ACCESS PTS

ACCelerated ThrombolySiS for Post-Thrombotic Syndrome Using the EKOS System

Protocol Number: EKOS – 11

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Investigator Confidentiality Statement

Receipt of Protocol

ACCESS PTS: ACCelerated ThrombolySiS for Post-Thrombotic Syndrome Using the EkoSonic® Endovascular System

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I acknowledge that the information contained in the Protocol is considered proprietary and confidential, and should not be distributed to anyone without the advance permission of EKOS Corporation (EKOS). Exceptions: Co- Investigators, Investigational Review Boards (IRBs), and Study Coordinator. These personnel will understand the confidential nature of the materials being given to them.

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

Principal Investigator Signature

PRINT NAME	TITLE
SIGNATURE	DATE

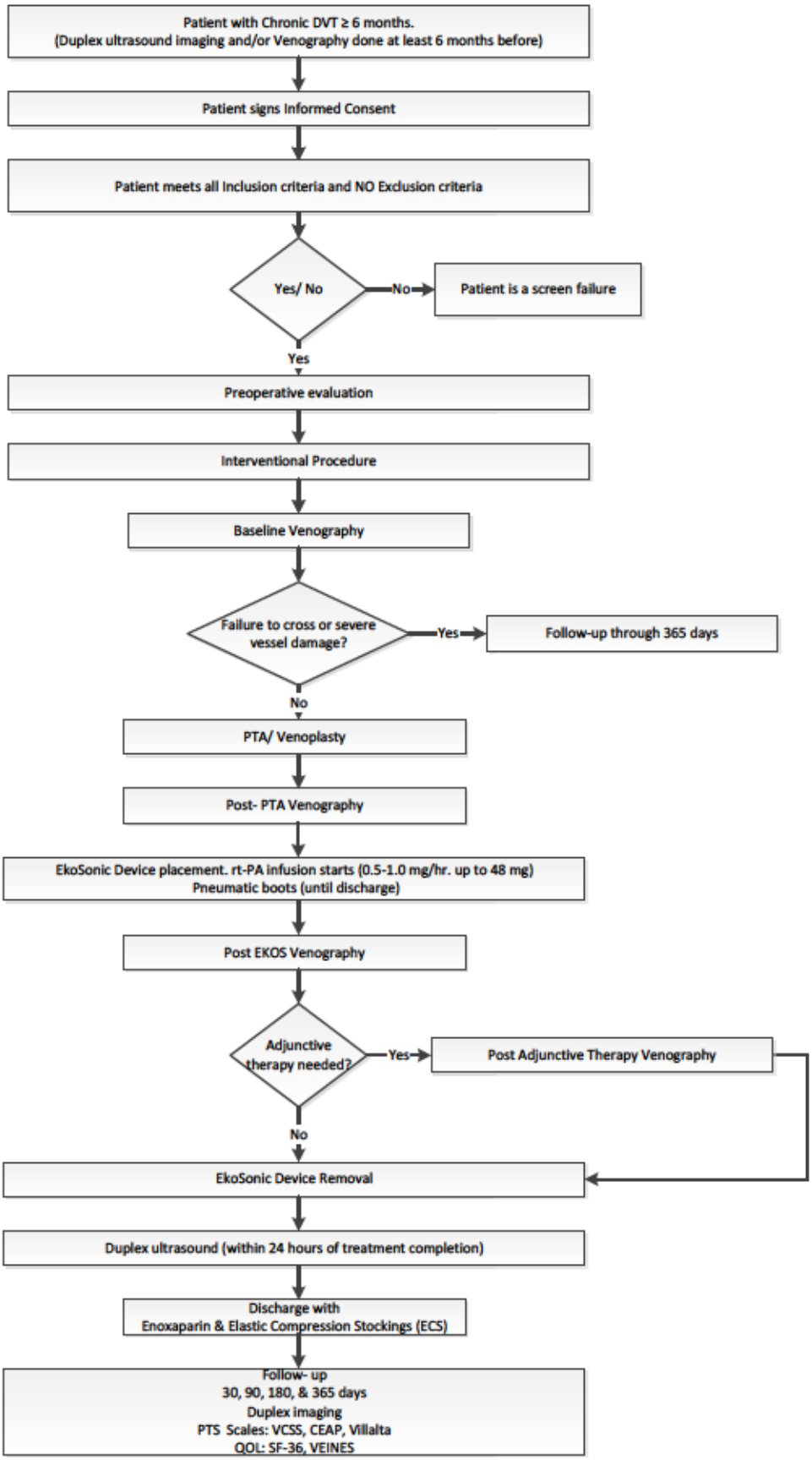
TABLE OF CONTENTS

APPENDICES

A. PROTOCOL SYNOPSIS

Title:	**ACCelerated ThrombolySiS for Post-Thrombotic Syndrome Using the EKOS System (ACCESS PTS)**
Design:	A prospective, single arm, multi-center study
Brief Device Description:	The EkoSonic® Endovascular System employs high frequency (2-3MHz), low power ultrasound to facilitate the delivery of therapeutic agents to the intravascular treatment site in the peripheral vasculature.
Purpose:	To evaluate the efficacy of ultrasound accelerated thrombolysis using the EkoSonic® Endovascular System with standard infusion of thrombolytic drug for post-thrombotic syndrome and chronic venous occlusion.
Primary Endpoint:	Clinical effectiveness will be evaluated using the Villalta score at Baseline compared to 30 days Post-EkoSonic® Study Treatment Procedure (EkoSonic® Treatment). Success will be defined by 50% of the subjects achieving at least a 4 point reduction in the Villalta score.
Population:	Subjects with lower extremity deep vein thrombosis (who have failed conservative treatment) objectively diagnosed with imaging ≥ 6 months; prior persistent DVT at enrollment evaluation; Villalta score ≥ 8. Subjects must be ≥ 18 years of age and ≤ 75 years of age.
Enrollment:	Up to 200 efficacy evaluable subjects, some with bilateral DVTs. Efficacy evaluable DVT limbs are those (1) with Villalta scores available at both Baseline and 30 days Post-EkoSonic® Treatment and (2) the clot in the affected segment was successfully crossed and received EkoSonic® Treatment.
Clinical Site Locations:	Up to 30 centers within the United States.
Time Course:	Enrollment period of up to 12 months with 365 day follow-up. Subject participation is approximately 12 months.

