is fully signed and dated and ends at the initiation of the APT procedure.

The following should be completed prior to data being collected about the patient:

- Review and signing of the ICF
- Review and confirmation of eligibility to participate in the registry

The following evaluations should be recorded if performed as part of routine clinical care at Screening/Baseline (within 48 hours of the initiation of treatment):

- Physical examination and collection of demographic, medical history, and clinical risk factors information
- sPESI
- CTA to evaluate the anatomic location of PE and degree of RV enlargement (as part of the initial diagnosis of PE). The RV/LV ratio at end-diastole will be determined from this image.

- Echocardiogram to measure: RV/LV ratio, TAPSE, estimated RVSP, and the collapse of the IVC with respiration
- Laboratory tests
    - Hemoglobin (Hgb), Hematocrit (Hct)
    - Platelet count
    - Creatinine
    - Bleeding Times: aPTT, PT, and INR
    - Biomarker measurements: Troponin (required for inclusion), BNP/NT-proBNP, lactate/lactic acid, and D-dimer.
- Anticoagulation medications leading up to the APT procedure

10.2 Procedure Visit (Day 0)

The following data should be recorded from the procedure:

- Vital signs immediately prior to the procedure
- APT procedure details

Select sites may also perform an integrated bedside assessment as described in Section 11.1.8.

10.3 Post Procedure Assessments

The following should be recorded if performed after the APT procedure is completed:

- Vital signs immediately after the procedure
- Laboratory test results from clinical routine will be collected at 24 (± 3) hours post-start of APT procedure:
    - Hemoglobin (Hgb)
    - Hematocrit (Hct)
    - Platelet count
    - Creatinine
    - Bleeding Times: aPTT, PT, and INR
    - Biomarker measurements: Troponin, BNP/NT-proBNP, lactate/lactic acid, and D-dimer
- Echocardiogram 24 – 48 hours after the start of the APT procedure to measure: RV/LV ratio, TAPSE, estimated RVSP, and the collapse of the IVC with respiration
- CTA 24 – 48 hours after start of APT procedure: RV/LV ratio
- Vital signs once at the same time each day of hospitalization until discharge.
- Quality of Life surveys: PEmb-QOL and EQ-5D-5L
- Change in anticoagulation medications until discharge.

10.4 Follow-Up

Patients will be followed per Investigator's SoC for up to 12 months post-APT procedure. At 3 months and 12 months post-APT procedure, the following data should be recorded, as

available. For patients with an abnormal post-treatment echocardiogram, a 3-month follow-up echocardiogram is recommended to assess for chronic pulmonary hypertension. For other patients, 3-month data can be collected via phone or on-site visit.

- Echocardiogram: RV/LV ratio, TAPSE, estimated RVSP, and the collapse of the IVC with respiration
- Review any SAEs, hospitalizations. Record any SAEs related to occurrence of VTE or bleeding events
- Review any changes in anticoagulation medications
- Quality of Life surveys: PEmb-QOL and EQ-5D-5L
- In case of mortality, review cause and time of occurrence
- In case of withdrawal, review cause and time of occurrence

If additional echocardiogram(s) are collected outside of the 3 and 12 month follow-up, the results should be recorded in the EDC.

11. Evaluations

11.1 Informed Consent Process

Patients with the potential to meet eligibility criteria for the prospective arm will be offered the opportunity to be evaluated for participation in this registry. All such patients must sign an ICF approved by the relevant IRB/EC before any trial-related evaluations can be performed.

Investigator or qualified delegate will review the registry consent form with the patient and the patient must have an opportunity to ask questions about what data will be collected, the follow-up schedule, and what options the patient has if they do not participate in the registry prior to signature. The patient will receive a copy of the signed ICF to keep for their records.

Subjects will be informed of any revisions of the ICF and relevant revisions will be signed and kept in the subject's file.

The consenting process, acquisition of the ICF and any revisions should be documented in the subject's medical record and the ICF should be signed and dated by the individual who conducted the informed consent discussion.

11.2 Eligibility Review

A patient is to review and sign an ICF prior to any evaluations to assess eligibility in the registry. Subjects who are found to meet all inclusion criteria and no exclusion criteria will be entered into the EDC system.

11.3 Assignment of Subject Identification Number

All retrospective cases and prospective subjects who meet eligibility criteria for the registry are assigned a subject identification (ID) number by the EDC system. The subject ID number is used to de-identify subject data of protected health information in the EDC. Investigator will maintain a subject ID list of subjects' names and associated IDs which allows Investigator to determine identity of all subjects.

