NCT #: NCT02159521

ACCESS PTS

ACCelerated ThrombolySiS for Post-Thrombotic Syndrome Using the EKOS System

Protocol Number: EKOS – 11

Amendment 3: Version 4; November 4, 2016

Statistical Analysis Plan through 365 Day Post Treatment

Version 1: December 3, 2018

Sponsor:

EKOS Corporation, a BTG International group company

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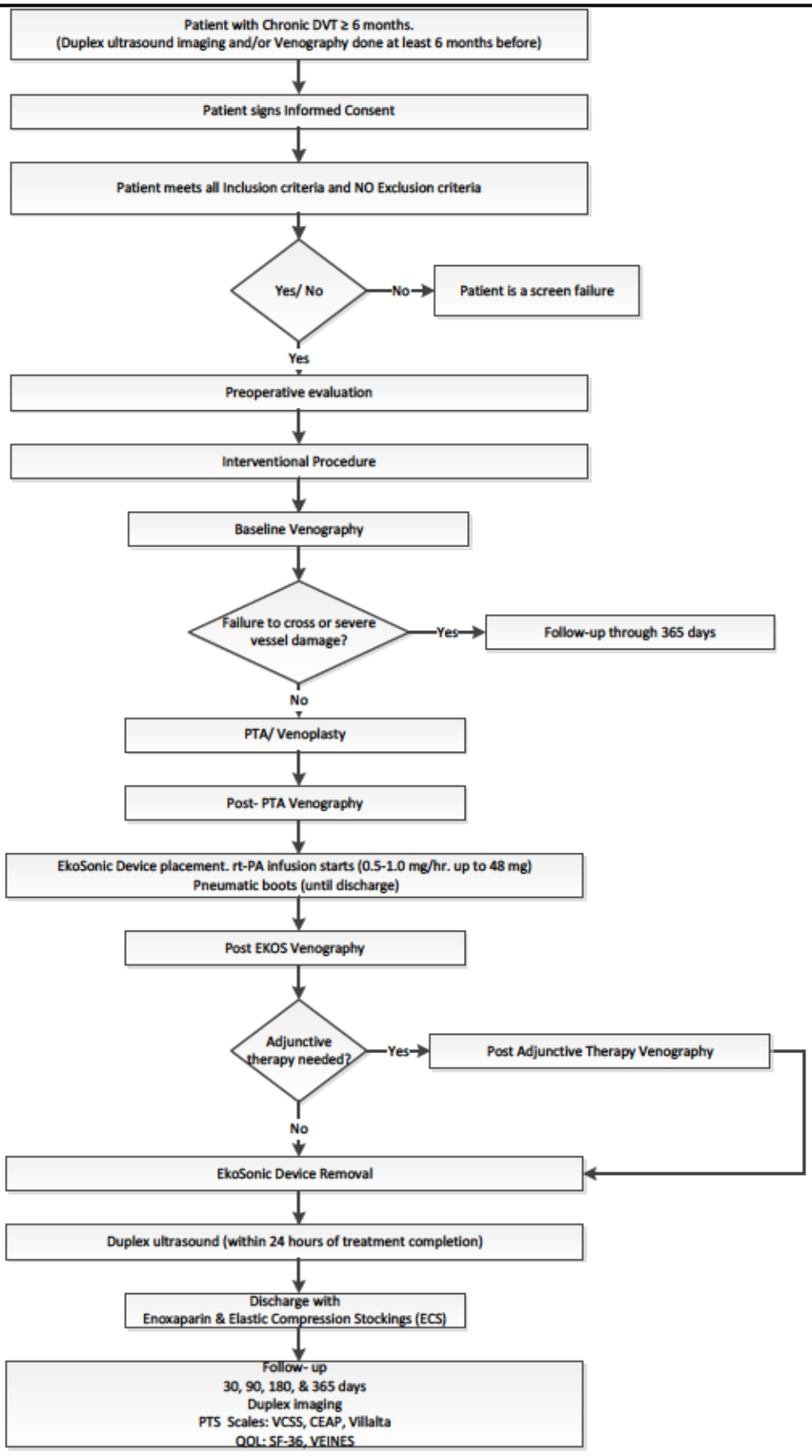
A. PROTOCOL SYNOPSIS

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 at least 50% ($p<0.05$) 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


Patient with Chronic DVT ≥ 6 months.
(Duplex ultrasound imaging and/or Venography done at least 6 months before)
Patient signs Informed Consent
Patient meets all Inclusion criteria and NO Exclusion criteria
Yes/ No
No
Patient is a screen failure
Yes
Preoperative evaluation
Interventional Procedure
Baseline Venography
Failure to cross or severe vessel damage?
Yes
Follow-up through 365 days
No
PTA/ Venoplasty
Post- PTA Venography
EkoSonic Device placement. rt-PA infusion starts (0.5-1.0 mg/hr. up to 48 mg)
Pneumatic boots (until discharge)
Post EKOS Venography
Adjunctive therapy needed?
Yes
Post Adjunctive Therapy Venography
No
EkoSonic Device Removal
Duplex ultrasound (within 24 hours of treatment completion)
Discharge with
Enoxaparin & Elastic Compression Stockings (ECS)
Follow- up
30, 90, 180, & 365 days
Duplex imaging
PTS Scales: VCSS, CEAP, Villalta
QOL: SF-36, VEINES

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

1.0 STUDY OBJECTIVES AND STUDY ENDPOINTS

1.1 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.

