VIRTUS
Safety and Efficacy of the Veniti Vici® Venous Stent System (Veniti Inc.) when Used to Treat Clinically Significant Chronic Non-malignant Obstruction of the Iliofemoral Venous Segment

Protocol Number: **STE-HUM-007P**

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Product: **Veniti Vici Venous Stent System**

Sponsored By:
Veniti, Inc.
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Statement of Compliance and Signature Page

I have read this Investigational Protocol and agree to adhere to the requirements.

I will provide copies of this Investigational Protocol and all pertinent information to the Study personnel under my supervision.

I will discuss this material with them and ensure they are fully informed regarding the Study products.

I will ensure that the study is conducted in compliance with the Investigational Protocol, Good Clinical Practice (GCP), the Declaration of Helsinki, ICH (Sixth Revision, 2008), ISO 14155-2011, EU Confidentiality Requirements, and all applicable regulatory and Independent Ethics Committee (EC) requirements.

Clinical Site Name: _____
Please print

The signature below constitutes the approval of this Investigational Protocol and any attachments, and provides the necessary assurances that this trial will be conducted according to the above conditions.

Site Principal Investigator:

_____
Print Name & Title

Signature: _____ Date: _____
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Abbreviations

List of Abbreviations	
ADE	Adverse Device Effect
AE	Adverse Event/Adverse Experience
ANOVA	Analysis of Variance
CEAP	Clinical-Etiology-Anatomic-Pathophysiologic
CEC	Clinical Events Committee
CFV	Common Femoral Vein
CIV	Common Iliac Vein
CIVIQ-2	Chronic Venous Insufficiency Questionnaire
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CT-V	Computed Tomography Venography
CVD	Chronic Venous Disorder(s)
CVI	Chronic Venous Insufficiency
DSMB	Data Safety Monitoring Board
DUS	Duplex Ultrasound
DVT	Deep Venous Thrombosis
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EIV	External Iliac Vein
EKG/ECG	Electrocardiogram
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
H_O	Null Hypothesis
H_A	Alternative Hypothesis
ICF	Informed Consent Form
ICH	International Conference on Harmonization

List of Abbreviations	
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intention to Treat
IVC	Inferior Vena Cava
IVUS	IntraVenous UltraSound
MAE	Major Adverse Events
MI	Myocardial Infarction
MR-V	Magnetic Resonance Venography
OUS	Outside the United States
PHI	Protected Health Information
PI	Principal Investigator
QoL	Quality of Life
RIE	Rate of Intervention of Extremity
RIL	Rate of Intervention Lesion
RVD	Reference Vein Diameter
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect
VCSS	Venous Clinical Severity Score
VKA	Vitamin K Agonists

1 KEY PROTOCOL DEFINITIONS

PRE-PROCEDURAL DEFINITIONS	
Term	**Definition**
Extremity thrombosis	Acute symptomatic thrombosis of the venous system of either lower extremity that is not located within the target vessel
Iliofemoral venous segment	The venous system comprised of the common femoral vein, the external iliac vein, and the common iliac vein (2012 SVS/AVF Guidelines. See Appendix 1).
Nonmalignant venous obstruction	Non-thrombotic or post-thrombotic obstruction of the iliofemoral venous segment that is not due to direct incursion of the vein by malignancy
Venous Obstruction	Reduction of the venous lumen diameter ≥ 50% when compared to the diameter of the normal vein/RVD immediately peripheral to the obstructed vein as measured by venogram.
Venous Occlusion	Total obliteration of the venous lumen
PROCEDURAL DEFINITIONS	
Term	**Definition**
Binary stenosis (or obstruction)	≥50% reduction of the venous lumen diameter when compared to the venous lumen diameter of the normal vein immediately peripheral to the obstructed vein as measured by venogram
Lesion success	Achievement of ≤50% residual diameter stenosis of the target lesion using any percutaneous method (including the use of non-study devices)
Migration	Device movement >10mm related to anatomical landmarks or any migration leading to symptoms or requiring therapy
Procedural success	Technical success without the occurrence of major adverse event between the index procedure and discharge
Residual diameter stenosis	The greatest degree of stenosis in the target lesion post-procedure, defined by the percent reduction in vessel lumen diameter when compared to the normal vein immediately peripheral to the target lesion as measured by venogram.
Stent Embolization	Dislodgement of the entire stent, which is carried by the blood flow to a different anatomical site of the vascular system, with no overlap in comparison to the original stent placement