B. STUDY FLOWCHART and SCHEDULE OF EVENTS



ACCESS PTS Schedule of Assessments	Visit 1 (Within 30 days of treatment) Screening/Baseline	Visit 2 Day 0 Pre-EkoSonic® Treatment	Visit 2 Day 0 Post-EkoSonic® Treatment	Discharge	Visit 3 Day 30 ± 7 days	Visit 4 Day 90 ± 10 days	Visit 5 Day 180 ± 14 days	Visit 6 Day 365 ± 14 days	Early Termination
ACTION									
Informed Consent	X								
Demographics	X								
Medical History & Risk Factors	X								
Inclusions/Exclusion Criteria	X								
Pregnancy test	X								
Physical Exam	X								
Duplex Ultrasound	X[1]		X[2]		X	X	X	X	X
Adherence to Conservative Therapy Form	X								
Laboratory Tests	X[3]	X[4]	X[2]						
Villalta Scale	X				X	X	X	X	X
CEAP Classification	X				X	X	X	X	X
VCSS	X				X	X	X	X	X
SF-36	X				X	X	X	X	X
VEINES-QOL	X				X	X	X	X	X
Venography		X[5]	X[6]						
Leg Circumference	X				X	X	X	X	X
Review of Treatment Compliance & Exercise					X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X
Concomitant medications	X				X	X	X	X	X

[1] Duplex ultrasound within 60 days prior to treatment or venography (Pre- EkoSonic® Treatment) will be performed to confirm persistent chronic DVT causing restrictive flow

[2] To be performed within 24 hours of the completion of treatment

[3] Test results may be obtained within 30 days prior to study treatment, unless otherwise specified in the exclusion criteria

[4] To be performed within 24 hours prior to the start of treatment

[5] To be performed pre- and post-venoplasty

[6] To also be performed post- adjunctive treatment

C. ACRONYMS AND ABBREVIATIONS

AE	Adverse event
aPTT	Activated partial thromboplastin time
CBC	Complete blood count
CEAP	Clinical, Etiologic, Anatomic, Pathophysiological
CFR	Code of Federal Regulations
CFV	Common femoral vein
CPK-MB	Creatine Phosphokinase-MB
CPR	Cardiopulmonary resuscitation
CT	Computed tomography
CTPA	Computed tomography pulmonary angiogram
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
eCRF	Electronic Case Report Form
ECS	Elastic compression stockings
FTC	Failure-to-Cross
FDA	Food and Drug Administration
GI	Gastrointestinal
ID	Identification
IDDC	Intelligent Drug Delivery Catheter
INR	International normalized ratio
ITT	Intention-to-treat
IVC	Inferior vena cava
MDR	Medical Device Reporting
MRI	Magnetic Resonance Imaging
MRV	Magnetic resonance venography
MSD	MicroSonic Device
PCB	Pneumatic compression boots
PCS	Physical component summary
PE	Pulmonary Embolism
PP	Per protocol
PTS	Post-thrombotic syndrome
PTT	Partial thromboplastin time
QoL	Quality of Life
rt-PA	Recombinant tissue plasminogen activator
SAR	Serious adverse reaction
SAE	Serious adverse event
SF-36	Short Form 36
SPECT	Single positron emission computed tomography
VEINES-QOL	Venous Insufficiency Epidemiological and Economic Study- Qualify of Life
VCSS	Venous Clinical Severity Score
VVI	Venous Volumetric Index
VQ	Ventilation-perfusion

1.0 INTRODUCTION

The purpose of this prospective study is to evaluate the efficacy of ultrasound accelerated thrombolysis using the EkoSonic® Endovascular System with standard infusion of thrombolytic drug in subjects who suffer from Post-Thrombotic Syndrome (PTS) as a result of chronic venous occlusion. This study will assess thrombus clearance and vein patency at the conclusion of the EKOS intervention, and will document subject symptoms before and after the EKOS intervention and at 30, 90, 180, and 365 days follow-up. The resulting data will support a journal publication.

Deep vein thrombosis (DVT) is a common problem affecting between 250,000 and 2 million people annually in the US.[1] The most common complication of DVT is PTS, which can affect from 25% to 60% of DVT subjects.[2] Despite therapeutic anticoagulation and elastic compression stocking (ECS) therapy, a significant proportion of DVT subjects progress to develop post-thrombotic sequelae which lead to significant limitations in their quality of life.[3,4]

Venous hypertension resulting from chronic obstruction of the vein lumen after DVT is considered to be a key pathophysiological feature of PTS. The goal in treating chronic obstruction is to restore flow in the occluded venous segment, thereby decreasing venous pressures and subsequently, the severity of PTS. Although as yet there are no Level 1 data, it has been shown in a single-center retrospective registry study that recanalization of chronically occlusive DVT can be safely and successfully performed to provide significant improvement in venous flow, and relief of symptoms.[5]

Combined ultrasound/lytic 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 and confirmed by other investigators.[6,7,8,9] 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.[10] Ultrasound energy also provides an acoustic pressure gradient to enable transportation 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 is an FDA cleared 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, the EkoSonic® Endovascular System has the potential to reduce time to lysis, effect more complete lysis, reduce drug dose and thereby reduce the risk of bleeding complications. In the case of chronic obstruction, it is hypothesized that the effects of ultrasound allow the infused thrombolytic agent to act on any fibrin remaining in retracted, chronic thrombus.

2.0 DEVICE

2.1 Intended use

The EkoSonic® Endovascular System employs ultrasound energy intended to facilitate the controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature.

2.2 Description

The following is a summary of the EkoSonic® Endovascular System. The Instructions for Use (IFU) is included in 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 EkoSonic® Endovascular System consists of two main components:

- EkoSonic® Device
  - Single-use sterile device, consisting of an
    - Intelligent Drug Delivery Catheter (IDDC)
    - MicroSonic Device (MSD)
- 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.

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 EkoSonic® Device and monitors operating parameters during operation. The Control System also provides the user interface through the front panel display and keypad.

2.3 Regulatory Status

The EkoSonic® Endovascular System has been cleared by the United States Food and Drug Administration (FDA) for the controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature and is marketed throughout the United States. In this study, the EkoSonic® Endovascular System is being used in accordance with its cleared indications for use.

The EkoSonic® Endovascular Devices used for this study will be "off the shelf". Therefore, no special labeling or tracking is required for study devices.

3.0 STUDY OBJECTIVES AND STUDY ENDPOINTS

3.1 Primary Objective

Evaluate the safety and efficacy of the EkoSonic® Endovascular System for the treatment of lower extremity DVT in subjects with PTS who have failed conservative treatment.

3.1.1 Primary Clinical Efficacy Endpoint

Clinical efficacy will be evaluated using the Villalta score at Baseline compared to 30 days Post-EkoSonic® Study Treatment Procedure. Study success will be defined by ≥50% of the efficacy evaluable limbs achieving at least a 4 point reduction.

3.1.2 Primary Technical Efficacy Endpoint

Increase in blood flow calculated by time to washout in the affected segments, measured at Baseline and Post-EkoSonic® Study Treatment Procedure. A statistically significant improvement in flow rate will be considered success.

3.2 Secondary Objectives

To further evaluate clinical efficacy, device and procedural safety, and potential quality-of-life improvement.