11.4 Demographics

For each subject, year of birth, and gender are collected. In some countries, race and ethnicity are collected.

11.5 Physical Examination

All prospective patients will undergo a physical examination at screening, in accordance with the Investigator's current practice, to include height and weight. Available data will be collected for retrospective cases.

11.6 Vital Signs

Vital signs including systolic/diastolic blood pressure, heart rate, respiratory rate, and SpO_2 will be collected. Vital signs will be collected at baseline, prior to and immediately after the APT procedure, and once per day of post-procedure hospitalization until discharge.

11.7 Anticoagulation and Concomitant Medications

History of anticoagulant medication up to three days prior to the start of the APT procedure will be obtained. Changes in anticoagulation medications after discharge will be recorded in the EDC system throughout the 12-month follow-up period.

Other concomitant (non-anticoagulation) medications will be recorded in the EDC system through 12 month follow-up only for medications prescribed to treat SAEs related to the procedure or device, bleeding events, or VTE events.

11.8 Quality of Life Assessments: PEmb-QoL and EQ-5D-5L

Two Quality of Life instruments, PEmb-QOL and EQ-5D-5L, will be used in this registry and are validated, widely used quality of life assessments.

The PEmb-QOL quantifies health-related quality of life after experiencing PE. This questionnaire consists of 10 questions for six health dimensions: frequency of complaints, activities of daily living limitation, work-related problems, social limitations, intensity of complaints, and emotional complaints.

The EQ-5D-5L is a patient reported outcome that provides a simple descriptive profile and single index value for health status. The questionnaire consists of 5 questions pertaining to specific health dimensions, including mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and overall health status rating scale.

Subjects' responses to the questionnaires are to be recorded and entered into the EDC system.

11.9 Integrated Bedside Assessment

At select participating sites: In addition to the vital signs specified in Section 10, bedside vital signs including systolic/diastolic blood pressure, heart rate, respiratory rate, capillary refill time and SpO_2 will be recorded at 30 minute intervals from the start of the APT procedure through four hours after the end of the APT procedure.

Along with the echocardiograms specified in Section 10, additional limited echocardiograms will be performed at the bedside for RV/LV ratio measurements hourly after the start of the APT procedure through four hours after the end of the APT procedure.

The purpose for the collection of vital signs every 30 minutes and focused echocardiography every hour is to correlate change in clinical parameters (vital signs) with change in markers of RV strain (RV/LV ratio) documented using echocardiography as a non-invasive imaging method. There is preliminary evidence from the first 100 patients in OPTALYSE PE that the right heart recovers within a couple hours of treatment. Confirmation for this finding will be important in identifying the best APT protocol. 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) does not increase the potential risk to the pts participating in the registry as they are non-invasive measurements that will be collected at the bedside from a limited number of sites during the conduct of the registry.

12. SAFETY REPORTING

12.1 Definitions

12.1.1 Adverse Event

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

12.1.2 Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence resulting in any of the following outcomes:

1. Death
2. Life-threatening (Note: The term “life-threatening” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
3. Inpatient hospitalization or prolongation of existing hospitalization
4. Persistent or significant disability/incapacity
5. Congenital abnormally or birth defect
6. Important medical event that may not result in death, be life-threatening, or require hospitalization but may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

12.1.3 Unexpected Adverse Event

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

12.1.4 Pre-Existing Medical Condition

Pre-existing medical conditions are those that are present at enrollment. If the frequency, severity, or character of the condition worsens significantly or unexpectedly during the registry, the condition will be an AE.

12.1.5 Device Failures and Malfunctions

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

12.1.6 Major Bleeding

The following definition[24] of major bleeding 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.

Note: For this protocol, a fall in Hgb of 20 gL^{-1} (1.24 mmol L^{-1}) or more with no objective evidence of bleeding or symptoms of bleeding will not be considered a major bleeding event.

12.2 Reporting Requirements

Investigators are not required to report all AEs that occur in the registry.

Investigators must report the following SAEs to Sponsor within one working day of becoming aware of the event for either retrospective or prospective patients. SAEs should be reported up to each subject's 12-month follow-up:

- those related to EKOS or APT procedure
- those related to a bleed
- VTE events

The type of event, severity, and relationship to EKOS, procedure, thrombolytic, and anticoagulation drug will be reported by the Investigator.

Device failures and malfunctions will be reported in the EDC system within one working day after Investigator or delegate learns of the event. For prospective patients, these will also be reported to the relevant IRB/EC as required per IRB/EC requirements.