Target lesion	The treated segment starting 5 mm peripheral and ending 5 mm centrally to the study device(s)
Target vessel	Native vein containing the target lesion such as the common iliac vein (CIV), external iliac vein (EIV) or common femoral vein (CFV)
Target vessel stenosis	Maximum percentage reduction in target lesion diameter when compared with the diameter of the normal vein/RVD immediately below the lesion as measured by venogram
Reference Vein Diameter (RVD)	Reference Vein Diameter (RVD) is defined as the normal diameter of the target vessel (CIV, EIV, or CFV)
Procedural technical success	Achievement of a final residual target vessel diameter stenosis of ≤50% as measured on the post procedural venogram, without skipped lesion regions, with placement of the study device alone with or without post-stenting balloon dilation as needed
POST-PROCEDURAL DEFINITIONS	
Term	**Definition**
Device or procedure related death	• Death specifically attributable to the Veniti Vici Venous Stent System or the stent placement procedure
Late technical success	• Absence of device movement >10mm related to anatomical landmarks or any migration leading to symptoms or requiring therapy • Absence of stent occlusion by thrombosis or restenosis, defined as reduction in treated segment lumen more than 50% from the post-procedure vessel lumen diameter as measured by post-procedural venogram or DUS • Structural integrity, defined as the absence of pinching (focal compression), recoil (poor radial resistive force) or kinking (stent bending upon itself) that results in >50% diameter reduction of the stent, or fracture
Patency (Primary Endpoint)	At 12 months post-intervention, freedom from occlusion by thrombosis AND freedom from surgical or endovascular intervention on target vessel with re-stenosis or stent occlusion to maintain patency AND freedom from in stent diameter stenosis more than 50% as measured by venogram. For patients refusing the venographic assessment at 12 months, DUS-determined patency will be used instead

Rate of intervention lesion (RIL)	Re-intervention within the target vessel with in-stent stenosis or thrombosis to achieve patency (constitutes failure on the primary endpoint)
Rate of intervention of extremity (RIE)	Re-intervention of a non-target lesion venous segment of the ipsilateral (target) extremity required to maintain ipsilateral extremity venous outflow (does NOT constitute failure of the primary endpoint)
In-stent stenosis (primary endpoint)	Non-occlusive reduction in the treated segment lumen diameter more than 50% from the post-procedural vessel lumen diameter per venogram or DUS
In-stent thrombosis (primary endpoint)	Occlusion of the stented target vessel due to thrombosis; early thrombosis is that which occurs ≤30 days; late thrombosis is that which occurs >30 days
Structural integrity	Absence of the following changes in stent morphology: • Pinching, defined as focal compression of the stent with >50% diameter reduction of the stent • Kinking, defined as >50% diameter reduction of the stent with the stent doubling or bending on itself • Recoil, defined a poor radial resistance to diffuse collapse, which results in >50% diameter reduction of the stent (i.e., stent diameters obtained throughout the study period as compared to the final stent diameter after insertion measured by DUS or venogram) • Fracture(s) as defined in Appendix 3