3.2.1 Secondary Clinical Efficacy Endpoints

1. Occlusive material burden using the Venous Volumetric Index (VVI) Score[11], measured at Baseline and Post-EkoSonic® Study Treatment Procedure, both as a continuous measure and as a binary variable for achievement of a ≥ 5 point reduction from Baseline to Post-Procedure.
2. Change in Villalta score from Baseline to 90 days, 180 days, and 365 days Post-EkoSonic® Study Treatment Procedure, both as a continuous measure and as a binary variable for having achieved a ≥4 point reduction from Baseline.
3. Absence of re-occlusion at 365 days of the treated segment, as documented by duplex imaging.
4. Change in SF-36 Quality of Life (QoL) and Physical Component Summary (PCS), CEAP classification, VEINES-QOL, and VCSS from Baseline to 30, 90, 180 and 365 days Post-EkoSonic® Study Treatment Procedure.
5. Symptomatic PTS-induced admission to emergency room or unplanned visit to physician office or hospitalization from Post-EkoSonic® Study Treatment Procedure up to 365 days thereafter
6. Time from starting initial thrombolytic infusion to discharge from hospital

3.3 Safety Endpoints

1. Frequency of major bleeding[12,13] within 72 hours of initiating treatment with the EkoSonic® Endovascular System, as defined by:
    a. Fatal bleeding, and/or
    b. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
    c. 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.
2. Rate of symptomatic pulmonary embolism (PE; diagnosed using computed tomography pulmonary angiogram (CTPA), single positron emission computed tomography (SPECT), ventilation-perfusion (VQ), etc.) during hospitalization for study procedure.

4.0 CLINICAL PLAN

Up to 200 efficacy evaluable subjects (see 6.1 for definition), some with bilateral DVT, will be enrolled in the study at up to 30 clinical sites, with a maximum of 30 subjects enrolled at any given site.

This is a prospective, single-arm, multi-center study intended to assess the clinical and imaging outcomes of subjects with chronic lower extremity venous obstruction after DVT and PTS who are treated with thrombolytic infusion using the EkoSonic® Endovascular System. Administration of the Villalta scale must be performed by a trained clinician at each visit. It is preferable that the same clinician performs the scale on an individual subject throughout the study.

Subjects that are diagnosed with a lower extremity DVT by duplex imaging and/or venography at least 6 months previously will be evaluated for inclusion in the study. Eligible subjects will provide written informed consent. Following baseline evaluation, venous access shall be obtained. For the purpose of this study, venous access is considered initiation of EkoSonic® Treatment. If the occlusion cannot be completely traversed by a guide wire or EkoSonic® Device or severe vessel damage has occurred, the subject will be considered as a "failure-to-cross" (FTC). FTC subjects will complete follow-up visits throughout the 12 month endpoint period and undergo the follow-up assessments.

After successful passage of the guide wire, an angioplasty balloon shall be placed and then dilated across the entire occlusive segment to promote enlargement of the channel to allow passage of the EkoSonic® IDDC.

Following successful placement of the IDDC, the MSD will be placed. Ultrasound accelerated EkoSonic® thrombolysis will be initiated with the use of alteplase. Follow-up venographic evaluation shall be performed of the entire affected limb once the EkoSonic® thrombolysis procedure is completed. At the discretion of the Investigator, adjunctive treatments such as angioplasty or stenting can be performed as necessary to enhance venous flow after treatment with the EkoSonic® Endovascular System. Additional venography shall be performed after all adjunctive treatment is completed.

Post-Procedure duplex imaging of the treated venous segments shall be performed within 24 hours of completing the interventional procedure (thrombolysis and any adjunctive therapy). Follow-up evaluation shall occur at 30, 90, 180, and 365 days.

It is anticipated that the clinical study duration will be 24 months including first subject enrollment through to last subject completed or until the study is formally terminated. An individual subject's participation will be approximately 12 months.

4.1 Study Population

4.1.1 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. Proximal DVT (iliac vein, common femoral vein, deep femoral vein, femoral vein) that was objectively diagnosed with duplex imaging and/or venography ≥ 6 months prior to study screening.
3. Persistent chronic DVT causing restrictive flow, as confirmed by imaging, within 60 days prior to the study procedure.
4. Villalta score ≥8 for the affected limb within 30 days prior to the study procedure.
5. Medically eligible for treatment with thrombolytic drugs (see alteplase package insert in Appendix B).
6. Informed of the nature of the trial, is willing and has provided written, informed consent as approved by the Institutional Review Board/Ethics Committee (IRB/EC) of the respective investigational site.

7. Failed a minimum of 3 consecutive months of conservative treatment (therapeutic anticoagulation and compression stockings) according to the completed Adherence to Conservative Treatment Form.
8. Agrees to comply with specified follow-up evaluations and to return to the same investigational site where the procedure was performed.

4.1.2 Exclusion Criteria

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

1. Treated with mechanical thrombectomy within 2 weeks of the study thrombolysis procedure.
2. Treated with thrombolysis drugs within 48 hours of the study thrombolytic procedure.
3. Life expectancy less than 1 year.
4. Body Mass Index (BMI) >40 kg/m^2 or per Investigator's discretion subject is able tolerate the procedure and be compliant with post-procedure increased physical activity.
5. No flow in popliteal vein on duplex imaging
6. Isolated iliac vein only thrombus.
7. Thrombus extending ≥ 3 cm into the inferior vena cava (IVC). If central venous occlusion, consider computed tomography (CT) or magnetic resonance venography (MRV). For subjects with bilateral DVT, it is recommended that central imaging be performed prior to treatment to evaluate the status of the IVC.
8. Active bleeding, recent (< 3 mo) gastrointestinal (GI) bleeding, active peptic ulcer, severe liver dysfunction, bleeding diathesis.
9. Recent (< 3 mo) internal eye surgery or hemorrhagic retinopathy; recent (< 10 days) major surgery, cataract surgery, trauma, cardiopulmonary resuscitation (CPR), obstetrical delivery, or other invasive procedure.
10. History of stroke or intracranial/intraspinal bleed, tumor, vascular malformation, aneurysm.
11. 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.
12. Hemoglobin < 9.0 mg/dl within 24 hours prior to the procedure
13. International normalized ratio (INR) ≥ 1.5 ng/dl within 24 hours prior to the procedure
14. Platelet count < 100,000 cells/mm^3 or >700,000 cells/mm^3 within 24 hours prior to the procedure.
15. Creatinine outside the normal range for the treating institution and considered clinically significant by the Investigator.
16. Uncontrolled hypertension, defined as systolic ≥ 175 mmHg and a diastolic ≥ 110 mmHg.
17. Use of clopidogrel, ticlopidine, or other thienopyridine antiplatelet drug within 7 days of the study procedurei.
18. In the judgment of the clinician, the subject is at high risk for catastrophic bleeding.
19. Known allergy, hypersensitivity, or thrombocytopenia from heparin, alteplase (rt-PA), or iodinated contrast except for mild-moderate contrast allergies for which steroid pre-medication can be used.