Because EKOS is a commercially-available medical device, Investigators will comply with any hospital user reporting requirements.

If additional safety information becomes available during the course of the registry, Sponsor will amend the protocol and ICF as necessary.

13. STATISTICAL CONSIDERATIONS

13.1 Statistical Analysis

The statistical analysis plan (SAP) will be a separate document finalized prior to data analysis. The SAP will be updated as required, in association with any protocol amendments. The plan will include detailed descriptions of analysis methods, tables, listings and figures and will describe statistical programming considerations.

For descriptive statistics, continuous data (e.g., age) will be summarized with n, mean, median, standard deviation, minimum and maximum and categorical data (e.g., gender) will be summarized with observed counts and percentages for each category.

Patients will be analyzed according to the APT treatment protocol they received (i.e. duration of treatment and dose, type of fluid received). Frequency of use of each of the APT treatment protocols before and after OPTALYSE PE results were made public will be summarized and compared using fisher's exact test.

Each outcome measure will be summarized for the full registry population as well as separately by the different APT treatment protocols, including 95% confidence intervals. Additionally, outcome measures will be summarized by the following subgroups: submassive and massive PE, each region, and by the retrospective and prospective portions of the registry.

13.2 Determination of Sample Size

For retrospective cases, up to 1000 cases will be collected to capture details of PE treatment with EKOS from the time it became commercially available to the time the site was activated. For prospective, up to 500 patients will be treated to collect data on current EKOS use at up to 100 sites.

13.3 Analysis Populations

The SP will be defined as all patients who receive the APT procedure. Safety and effectiveness summaries will be reported for the SP.

The EP will be defined as all patients who meet eligibility criteria. An additional effectiveness summary will be reported for the EP.

13.4 Patient Disposition

The number of patients with the study completion status and the reasons for discontinuation will be summarized.

13.5 Baseline and Demographics Characteristics

Descriptive statistics will be used to summarize demographics and baseline characteristics including pertinent PE history.

13.6 Measurement of APT treatment

APT treatment and procedure details will be summarized. Patients will be analyzed according to the APT treatment protocol they received (e.g., >6h/>24mg; 6h/12-24mg; 6h/6-12mg; 4h/4-8mg; 2h/4-8mg, other). Frequency of use of each of the APT treatment protocols before and after OPTALYSE PE results were made public will be summarized and compared using fisher's exact test.

13.7 Efficacy Outcome Measures Analyses

Descriptive statistics will be used to summarize efficacy outcome measures RV/LV, TAPSE, IVC Collapse, estimated RVSP and pulmonary arterial pressure by time point and/or study visit including change from baseline for continuous endpoints.

Each efficacy outcome measure will be summarized for the full registry population as well as separately by the different APT treatment protocols, including 95% confidence intervals. Additionally, efficacy outcome measures will be summarized by the following subgroups: submassive and massive PE, each region, and by the retrospective and prospective portions of the registry.

13.8 Additional Outcome Analyses

Descriptive statistics will be used to summarize additional outcome assessments including:

- Healthcare utilization during hospitalization will be summarized for time from hospital admission to ICU and time from hospital admission to discharge.
- Quality of life (QOL) measures PEmb-QOL and EQ-5D-5L will be summarized by time point and /or study visit including change from baseline for continuous endpoints and shift tables for categorical endpoints.
- Frequency and outcomes of adjunctive therapies post APT procedure during hospitalization
- Number of patients with non or partial response to other interventional procedures prior to APT procedure for index PE
- IVC filter placement (measured by number of occurrences)

13.9 Safety Analyses

Safety analyses will be conducted on the SP during hospitalization and through the 12-month follow-up period. AEs and SAEs will be summarized by MedDRA System Organ Class and Preferred Term.

In addition, occurrence of safety outcomes will be summarized, including diagnosis of pulmonary hypertension, all-cause mortality during first 12 months, composite measure of recurrent symptomatic PE, PE related death or hemodynamic collapse at 30 days.

13.10 Interim Analysis

Periodic statistical summaries will be prepared annually.

13.11 Handling of Missing Data

All observed data will be summarized without imputation for missing values.

14. DATA MANAGEMENT

All data management (DM) processes up to and including post database lock will be detailed in the Data Management Plan (DMP), including the processes for import of external data (e.g. Laboratory Data), coding and SAE reconciliation..

Data from the study will be collected via EDC. Clinical data will be extracted in the required format by BTG DM from the Datatrak EDC database on an ongoing basis.