2 PROTOCOL SUMMARY

Study Title	VIRTUS: Safety and Efficacy of the Veniti Vici® Venous Stent System (Veniti, Inc.) when Used to Treat Clinically Significant Chronic Non-malignant Obstruction of the Iliofemoral Venous Segment
Study Device	Veniti Vici Venous Stent System
Regulatory Status	The Veniti Vici Venous Stent System has the CE mark. In the United States, the Veniti Vici Venous Stent System will be studied under an Investigational Device Exemption (IDE), upon approval/conditional approval of an IDE submission.
Study Objective	The objective of this study is to assess the safety and efficacy of the Veniti Vici Venous Stent System in achieving patency of the target venous lesion in patients who present with clinically significant chronic non-malignant obstruction of the iliofemoral venous outflow tract.
Study Design	Prospective, multicenter, single arm, non-randomized study to define safety and efficacy of the Veniti Vici Venous Stent System in relation to pre-defined Objective Performance goals.
Patient Population	A maximum of 200 patients at 45 centers worldwide will be enrolled. Thirty (30) feasibility patients will be enrolled at approximately 7-10 centers and 170 pivotal patients will be enrolled at approximately 45 centers worldwide. Both the feasibility and the pivotal patient populations will include symptomatic adults ≥18 years of age with clinically significant chronic non-malignant obstruction of the iliofemoral venous outflow tract.
Number of Centers	There will be up to 45 centers worldwide. Approximately 7-10 of these centers are anticipated to be in the European Union.
Inclusion Criteria – Pre Procedural	1. Age ≥18 years 2. Willing and capable of complying with all follow-up evaluations at the specified times 3. Able and willing to provide written informed consent prior to study specific procedures 4. Presence of unilateral, clinically significant, chronic non-malignant obstruction of the common femoral vein, external iliac vein, common iliac vein, or any combination thereof, defined as a ≥50% reduction in target vessel lumen diameter (to be measured by venogram during procedure, per Exclusion 25).

	5. Clinically significant venous obstruction defined as meeting at least one of the following clinical indicators: • Clinical severity class of CEAP classification ≥3 (See Appendix 4.) • VCSS Pain Score ≥2 (See Appendix 7.) 6. Negative pregnancy test in females of child-bearing potential 7. Intention to stent the target lesion only with the Veniti Vici Venous Stent
Exclusion Criteria – Pre-Procedural	8. Presence or history of clinically significant pulmonary emboli within 6 months prior to enrollment. 9. Venous obstruction that extends into the inferior vena cava 10. Contralateral disease of the common femoral vein, external iliac vein, common iliac vein, or any combination thereof with planned treatment within 30 days after subject enrollment 11. Life expectancy <12 months 12. Female of childbearing potential who is pregnant or plans to become pregnant during the duration of the clinical study 13. A. Uncontrolled or active coagulopathy OR B. Known uncorrectable bleeding diathesis with the following definitions: • Uncorrected INR ≥2.0 or aPTT ≥1.5 X normal local lab value • Platelet count <80,000 14. Uncorrected hemoglobin of ≤9 g/dL 15. Patients with an estimated glomerular filtration rate (eGFR) <30 mL/min. In patients with diabetes mellitus, eGFR <45 mL/min. 16. Known hypersensitivity to nickel or titanium 17. Contrast agent allergy that cannot be managed adequately with pre-medication 18. Intended concurrent thrombolysis or thrombectomy procedure OR intended or planned (within 30 days) adjuvant procedure such as creation of temporary AV fistula,

	placement of IVC filter, endovenectomy or saphenous vein ablation 19. Current or recent (within 30 days) active participation in another drug or device clinical trial (Participation in observational studies is acceptable.) 20. Patient judged to be a poor candidate by the primary investigator 21. Patients who have had any prior surgical or endovascular intervention of the target vessel Note: Patients who have had catheter-directed or mechanical thrombolysis in the target vessel for DVT at least 3 month (90 days) prior to the VIRTUS index procedure may be included in the trial.
Exclusion Criteria – Intra-Procedural	22. Patients in whom the lesions cannot be traversed with a guide wire. These patients will not count against the study sample size. 23. Patients where the obstruction extends into the inferior vena cava or below the level of the lesser trochanter. These patients will not count against the study sample size. 24. Patients whose vein diameters are not within limits stated in current Instructions for Use as determined by venogram. These patients will not count against the study sample size. 25. Patients who do not meet the venogram binary stenosis definition above, as determined by the treating physician. These patients will not count against the study sample size.
Follow-Up	The follow-up period is 60 months. The 12-month data from at least 156 patients will be submitted to FDA to support a Pre-Market Approval (PMA) application.
Primary Efficacy Endpoint	The primary efficacy endpoint for this study will be the primary patency rate at 12 months post-intervention, defined as freedom from occlusion by thrombosis AND freedom from surgical or endovascular intervention on target vessel which are found to have re-stenosis or stent occlusion to maintain patency AND freedom from in-stent stenosis more than 50% by venogram. For patients refusing the venographic assessment at 12 months, DUS-determined patency will be used instead.
Primary Safety	The primary safety endpoint for this study will be a composite endpoint of any major adverse event within 30 days, as adjudicated