20. Inability to tolerate the procedure due to acute systemic illness or other comorbidities that in the opinion of the Investigator place the subject at high risk for complications.
21. Subject is pregnant (positive pregnancy test; women of childbearing age must be tested), breast feeding, or planning to become pregnant during the study.
22. Inability to provide informed consent or to comply with study assessments (e.g. due to cognitive impairment or geographic distance).

    NOTE: Subjects excluded because of time-related exclusion criteria may be re-evaluated for inclusion in the study when the proper time interval has passed, i.e., >10 days after surgery, >3 months after GI bleed.

4.2 Procedures

4.2.1 Screening/Baseline Evaluation

All subjects presenting for evaluation and treatment of chronic lower extremity venous obstruction after DVT will be considered for the study. The date of evaluation will be captured along with whether the subject was included in the study or the reason for exclusion.

All subjects that meet the study's inclusion criteria and do not meet any exclusion criteria are eligible for this study. Subject Informed Consent shall be obtained prior to performing study related procedures. No subject will be enrolled without signing the Subject Informed Consent. A subject who was screened but was not eligible for the trial will be considered a screen failure. The site will maintain a log that includes each screen failure subject along with the reason for study exclusion.

EKOS will ensure that the confidentiality of subjects' identification is maintained and medical records are protected. A unique subject identification (ID) will be assigned by the data collection system for each subject enrolled in the clinical study. Subject records may be reviewed by EKOS representatives to verify the quality of the reported data; however, confidentiality will be maintained.

The following assessments shall be performed within 60 days prior to the study procedure:

- Imaging (duplex ultrasound or venography) to confirm presence of chronic DVT causing restrictive flow as well as some degree of flow in the popliteal vein. A subject who does not meet the imaging criteria will be considered a screen failure.

The following assessments shall be performed within 30 days prior to the study procedure:

- Demographics
- Pregnancy test for women of child bearing potential
- Medical history and risk factors, including any coagulopathies
- Physical exam with documentation of PTS signs and symptoms
- Villalta scale (both legs)
- CEAP classification (both legs)
- VCSS (both legs)
- SF-36
- VEINES-QOL
- Laboratory tests: hemoglobin, INR, and platelet count must be obtained within 24 hours prior to the EkoSonic® Treatment procedure in order to confirm eligibility.
- Leg circumference (both legs)

Subjects with bilateral DVT may be enrolled, so long as the study limb(s) meet inclusion/exclusion criteria, including IVC patency. If one limb meets enrollment criteria and the other does not, the limb which does not meet enrollment criteria cannot be treated until the subject is off-study. It is recommended that in a subject with bilateral DVT, central imaging be performed prior to treatment to evaluate the status of the IVC. Only one limb may be treated at a time, separated by a minimum of 30 days. Each limb will be evaluated separately and appropriately through 90 days, in accordance to the Schedule of Assessments. Subjects may have both limbs evaluated at the same visit at 180 days, and 365 days Post- EkoSonic® Study Treatment Procedure rather than separate visits for each limb.

4.2.2 Pre-EkoSonic® Study Treatment Procedure

Anticoagulation therapy with enoxaparin sodium (1 mg/kg twice a day) shall be initiated at least 48 hours prior to initiation of study treatment. See Appendix D and Section 4.3 Concomitant Medications for specific guidance on anticoagulation management. Hemoglobin, INR, and platelet count must be obtained within 24 hours prior to the EkoSonic® Treatment procedure in order to confirm eligibility.

4.2.3 EkoSonic® Study Treatment Procedure

The access site is determined by the extent of occlusive disease. When treating a single limb at a time, access via the popliteal vein is reasonable.

Once venous access has been achieved, baseline venography shall be obtained following the guidelines provided in the Venographic Imaging Manual of Operations and Procedures. Confirm presence of chronic DVT causing restrictive flow as well as some degree of flow in the popliteal vein.

Standard catheter and wire techniques are to be utilized to cross the chronic, occlusive clot. Techniques used to cross the occluded segments may include the use of a stiff Glidewire (Terumo Interventional Systems, Somerset, NJ), sharp recanalization, and chronic total occlusion catheters and wires. If a wire can be passed but not the diagnostic catheter, then serial dilatation may be used to create some "working space." Support for better pushability can be obtained by using a graduated system, such as a 4F tibial sheath coaxially through a 6F standard sheath placed through an 8F sheath.

If the occlusion cannot be crossed by the guidewire or EkoSonic® Device or there is severe vessel damage that could be further complicated by thrombolysis, such as perforation, the procedure shall be abandoned and considered a technical failure. The FTC subject shall be followed through 365 days.

Once the occlusion has been successfully crossed, balloon dilatation of the chronic clot shall be performed to create working space and to macerate/crack the hard thrombus. Vessels to be dilated should be sized for appropriate balloon sizing. Example guidelines are: 12-16 mm for IVC, 10-12 mm for iliac veins, 8-10 mm for femoral veins and 6-8 mm for popliteal veins. Cracking the chronic clot may allow for better penetration of alteplase. Once venoplasty has been performed throughout the entire diseased segment, venography imaging shall be obtained prior to placement of the IDDC. Care should be taken to obtain the same images as obtained at baseline venography.

An EkoSonic® IDDC with the treatment zone length selected to cover the entire occlusive segment is placed over the guide wire. The guide wire is then removed and the MSD inserted into the IDDC and luer locked in place. See Appendix C for specific guidance on EkoSonic® Device selection and placement.

Alteplase infusion shall be started at 0.5-1.0 mg per hour, with coolant (e.g. saline) infusing at 35-120 ml/hr as the subject will tolerate. Any commercially available formulation of alteplase may be used. See Appendix C for specific thrombolytic infusion guidelines.

NOTE: A saline infusion should be connected to the side port of the introducer sheath to place the IDDC and/or angioplasty balloon. Heparinization of this infusion is not necessary as the subject will be on enoxaparin during the infusion.

Thrombolytic infusion shall be planned for at least 12 hours and overnight as needed up to a maximum of 48 hours. The EkoSonic® Device is designed to provide optimum acoustic output during the first 24 hours of operation. If the device is to be run for longer than 24 hours, a new MSD should be placed. The alteplase dose may be adjusted per Investigator discretion but should not exceed 1 mg/hour for the infusion rate and a total dose of 48 mg. The subject shall return to the nursing floor with orders to place pneumatic compression boots (PCB) on both legs during the infusion procedure. Weight based enoxaparin BID injections shall continue throughout the interventional procedure.

4.2.4 Post-EkoSonic® Procedure

The following assessment should be performed immediately after the completion of the EkoSonic® Procedure.