1.1.1 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% ($p<0.05$) of the efficacy evaluable limbs achieving at least a 4 point reduction.

1.1.2 Primary Technical Efficacy Endpoint

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

1.2 Secondary Objectives

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

1.2.1 Secondary Clinical Efficacy Endpoints

1. Occlusive material burden using the Venous Volumetric Index (VVI) Score[i], 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

1.3 Safety Endpoints

1. Frequency of major bleeding[ii,iii] 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.

2.0 STATISTICAL ANALYSIS

2.1. Safety Subject Set, Efficacy Evaluable Subject Set and Missing Data Handling Convention

Safety Subject Set

The **Safety Subject Set** (also referred to as **ITT population**) includes all enrolled subjects for whom the EkoSonic® Treatment is initiated, i.e. the EkoSonic® Placement Start Time (exsttm) in Interventional Procedure CRF is non-blank. The **Safety Subject Set** will be used for all safety analyses.

The **Efficacy Evaluable Subject Set** includes all eligible (per protocol inclusion/exclusion criteria) and enrolled subjects, for whom the EkoSonic® Treatment is initiated, and both baseline and 30-day follow-up data are available for the primary efficacy endpoint Villalta score.

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.

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.

2.2. Statistical Analysis Plan

2.2.1 General Methodology

For baseline demographics and subject characteristics, continuous measures will be summarized as number of subjects with non-missing data (n), 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, 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 n, 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 Mixed or GLIMMIX procedures 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 with subject as the analysis unit. Statistical significance for testing changes from baseline against 0 will be assessed by t-test or a nonparametric test appropriate for the data distribution. All p values will be 2-sided unless otherwise specified.

2.2.2 Efficacy

Efficacy analysis units will be segments or subjects 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 with a 2-sided $p < 0.05$. 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 2.2.1 General Methodology.

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.

Primary Technical Efficacy Analysis:

The change in blood flow, as calculated by time to washout in the affected segment, from Baseline to Post-EkoSonic® Treatment and post adjunctive 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 1.2.1, i.e. VVI score change from Pre-EkoSonic® Treatment to Post-Treatment, change from Baseline to 30 days for SF-36 QOL and PCS component scores, CEAP classification, VEINES-QOL, VCSS, and occurrences of symptomatic PTS-induced admission to emergency room or unplanned visit to physician office or hospitalization from post EkoSonic® Treatment up to 30 days thereafter, and time from starting initial thrombolytic infusion to discharge from hospital; analyses will be performed as described above in 2.2.1 General Methodology. For symptomatic PTS-induced healthcare utilization, the number of occurrences will be summarized for each of (a) admission to emergency room, (b) unplanned visit to physician office, (c) hospitalization, and (d) any of (a) through (c).

2.2.3 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.

2.2.4 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

2.2.5 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.

Appendix: List of Tables

Analysis Unit = Subject Unless Otherwise Specified

1) Subject Disposition

   Present N for all enrolled, Safety Subject Set, Efficacy Evaluable Subject Set and number of subjects with 2 treated segments

2) Demographics

   a) Age

   b) Weight

   c) BMI

   d) Gender

   e) Ethnicity (Hispanic vs. not Hispanic)

   f) Race

3) Clinical History and Risk Factors

   (a) – (u) on Clinical History and Risk Factors CRF.

   a) Hypercholesterolemia

   b) Congestive Heart Failure

   c) Hepatic Insufficiency

   d) Renal Insufficiency

   e) TIA or Stroke

   f) Active Cancer

   g) Diabetes

   h) Hypertension

   i) Tobacco use

   j) BMI ≥ 30.0

   k) COPD

   l) History of Cancer in Remission

   m) Family History of VTE

   n) Chronic Inflammatory Disorders

   o) Acute Infectious Illness within 30 Days of signing ICF

p) Atherosclerotic Cardiovascular Disease

q) Currently taking a Hormonal Contraceptive or Replacement Therapy

r) Osteoarthritis of Either Hip or Knee

s) All co-morbid conditions under A23 of Clinical History and Risk Factors eCRF, i.e. Recent (within 2 weeks) major surgery, Recent trauma (within 2 weeks), High Liklihood of Left Heart Thrombus, Acute Pericarditis, Subacute Bacterial Endocarditis, Hemostatic Defects, Significant Hepatic Dysfunction, Diabetic Hemorrhagic Retinopathy or Other Hemorrhagic Opthalmic Conditions, Septic Thrombophlebitis or Occluded AV Cannula at Seriously Infected Site, Any other Condition in which Bleeding Constitutes a Significant Hazard or Would be Particularly Difficult to Manage Because of its Location