Data must be accurately transcribed into the eCRF (ideally within 48 hours after the visit has occurred for the patient) by the study site and must be verifiable from source data. Examples of source documents are hospital records which include the patient's medical notes, laboratory and other clinical reports etc.

Where copies supporting source documentation (e.g. CT scan images etc.) are being submitted for the study, the patients' study number must be clearly indicated on all material and any patient identifiers removed/redacted prior to sending to maintain confidentiality.

Training will be provided in the form of eTrain to all users accessing the EDC system from Datatrak. Details of the requirement will be outlined in the DMP.

15. LEGAL/ETHICS AND ADMINISTRATIVE PROCEDURES

15.1 Good Clinical Practice/Regulatory Compliance

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this registry, are designed to ensure that Sponsor and Investigators abide by the Declaration of Helsinki, International Conference on Harmonisation Guideline E6 (R2): Good Clinical Practice (GCP).

It is Investigator's responsibility to ensure that adequate time and appropriate resources are available at the investigational site prior to commitment to participate in this registry. Investigator should also be able to estimate or demonstrate the potential for recruiting the required number of suitable subjects within the agreed recruitment period. Investigator maintains a list of appropriately qualified persons to whom Investigator has delegated significant registry-related tasks.

15.2 Site and Investigator Qualification

All participating investigational sites are assessed by Sponsor to verify that they are able to conduct the registry. Each participating institution must have an established IRB/EC and clinical protocol review process that is compliant with the relevant government regulation, ensuring the clinical protocol can be adequately evaluated and approved at the institutional level.

The Institution must have appropriately qualified investigators and clinical and administrative support staff in place to adequately conduct the registry according to the principles of International Conference on Harmonisation GCP in general and must have the adequate expertise and staff to conduct this registry in compliance with the relevant guidelines and regulations and to treat PE with EKOS.

This registry is scheduled to be performed by qualified, experienced investigators at up to 100 research facilities in the United States, Europe, and Asia. Given that the registry is intended to collect data related to SoC treatment with EKOS, special care will be taken to select investigators with experience in the treatment of PE with EKOS.

Site and Investigator qualification is primarily accomplished through a Site Qualification Form and a qualification phone interview. In some cases, a remote or on-site qualification visit may be performed.

15.2.1 Investigator Curriculum Vitae (CV)

Investigator and all investigational site staff will provide Sponsor with his/her current (signed and dated within 2 years upon site activation) CV and any revisions/updates.

15.2.2 Statement of Investigator

Investigator must sign and date the Statement of Investigator/Protocol Signature Page of this protocol for the original and each subsequent amendment of the protocol and return a signed copy to Sponsor.

15.3 IRB/EC Protocol Approval

It is the responsibility of Investigator or delegate to submit this protocol, the ICF (approved by Sponsor), relevant supporting information and all types of subject recruitment information to the IRB/EC for review and approval prior to investigational site initiation. A copy of the written approval of the protocol and ICF and/or protected health information authorization waiver must be received by Sponsor prior to the collection of patient case data or recruitment of subjects.

Investigator or delegate is responsible for keeping the IRB/EC apprised of the progress of the registry, any changes to the protocol, deviations from the protocol and reportable adverse events.

15.4 Informed Consent – Ethical Compliance

For participation in the prospective portion of the protocol, Investigator or delegate provides Sponsor with a copy of the IRB/EC-approved consent form and a copy of the IRB/EC written

approval, prior to investigational site initiation. Additionally, if the IRB/EC requires modifications to the ICF, the documentation supporting this requirement must be provided to Sponsor.

It is the responsibility of Investigator or delegate to obtain written informed consent from subjects prior to enrolling them into the prospective part of the study. All consent documentation must be in accordance with applicable regulations and the principles of International Conference on Harmonisation GCP Guidelines. Each subject or the subject's legally authorized representative (where applicable) is requested to sign the ICF after the subject has received and read written information and received an explanation of the registry, including but not limited to: the objectives, treatment plan, potential benefits and risk, inconveniences, alternative treatment options and the subject's rights and responsibilities. A copy of the ICF must be given to the subject or the subject's legally authorized representative (where applicable). If applicable, it is provided in a certified translation of the subject's local language.

Acquisition of the informed consent should be documented in the subject medical record and the ICF should be signed and dated by the subject and the individual who conducted the informed consent discussion. Signed consent forms must remain in each subject's registry file and must be available for review by the clinical research associate (CRA) or auditor at any time.

15.5 Subject Privacy and Confidentiality

Sponsor and Investigator affirm and uphold the principle for the subject's right to protection against invasion of privacy. Throughout this registry, all data collected and analyzed by Sponsor is treated confidentially and identified by a subject ID number.