- Venography

Adjunctive therapy may then be considered, as necessary. Stenting across the inguinal crease is only considered when there is poor flow from the femoral vein into the common femoral vein (CFV) and iliac veins, and all other measures have been exhausted. If stenting is necessary, IDEV Supera 8 mm stent is recommended for crossing of the inguinal ligament and CFV. If adjunctive therapy is performed, the following assessment should be performed immediately following the procedure.

- Venography

Upon completion of study treatment, the catheter and sheath shall be removed and hemostasis obtained with pressure over the insertion site followed by placement of a pressure dressing. PCB shall remain placed on both legs until hospital discharge. Anticoagulation therapy with weight based enoxaparin sodium shall also be continued through discharge (see Concomitant Medication section below). The following assessments should be performed following the completion of study treatment.

- Duplex imaging (within 24 hours of the completion of treatment)
- Laboratory tests (within 24 hours of the completion of treatment)
- Adverse Events

4.2.5 Discharge

The subject shall be discharged with prescriptions for enoxaparin (1 mg/kg bid for 90 days) and a pair of 30 to 40 mm Hg ECS. If necessary, enoxaparin may be converted to an oral anticoagulant after 30 days (e.g. 20 mg rivaroxaban daily). Treatment with the ECS and oral anticoagulation should continue for the duration of the study.

If limb swelling and discomfort is too great for standard ECS use, leg wraps, leg elevation, and pumps can be used to reduce the swelling and pain and allow for earlier ECS use. One may also consider using 20-30 mmHg ECS if necessary. The subject shall be encouraged to ambulate and exercise early and often, as tolerated.

4.2.6 Follow- Up Visits and Early Termination

At each of the follow-up visits: **Days 30± 7 days, 90± 10 days, 180± 14 days, 365 ± 14 days and at early termination,** the following assessments shall be performed:

- Duplex imaging
- Villalta scale (both legs)
- CEAP classification(both legs)
- VCSS (both legs)
- SF-36
- VEINES-QOL
- Leg circumference (both legs)
- Review of compliance with anticoagulant therapy, ECS, and exercise
- Serious Adverse and bleeding events
- Concomitant medications

4.3 Concomitant Medications

Anticoagulation therapy with enoxaparin sodium (1 mg/kg twice a day) will be initiated at least 48 hours prior to initiation of study treatment. Subjects not currently anticoagulated with enoxaparin will be transitioned to enoxaparin. Transition to enoxaparin should occur when the next dose of anticoagulant is due i.e. there shall be no overlap in anticoagulant dosing. When the subject is due for their next dose of anticoagulant, enoxaparin should be started at 1 mg/kg twice daily. When the subject has been solely on enoxaparin for at least 48 hours, the study treatment may be performed.

Following conclusion of treatment, the subject should remain on enoxaparin 1 mg/kg bid for 90 days. The subject may then be transitioned to long term anti-coagulation at the Investigator's discretion. If necessary, enoxaparin may be converted to an oral anticoagulant after 30 days (e.g. 20 mg rivaroxaban daily).

4.4 Prohibited Medications

The use of platelet glycoprotein IIb/IIIa receptor antagonists (abciximab, tirofiban, eptifibatide) and oral thienopyridine anti-platelet drugs during or within 24 hours of the completion of study treatment is not permitted. The use of aspirin and non-steroidal anti-inflammatory drugs is discouraged while subjects are receiving anticoagulant therapy unless there is a compelling indication.

4.5 Subject Withdrawal

Subjects may withdraw from participation at any time during the clinical study. All data collected prior to withdrawal shall remain part of the study. Every effort shall be made to encourage the subject to remain in the trial. If the subject declines, determine and document the reason for withdrawal.

4.6 Revascularization

If, at any time during the follow-up period a subject is found to have re-occlusion of a venous segment that is associated with escalation of symptoms, the subject may undergo revascularization using any method the treating physician feels is appropriate. The subject shall remain in the study and shall attend all planned follow-up visits. All revascularization procedures shall be documented on the revascularization case report form.

5.0 SAFETY REPORTING

5.1 Adverse events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of an investigational intervention in humans, 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. An AE can arise with any use of the intervention.

5.2 Suspected Adverse Reaction

Suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the intervention caused the AE. For the purpose of reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the intervention and the AE. A SAR implies a lesser degree of certainty about causality than adverse reaction. An adverse reaction means any AE caused by an intervention. Adverse reactions (ARs) are a subset of all SAR s where there is reason to conclude that the intervention caused the event.

5.3 Serious

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 or prevent one of the outcomes listed in this definition.

5.4 Unexpected

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; or, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

5.5 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.

5.6 Device Deficiency, Device Failures and Malfunctions

Manufacturers must report device-related deaths, serious injuries and malfunctions to the FDA 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).

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.

Reporting Requirements

All device failures and malfunctions will be documented on the electronic case report form (eCRF), reported to EKOS within one working day after the designated study site personnel first learn of the event, and reported to the IRB (if required) within the IRB required timeframe.

Device malfunction

In the event of a device malfunction the EKOS Customer Helpline [redacted] shall be contacted for assistance. If the device cannot be restarted or is damaged in some way, if possible, the malfunctioning device should 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 malfunctioning device should be retained for return to EKOS. When the malfunction is reported to EKOS, product return information will be provided.

Return devices to the address below:

EKOS Corporation
11911 North Creek Parkway South
Bothell, WA 98011
[redacted]
Fax: [redacted]
Email: [redacted]

5.7 Documentation of adverse events

AEs shall 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 shall be encouraged to report AEs spontaneously or in response to non-directed questioning by their usual healthcare providers (for example, in response to the question "How has your health been since you last visit?"). If it is determined that an AE has occurred, the study staff member entering data into the eCRF should obtain all of the information necessary to complete the AE section.

5.8 Reporting and duration of AE reporting period

Because the EkoSonic® Endovascular System 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 or the EkoSonic® treatment will be collected.

5.9 Adverse events related to alteplase and definition of major bleeding

AEs related to alteplase are well-described and consist mainly of bleeding complications, including major and intracranial hemorrhage. The incidence of these complications has been quantified in subjects receiving comparatively large systemic doses of alteplase for acute myocardial infarction, stroke, and acute pulmonary embolism. Any bleeding that is attributable to alteplase is most likely to occur within 24 hours of treatment and is very unlikely to occur after 72 hours. Therefore, all bleeding events that occur within 72 hours of ultrasound-accelerated catheter-directed fibrinolysis will be attributed to the use of alteplase.

The following definition of major bleeding[12] (ISTH) shall be used: As general principles, a definition of major bleeding needs to 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

5.10 Specific reporting guidelines

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

Use recognized medical terms.

Avoid the use of colloquialisms and non-standard abbreviations

If known at the time of AE reporting, a diagnosis should be reported instead of individual symptoms and signs (for example, record only "pneumonia" rather than "productive cough" and "elevated white blood cell count").