t) All hypercoagulables under A24 of Clinical History and Risk Factors eCRF, i.e. Anticardiolipin Antibodies, Antiphospholipid Antibody Syndrome, Lupus Anticoagulant, Activated Protein C Resistance, Factor V Leiden Mutation, Prothrombin Gene Mutation (20210a), other *(make a listing for other hyperanticoagullables by arm)*

u) Inferior Vena Cava Filter Currently Present

v) Platelet count <100,000 (*Baseline labs*)

w) Venous Thromboembolism History (*Venous Thromboembolism History CRF)*

a) Type
b) Affected limbs if type = DVT

4) Anticoagulation Medication

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

5) Venography Data by Segment at Baseline, Post PTA, Post EkoSonic Treatment, Post Adjunctive Therapy, Other

a) Locations of venous thromboembolism *(frequency and % segments with either partial or occluded checked for each of Venography Data – Core Lab CRF A7 – A18)*

b) Total number of locations per segment with (a) any occlusion, partial or occluded, (b) partial occlusion only, (c) occluded checked on CRF (*Venography Data – Core Lab CRF*) *(n, mean, standard deviation, median, minimum, maximum)*

c) Ouriel score also referred to as VVI Score), Marder score, and American Venous Registry Score *(summarize each as a continuous measure at time point and for absolute and percent changes from baseline to each post baseline assessment. For each change from baseline, i.e. each outcome and separately at each post baseline assessment, also perform MMRM with subject as a random effect and no fixed effect, provide 2-sided p value for testing the intercept = 0.)*

d) Time to Washout – (Femoral Vein (FV), External Iliac Vein (EIV) - The change in blood flow as calculated by time to washout in the affected segment from Baseline to Post-EkoSonic® Treatment (Time to washout data (seconds) to come from Core Lab[redacted]; analyze the same way as for Villalta score without the binary data portion.)

Duplex Ultrasound: Absence of re-occlusion at 365 days of the treated segment, as documented by duplex imaging.

Combine two populations of note

Subjects with "yes" to patency across all follow up time points (30 days, 90 days, 180 days, and 365 days)

Subjects with "no" to patency across, but "yes" occlusion at any time point and does not match treated venous segment (based on vein mapping table).

Vein Mapping Table						
Duplex Ultrasound Venous Segment	**CIV**	**EIV**	**CFV**	**Proximal FV**	**Distal FV**	**Popliteal Vein**
Interventional Procedure Venous Segments	Common iliac vein (L/R) IVC Internal iliac vein (L/R)	External iliac vein (L/R)	Common femoral vein (L/R) Profunda Vein (L/R)	Proximal femoral vein (L/R)	Distal femoral vein (L/R)	Popliteal vein (L/R) Anterior tibial vein (L/R) Posterior tibial vein (L/R) Peroneal vein (L/R)

Provide N and percentage of patients and segments with re-occlusion at each time point.

6) Laboratory Data at Baseline, Pre Procedure, and Post Procedure: Hgb, Hct, Platelet *(n, mean, standard deviation, median, minimum, maximum)*

7) Interventional Procedure by Segment

a) Failure to treat *(n/% Yes/No, footnote reasons for failures)*

Below for non-failure-to-treat segments only

b) Access Site Location

c) Treatment Zone

d) Ultrasound Treatment Duration (hours) *(n, mean, standard deviation, median, minimum, maximum)*

e) Total r-tPA Dose (mg) *(n, mean, standard deviation, median, minimum, maximum)*

f) Ultrasound Termination Reason *(n/% planned thrombolytic infusion completed, adverse event, other/footnote specifications)*

g) Adjunctive Therapy *(n/% Yes/No, type of adjunctive therapy if Yes)*

h) Number of EkoSonic Devices Successfully Placed and Used for the Entire Study Treatment *(Footnote # devices not "successfully placed and used for the entire study treatment" with reasons.) (EkoSonic Device [eko] CRF)*

8) Protocol Deviations by Reason *(number of occurrences for each reason)*

9) Discharge

a) Days in ICU

b) Days in Hospital

c) Location subject discharged to

10) Revascularization: Number and Proportion of Subjects with revascularization procedures within 30 days and 365 days of EkoSonic procedure date. Also summarize time to revascularization.