To verify compliance, Sponsor may require access to the subject's primary medical record to review those portions that directly concern this registry (including but not limited to radiology images and hospital and outpatient records).

As part of required content of the ICF, the patient must be informed that his/her records may be reviewed by Sponsor, Sponsor representative and/or a representative of the appropriate regulatory agency. The ICF or related document must also state that patient privacy will be maintained pursuant to local regulations. Should access to such medical records require a waiver or authorization separate from the statement of informed consent, Investigator obtains such permission in writing from the subject before the subject is entered in the registry.

Data collected during this registry may be used to support the development or marketing of EKOS. Collected data may be reviewed by Sponsor and/or its representatives, independent auditors who validate the data on behalf of Sponsor, national or local regulatory authorities and the IRB/EC which granted approval for this registry to proceed.

15.6 Monitoring

Monitoring the subject data is performed using three methods: centralized, remote and on-site. All monitoring activities are performed by qualified personnel from Sponsor. Investigator and his/her staff are expected to cooperate with the Sponsor and be available during the visit to answer questions and resolve action items.

Monitoring activities are documented through various means, which include monitoring visit reports and documentation of centralized monitoring activities. For on-site visits, the CRA records the date, a summary of the status and progress of the registry, and proposed actions.

15.7 Modification of the Protocol

All amendments to this protocol must be documented in writing, reviewed and approved by Investigator, Sponsor, and IRB/EC prior to implementation. If the protocol amendment substantially alters the design or potential risk to the subject, new written informed consent must be obtained from each subject for continued participation in the registry.

15.8 Suspension or Termination of Registry

If conditions arise requiring further clarification before the decision can be reached to proceed with or terminate the registry, the registry will be suspended until the situation has been resolved.

Sponsor has the right to terminate this registry at any time. Examples of situations where this might occur include:

- It becomes apparent that enrollment is unsatisfactory with respect to quality and/or quantity or data recording is chronically inaccurate and/or incomplete.
- The incidence and/or severity of adverse events in the registry indicate a potential health hazard caused by the treatment.

15.9 Protocol Deviations/Violations

Protocol deviations/violations not related to the informed consent process or eligibility are not required to be reported to Sponsor for this registry. Every attempt should be made to perform procedures and collect data according to this protocol. Protocol deviations/violations related to informed consent or eligibility should be reported to the IRB/EC, per IRB/EC reporting requirements. Copies of these reports and IRB/EC notification of receipt of these reports shall be submitted to Sponsor.

15.10 Recording, Access to and Retention of Source Data

Investigators are required to prepare and maintain adequate source documentation which includes:

- Documents that verify eligibility criteria
- Records covering subject participation in the registry including basic identification information, results of physical examinations and diagnostic tests, treatment administration, and visit/consult notes

All key data must be recorded in the subject's source documents including the informed consent acquisition.

The CRA, auditors, IRB/EC, or regulatory inspectors may check data entered against the source documents. The consent form must include a statement by which the subjects allow the above-named access to source data that substantiate data entered in the EDC system. These

personnel, bound by privacy laws and professional secrecy, will not disclose any personal information or personal medical information.

As described in the International Conference on Harmonisation GCP Guidelines, 'essential documents', including final data set, source documents, IRB/EC approvals, and consent forms should be retained by Investigator until at least two years have elapsed since the formal discontinuation of the registry. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with Sponsor. Investigator must obtain written permission from Sponsor prior to destruction of any registry document.

15.11 Final Data

Investigator is responsible for maintaining adequate and accurate source documents from which accurate information is transcribed into the EDC system, which is designed to capture all pertinent data for the registry. Data entry should be completed by Investigator or delegate, as delegated on the Delegation of Authority Log.

Once the data have been reviewed by the CRA, queries may be raised in the EDC system if the data are missing, unclear or contradictory. Once all data is entered and all queries resolved, Investigator will sign the completed data electronically via the Investigator Signature section of the EDC system and the database will be locked. The final data set will be provided to the site by Sponsor for archiving.

15.12 Publications

No individual Investigator may publish results from his/her investigational site until after publication of the primary manuscript describing the full population.

The detailed obligations regarding the publication of any data, material results or other information that is generated or created in relation to the registry is set out in the Clinical Trial Agreement between Investigator and Sponsor.

15.13 Audit/Inspections

To ensure compliance with relevant regulations, data generated by this registry must be available for inspection upon request by representatives of Sponsor and the IRB/EC for each investigational site.

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