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 should be reported. If a diagnosis is subsequently established, it should be reported as follow-up information as described earlier.

A cascade of clinical events (such as sequelae of an adverse event) should be identified as the primary, causative event. The cascade of events can be further described in the primary AE narrative. For example, when recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the serious adverse event. If the cause of death is unknown and cannot be determined at the time of reporting, "unknown cause of death" should be recorded as the adverse event.

Any AE potentially related to the study procedure that results in inpatient re-hospitalization or prolongs the index hospitalization (for study treatment) should 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) should 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.

All observed or reported serious bleeding events occurring through the 365 day follow-up period, must be recorded.

Previously scheduled hospitalizations required for diagnostic or elective surgical procedures for the management of unchanged pre-existing medical conditions shall not be considered AEs.

5.11 Pregnancy

If a subject becomes pregnant within 90 days of receiving alteplase and undergoing ultrasound-accelerated catheter-directed thrombolysis, follow-up should 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.

5.12 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 should 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 should be evaluated as to whether it was related to the study procedures, thrombolytic and anticoagulation drugs, or EkoSonic® Endovascular System as follows:

Definite	An AE that has a causal relationship to the drug (recombinant t-PA), anticoagulation medication, or the EkoSonic® Endovascular System
Probable	An AE that has a 'reasonable possibility' of a causal relationship to the use of recombinant t-PA, anticoagulation medication, or the EkoSonic® Endovascular System; another etiology is significantly less likely
Not related	An AE is not related to the use of recombinant t-PA, anticoagulation medication, or the EkoSonic® 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 recombinant t-PA, anticoagulation medication, or the EkoSonic® Endovascular System cannot be determined.

Outcome

The clinical course of all AEs should 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 should 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 initiation, interruption, dose reduction, dose increase, or discontinuation
None	No action was taken

5.13 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 via the e-mail address [redacted]

At the time of Sponsor notification, the Investigator shall enter into EDC as much of the information listed below as possible.

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 including dose, route of administration, frequency, dates, lot number, expiration date, and concomitant medications

When a 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 the EkoSonic® System.

When reporting a death, the primary event or condition that caused or contributed to the fatal outcome should 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, report "unknown cause of death".

5.14 Safety Monitor

A safety monitor shall review and adjudicate all SAEs and bleeding events during the study. The safety monitor will determine if the AE meets the definition of serious and unexpected and shall notify the sponsor if the number or type of events is of concern.

5.15 Data Collection

All study data shall be recorded on paper or eCRFs. Images shall be provided to the core labs as described in the lab manual provided to the sites

Data gathered during the course of the study shall be entered into a secure electronic data capture (EDC) website as soon as possible and at least within 7 days of subject enrollment or follow-up visit. Instructions and training on data collection/entry shall be provided to the Investigator and their staff during site initiation. Data shall be reviewed on a periodic basis and any incomplete or inconsistent data will be requested from the Investigator.

6.0 STATISTICAL ANALYSIS

6.1. Analysis Subject Sets, Evaluable Subjects and Missing Data Handling Convention

Efficacy Evaluable Segments are defined as DVT segments from enrolled subjects which: (a) were successfully crossed and received EkoSonic® Treatment, and (b) had Villalta scores available at both Baseline and 30 days Post-EkoSonic® Treatment visit. The **Efficacy Segment Set** includes all efficacy evaluable segments and will be used for all segment specific efficacy analyses. A treated segment that received a revascularization procedure within 30 days Post-EkoSonic® Treatment will be regarded as a failure for the primary efficacy endpoint, i.e. without a ≥4-point reduction in Villalta score from Baseline to 30 days Post-EkoSonic® Treatment.

Efficacy Evaluable Subjects are defined as enrolled subjects for whom at least one affected segment: (a) was successfully crossed and received EkoSonic® Treatment, and (b) had Villalta scores available at both Baseline and 30 days Post-EkoSonic® Treatment visit. The **Efficacy Subject Set** includes all efficacy evaluable subjects and will be used for all subject specific efficacy analyses such as for quality of life measures.

Safety Subject Set
Safety evaluable subjects are defined as enrolled subjects for whom the EkoSonic® Treatment was initiated, i.e. venous access attempted for catheter introduction. The **Safety Subject Set** includes all safety evaluable subjects and will be used for all safety analyses.

Missing data will not be imputed for the primary efficacy and safety analyses. However sensitivity analyses may be performed to assess the robustness of study results with respect to missing data.

6.2. Statistical Analysis Plan

6.2.1 General Methodology

For baseline demographics and subject 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. As appropriate, characteristics of affected segments may be similarly summarized.

For segment specific efficacy endpoints of interest, the analysis unit will be treated segment as opposed to subject. That is, assuming no missing data, subjects with bilateral DVTs will have two segments for analysis. Efficacy results will be summarized for the Efficacy Segment Set at each measurement time point. For changes from baseline at follow-up time points, continuous measures will be summarized as mean, standard deviation, median, minimum, maximum. Categorical outcomes will be summarized in two-way tables. All statistical analyses will take into account the repeated measures nature of multiple segments per subject. With subject as a random effect, the SAS GLIMMIX procedure will generally be used to evaluate the statistical significance for changes from baseline.

Analysis for subject specific efficacy measures such as SF-36 will be performed on the Evaluable Subject Set with subject as the analysis unit. Statistical significance for changes from baseline will be assessed by t-test or a nonparametric test appropriate for the data distribution.

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

6.2.2 Efficacy

Efficacy analyses will be performed on the Efficacy Segment Set or Efficacy Subject Set as appropriate for the nature of the data.

Primary Clinical Efficacy Analysis:

The 30 day Villalta score change from Baseline will be analyzed as a binary variable for a segment's status as having achieved a ≥ 4 point reduction or not. Study success will be defined by ≥ 50% of the efficacy evaluable segments achieving at least a 4 point reduction. In addition, as a continuous measure, change in Villalta score from Baseline to 30 day Post-EkoSonic® Treatment will also be summarized and analyzed as described above in 6.2.1 General Methodology.

Primary Technical Efficacy Analysis:

The change in blood flow calculated by time to washout in the affected segment from Baseline and Post-EkoSonic® Treatment will be analyzed as a continuous measure. A statistically significant (2-sided $p < 0.05$) improvement in flow rate, i.e. reduction in time to washout, will be considered a success for the study.

Secondary Efficacy Analyses:

For all secondary efficacy endpoints described in Section 3.2.1, i.e. VVI score change from Pre- EkoSonic® Treatment to Post-Treatment, Villalta score change from Baseline to 90, 180, and 365 days, re-occlusion rate up to 365 days, change from Baseline to all follow-up time points for SF-36 QOL and PCS component scores, CEAP classification, and VCSS, occurrences of symptomatic PTS-induced admission to emergency room or unplanned visit

to physician office or hospitalization from post EkoSonic® Treatment up to 365 days thereafter, time from starting initial thrombolytic infusion to discharge from hospital, analyses will be performed as described above in 6.2.1 General Methodology. For symptomatic PTS-induced healthcare utilization, time to event analyses will be performed for days from EkoSonic® Treatment to first occurrence for each of (a) admission to emergency room, (b) unplanned visit to physician office, and (c) hospitalization.