11) Villalta Score by Segment

Summarize as continuous data for Baseline, 30 days, 90 days, 180 days, 365 days post EkoSonic procedure, absolute and percent changes at 30 days from baseline, i.e. n, mean, SD, median, minimum, maximum. Perform MMRM analysis with subject as a random effect and provide estimate for mean change at 30 days with SE, 95% CI and 2-sided p value testing mean change = 0.

In addition, provide total N, number and proportion of subjects with a 4-point or more reduction from baseline. Perform MMRM logistic regression analysis with subject as a random effect and provide the estimated proportion of subjects with a 4-point or more reduction with 95% CI and 2-sided p value testing the proportion = 50%. A treated segment that received a revascularization procedure within 30 days Post-EkoSonic® Treatment will be regarded as a failure of the limb for this analysis.

14) SF-36 Quality of Life Total Score and Physical Component Summary (PCS) Score at Baseline and 30 Days, 90 Days, 180 Days, and 365 Days.

For each outcome, analyze the same way as for Villalta score without the binary data portion.

15) CEAP classification at Baseline, 30 Days, 90 Days, 180 Days, 365 Days by Leg

Separately for study leg and non-study leg, summarize leg circumference and as n/% for both symptoms and condition at Baseline, 30 Days, 90 Days, 180 Days, and 365 Days. For change from Baseline to 365 Days, summarize as an 8 X 8 table for symptoms and 2 X 2 table for condition. Calculate p values by exact McNemar's method. For the 8 X 8 table, also do a Wilcoxon signed rank test for the paired differences between two ordinal scores (1-8 for C0, C1, C2, C3, C4a, C4b, C5, C6 respectively. For study leg only, perform MMRM analysis with subject as a random effect. For

symptoms, analyze the 30 day, 90 Days, 180 Days, and 365 Days – baseline difference for the 1-8 ordinal score. For condition, include only those whose baseline and 30 day conditions differ in analysis, i.e. exclude those whose condition did not change from baseline to 30 day. Analyze by logistic MMRM the yes/no binary outcome for changing from symptomatic at baseline to asymptomatic at 30 day).

16) VEINES-QOL at Baseline and 30 Days, 90 Days, 180 Days, and 365 Days

Analyze the same way as for Villalta score without the binary data portion.

17) VCSS at Baseline and 30 Days, 90 Days, 180 Days, and 365 Days by Leg

Separately for study leg and non-study leg, analyze the same way as for Villalta score without the binary data portion. Perform MMRM for study leg only.

18) Symptomatic PTS-induced admission to emergency room, or unplanned visit to physician office, or hospitalization from Post-EkoSonic® Study Treatment up to 365 days thereafter

Summarize as n/% separately for ER visit, unplanned visit to physician office, hospitalization, and any of the above using the Follow-Up CRF (fu)

19) Major Bleeding Events within 72 hours, 30 days, and 365 days of initiation of EkoSonic Treatment

Summarize as number and % of subjects with events for all major bleeding events with a 95% Wilson score confidence interval, and by relationship to thrombolytic/angiographic procedure, EKOS system, thrombolytic drug, anticoagulant drug, post-procedure adjunctive treatment. Categorize by severity of bleed (mild, moderate, severe)

20) Symptomatic Recurrent PE during Hospitalization for Study Procedure

Number and % of subjects with symptomatic PE with a 95% confidence interval (AE CRF)

21) Mortality up to 30 Days and 365 Days

Number and % of death with a 95% confidence interval (note: per AE and study exit CRFs)

22) Adverse Events Reported up to Day 30 *(Date of 30 Day Follow Up Visit per Follow-Up CRF)* and up to Day 365 (inclusive of 30 days)

a) All reported events

b) Related to thrombolytic/angiographic procedure

c) Related to EKOS system

d) Related to thrombolytic drug

e) Related to anticoagulant drug

f) Related to post-procedure adjunctive treatment

g) Bleeding events *(Make tables for*

-All reported bleeding events

-Those within 72 hours of starting EkoSonic Treatment

-Those:

a) Related to thrombolytic/angiographic procedure

b) Related to EKOS system

c) Related to thrombolytic drug

d) Related to anticoagulant drug

e) Related to post-procedure adjunctive treatment)

h) SAEs up to Day 30 and up to Day 365 (inclusive of 30 days)

i) Recurrent DVT and PE up to Day 30 and up to Day 365 (inclusive of 30 days)

[i] Ouriel K, Greenberg R, Green R, et al. A volumetric index for the quantification of deep venous thrombosis. *J Vasc Surg* 1999;6:1060-1066.

[ii] Shulman S, Kearon C, Definition of major bleeding in clinical investigation of antihemostatic medicinal product in on-surgical patients. *J Thromb Haemost* 2005;3:692-694

[iii]Vedantham, S, Grassi C, Ferral H, et al. Reporting standards for endovascular treatment of lower extremity deep vein thrombosis *J Vasc Interv Radiol* 2006; 17:417–434