6.2.3 Safety Analysis

Safety analyses will be performed for the Safety Subject Set.

For the primary safety analysis, the number and percentage of subjects with major bleeding within 72 hours of initiation of EkoSonic® Treatment will be reported with a 95% Wilson confidence interval.

Secondarily, the frequencies and proportions of subjects with symptomatic PE (diagnosed using CTPA, SPECT VQ, etc.) during hospitalization for the study procedure, 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.

6.2.4 Power Estimation

For the primary efficacy endpoint of change in Villalta score at 30 days from Baseline, study success will be defined by ≥ 50% of the evaluable DVT segments achieving at least a 4 point reduction. Assuming the true underlying proportion of such segments to be 55%, the probability for observing a ≥ 50% success proportion in a study with 70 evaluable independent segments is 0.83. On the other hand, should true underlying success proportion be <40%, e.g. 39%, the probability for observing a ≥ 50% success proportion in 70 independent segments is ≤0.04.

6.2.5 Interim Clinical Efficacy Futility Analysis

At the time of November 2016 administrative change to the protocol, an interim futility analysis had been performed on the primary clinical efficacy endpoint. The futility stopping criterion was not met and the study continued. It was pre-specified that when data for the primary efficacy endpoint (i.e. change in Villalta score from Baseline to 30 day Post-EkoSonic® Treatment) are available for 35 evaluable subjects segments, an interim futility analysis will be conducted. If 14 or fewer of the 35 segments have achieved a ≥ 4 point reduction for an interim success rate of 40% (1-sided 95% confidence upper limit of 53.9%), early trial termination would be considered due to futility. Should the true success rate be 40% as observed in the interim, the chance of reaching a 50% success rate at full enrollment of 70 evaluable subjects segments (i.e. 21 or more segments in the remaining 35 segments), is ≤0.013. Should the underlying success rate be 53.9%, i.e. the 95% confidence upper limit of the interim success rate, the chance of observing a 50% success rate at full enrollment is still only 0.29. Therefore it is highly unlikely that the trial would meet its efficacy success criterion at full enrollment and early trial termination would be recommended. The negative impact of this futility analysis on the study's power is <0.05.The study would not stop early due to favorable interim efficacy results; therefore this interim analysis will not incur an alpha cost due to potentially false positive findings.

7.0 RISK ANALYSIS

7.1 Description and Analysis of Risks

The risks that are associated with use of the EkoSonic® Endovascular System 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 IFU Appendix A. Potential risks associated with thrombolytic drugs are listed in the package insert for alteplase (Appendix B). Potential risks for subjects undergoing the procedure are listed in the following table.

Table 1 Anticipated Adverse Events During EkoSonic® Treatment

Adverse Event	Definition
Amputation	Surgical removal of any portion of the involved leg, foot or toes.
Arrhythmia	Irregularity or loss of rhythm of the heartbeat requiring treatment with drugs, cardioversion, or pacemaker.
Bleeding – Access site	Clinically significant bleeding at the catheter access site
Bleeding - Other	Clinically significant bleeding at any site other than the access site
Congestive Heart Failure	Development of an acute episode of or exacerbation of existing low cardiac output accompanied by distal and/or pulmonary edema requiring tracheal intubation or Intensive Care Unit care.
Contrast Reaction	Documented reaction directly attributed to contrast medium used during the angiography or venography.
Death	All deaths should be reported regardless of cause
DVT – Recurrent, same limb	A new episode of DVT in the study limb. If subject was discharged, any returns for DVT symptoms will be considered recurrent.
DVT – Recurrent, other	A new episode of DVT in a non-study limb.
Device Issue	Any device operation / malfunction that results in a negative clinical occurrence for the subject. Failure to lyse or automatic shut off as outlined in the IFU will not be considered a Device Issue.
Distal Embolization	Filling defect with an abrupt 'cutoff' in one of the peripheral vessels distal to the site of treatment.
Dyspnea	Labored or difficult breathing
Embolism	Blockage of a vessel by dislodged thrombus confirmed by angiography
Hematoma - Access site	Clinically significant localized collection of blood at catheter access site
Hematoma - Other	Clinically significant localized collection of blood at any site other than access site
Infection - Systemic	Systemic infection as indicated by increase in white blood cell count sufficient to warrant antibiotic therapy.
Infection - Wound	Wound drainage or erythema of the access site documented by positive culture and requiring drainage, debridement, and/or antibiotic therapy.

Adverse Event	Definition
Inflammation - Wound	Prolonged or abnormal pain, redness, and swelling at the access site.
Intracranial Hemorrhage	Intracranial hemorrhage related to a decline in neurological status and consistent with new or worsening symptoms in the judgment of the Investigator.
Medication Reaction	Documented reaction directly attributed to prescribed medication.
Myocardial Infarction	Significant elevation of CPK-MB (based on local norms), appearance of new significant Q wave or loss of R waves.
Neurovascular	Documented complication of both the nervous and vascular systems of the involved limb.
PE - Proved	Intravascular migration of a venous thrombus to the pulmonary arterial circulation proved by a positive pulmonary angiogram, a positive helical CT scan, a high-probability ventilation-perfusion scan or autopsy.
PE - Suspected	Intravascular migration of a venous thrombus to the pulmonary arterial circulation suspected based on clinical symptoms / signs but where no diagnosis has been made by imaging or autopsy.
Renal failure	Creatinine level increase >30% of the preoperative level or requiring dialysis.
Respiratory Failure	The need for mechanical ventilation or the need for intubation and ventilator support any time during the study (unless the subject was ventilator dependent when he/she entered the study).
Stroke	Development of a new permanent neurologic deficit or exacerbation of a prior deficit as determined by CT/MRI Scan and/or clinical exam
Thrombosis, vascular	A new or recurrent occlusion
Transient ischemic attack	Development of a new transient neurologic deficit as determined by CT/MRI Scan and/or clinical exam that occurs
Vascular complication	Any complication of the treated vessel including dissection, perforation, spasm, pseudoaneurysm, occlusion, or arteriovenous fistula (AV fistula).
Other	Complications not specifically listed, which are determined to be associated with the device, the procedure or condition.

7.2 Summary of Expected Benefits

Based on existing, limited evidence, the procedures performed in this study may result in reduction of symptoms/signs of PTS and improvement in quality of life in subjects with persistent venous obstruction subsequent to previous DVT who have PTS.

8.0 STUDY PROCEDURES

8.1 Adherence to Conservative Therapy Form

The Adherence to Conservative Therapy Form must be completed at Screening/Baseline (Visit 1). Appropriate study personnel should review the questionnaire for accuracy and completeness and then sign the document.

8.2 Pregnancy Test

A pregnancy test must be performed at Screening/Baseline (Visit 1) prior to study enrollment for any women of child bearing potential.

8.3 Physical Exam

A physical exam will be performed at Screening/Baseline (Visit 1) prior to study enrollment. The physical exam should include an assessment of all major body systems with emphasis placed on the documentation of PTS signs and symptoms. Significant findings should be recorded in the subject's Medical History according to the Investigator's clinical judgment.

8.4 Duplex Ultrasound

Baseline duplex ultrasound 60 days prior to the study procedure or venography (Pre-EkoSonic® Treatment) will be performed to confirm persistent chronic DVT causing restrictive flow. Duplex ultrasound will also be performed Post-EkoSonic® Treatment (Visit 2), Day 30 (Visit 3), Day 90 (Visit 4), Day 180 (Visit 5), Day 365 (Visit 6), and Early Termination. Please refer to the duplex ultrasound manual for details regarding image capture and submission.

8.5 Venography

Venography will be performed Pre- and Post-EkoSonic® Treatment and prior to adjunctive treatment, if adjunctive therapy is necessary (Visit 2). Pre- EkoSonic® Treatment venography should confirm persistent chronic DVT causing restrictive flow if not already confirmed via duplex imaging within 60 days prior to the study procedure Please refer to the Venographic Imaging Manual of Operations and Procedures for details regarding image capture and submission.

8.6 Laboratory Tests

CBC and creatinine levels will be obtained within 30 days prior to the EkoSonic® Treatment procedure, at Screening/Baseline (Visit 1). CBC and creatinine levels will also be obtained Post-EkoSonic® Treatment (Visit 2). Hemoglobin, INR, and platelet count must be obtained within 24 hours prior to the EkoSonic® Treatment procedure in order to confirm eligibility.

8.7 Post- Thrombotic Syndrome and Quality of Life Assessments

All efforts should be made to schedule and perform assessments at approximately the same time of day, preferably the afternoon. Subjects' symptoms generally become more pronounced later in the day, thus performing the assessments at this time will provide the most accurate representation of the subject's PTS symptoms. Consistently performing the follow-up assessments at approximately the same time of day as the Screening/Baseline (Visit 1) assessment will help to reduce variability as a result of the inherent symptom worsening late in the day. The subject should be asked not to wear their ECS on the day of assessment.

Self-rated portions of the assessments should by performed by the subject before they arrive at the follow-up visit. If the self-rated portion is not completed prior to the follow-up visit, the subject must be provided a private place to complete the self-reporting such that the clinician performing the rest of the assessments cannot overhear the subject or see the subject's completed forms.

It is preferable that the same clinician performs the assessment on an individual subject throughout the study.

8.7.1 Villalta Scale

The Villalta scale will be administered for both legs at Screening/Baseline (Visit 1), Day 30 (Visit 3), Day 90 (Visit 4), Day 180 (Visit 5), Day 365 (Visit 6), and Early Termination.

Administration of the Villalta scale must be performed by a trained clinician at each visit. Following the clinician administrated portion of the Villalta scale and prior to the subject leaving, the clinician should review the subject's Villalta scale forms for completion. If there are any missing values, the trained study staff should ask the subject if they would like to complete those questions.

8.7.2 CEAP Classification

The CEAP classification will be performed for both legs at Screening/Baseline (Visit 1), Day 30 (Visit 3), Day 90 (Visit 4), Day 180 (Visit 5), Day 365 (Visit 6), and Early Termination. Only the "C" portion of the classification will be performed.

8.7.3 VCSS

The VCSS will be administered for both legs at Screening/Baseline (Visit 1), Day 30 (Visit 3), Day 90 (Visit 4), Day 180 (Visit 5), Day 365 (Visit 6), and Early Termination.

8.7.4 SF-36

The SF-36 will be administered at Screening/Baseline (Visit 1), Day 30 (Visit 3), Day 90 (Visit 4), Day 180 (Visit 5), Day 365 (Visit 6), and Early Termination.

8.7.5 VEINES-QOL

The VEINES-QOL will be administered at Screening/Baseline (Visit 1), Day 30 (Visit 3), Day 90 (Visit 4), Day 180 (Visit 5), Day 365 (Visit 6), and Early Termination.

8.8 Leg Circumference

Leg circumference will be measured on both legs at Screening/Baseline (Visit 1), Day 30 (Visit 3), Day 90 (Visit 4), Day 180 (Visit 5), Day 365 (Visit 6), and Early Termination. The following three measurements should be taken of each leg:

- 15 cm above uppermost margin of the patella
- 10 cm below the lower margin of the patella
- Just above the medial malleolus

8.9 Review of Compliance, & Exercise

The following items should be reviewed with the subject at Day 30 (Visit 3), Day 90 (Visit 4), Day 180 (Visit 5), Day 365 (Visit 6), and Early Termination:

- Frequency, duration, and type of exercise
- Compliance with anticoagulant therapy
- Compliance with wearing ECS or alternative option

9.0 RECORD RETENTION

All study records and reports will remain on file at the sites for a minimum or 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.

10.0 INVESTIGATOR RESPONSIBILITES

10.1 General

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

- The Investigator shall ensure that all work and services described herein, shall be conducted in accordance with the highest standards of medical and clinical research.
- The Investigator will be responsible for ensuring the clinical trial is conducted according to Compliance with ICH Good Clinical Practice (GCP) guidelines and this protocol, and all conditions of the Investigational Review Board (IRB).
- The Investigator will ensure that the protocol is available to all Sub Investigators and other site personnel responsible for the study. The Investigator will ensure that study personnel conduct the study to the protocol and study procedures.
- The Investigator is responsible for protecting the rights, safety, and welfare of subjects under the Investigator's care.
- The Investigator is responsible for ensuring that Informed Consent is obtained and maintained.
- Subjects must be informed that their medical records may be subject to review by EKOS, its representatives, and government agencies.
- Notify EKOS if the investigator plans to leave the investigational site.

10.2 Source documentation

Regulations 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 EKOS 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.

10.3 Study Deviations

A study deviation is defined as an event where the Investigator or site personnel did not conduct the trial according to the protocol, applicable laws or regulations, or the Investigator

Agreement. Regulations require 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 EKOS.

Investigators are required to obtain prior approval from the EKOS Clinical Affairs Department before initiating changes in or deviations from the protocol except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval will be documented in writing and maintained in the study files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control (e.g. subject did not return for scheduled visits, lost laboratory samples) however, the event is still considered a deviation. Subject specific deviations will be reported on the protocol deviations case report form.

10.4 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 EKOS Clinical Affairs Department. All publications of results from this study must be approved by the EKOS Clinical Affairs Department.

11 REFERENCES

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