Endpoint	by a Clinical Events Committee. Major Adverse Events are listed in Section 11.1.4.
Secondary Efficacy Endpoint	The formal secondary endpoint for this study will be a binary response variable based on an improvement in VCSS by at least 50% at 12 months post-intervention.
Ancillary Analyses	<u>Procedural Endpoints</u> • *Procedural technical success*, defined as achievement of a final residual diameter stenosis of ≤50% as measured by venogram without skipped lesion areas with placement of the study device alone with or without post-stenting balloon dilation • *Lesion success* defined as achievement of ≤50% residual diameter stenosis using any percutaneous method (including use of non-study devices) • *Procedural success* defined as procedural technical success without the occurrence of major adverse event between the index procedure and discharge

Ancillary Analyses (continued)	*Late technical success* (through 12 months) defined as:
	• Absence of migration
	• Absence of stent embolization
	• Achievement of primary patency
	• Structural integrity, defined as the absence of:
	  • Pinching, defined as focal compression of the stent with > 50% diameter reduction of the stent
	  • Kinking, defined as >50% diameter reduction of the stent with the stent doubling or bending on itself
	  • Recoil, defined a poor radial resistance to diffuse collapse, which results in >50% diameter reduction of the stent (i.e., stent diameters obtained throughout the study period as compared to the final stent diameter after insertion measured by DUS or venogram).
	  • Fracture(s)
	  Fractures will be assessed as per Jaff, et al.[1] (See Appendix 3.) Data to be collected for each fracture identified includes:
	  ○ Limb (right or left)
	  ○ Venous segment(s) where fractures are located
	  ○ Overlapping versus non-overlapping
	  ○ Type of fracture (Type I, II, III, IV)

	• Subgroup analysis to evaluate device performance across genders.

3 KEY ROLES AND STUDY CONTACTS

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4 INTRODUCTION

4.1 Etiology and Pathophysiology of Venous Disease

Chronic venous disorders (CVD) have a significant social and economic cost, impacting an estimated 50% of Western populations, and consuming an estimated 2-3% of healthcare budgets.[2] Although CVD is recognized to have several contributing pathophysiological factors, the main emphasis has for decades been on valve incompetence with reflux. Other aspects, such as obstruction to the outflow, a poor calf muscle pump, low compliance and geometrical changes of the flow channels were largely ignored. Endovascular treatment of iliofemoral venous outflow obstruction, introduced in the 1990s, has shown that obstruction of this anatomical site plays an important role in the clinical expression of CVD, particularly pain and ulcer development.[3,4] Chronic obstruction of the iliofemoral vein (common iliac, external iliac and common femoral veins) often results in severe symptoms (venous claudication[5], extensive edema, skin changes, limb ulcer[6,7,8], disability[9] and decreased quality of life)[10,11]. It has been shown that, following a conservatively treated DVT of the iliofemoral vein segment, there is remaining, variable obstruction in approximately 80% of patients.[6] Additionally, the recurrence rate of DVT is increased 2.4 times[12], and the risk of developing post-thrombotic symptoms is increased 3.4 times.[13]Over a 5-year period, chronic venous obstruction results in venous claudication[5] in 15-44% of patients, with 15% developing venous ulcers.[4,5,6] Although the initiating cause can be either simple anatomic compression of the iliac vein or chronic post-thrombotic disease, chronic venous obstruction frequently leads to thrombotic events regardless of the inciting index event.

4.2 Benefits and Risks of Venous Stenting

Percutaneous stenting of the iliofemoral venous outflow system has developed over the past decade as the "method of choice" to manage chronic venous obstruction. The procedure can be performed with low morbidity, no mortality, long-term high patency rate, and low rate of in-stent restenosis. It has replaced bypass surgery as the primary treatment. In 2007, the American Venous Forum stated that "iliocaval venoplasty and stenting has emerged as the 'method of choice' in relieving proximal iliofemoral obstruction". In 2011, the American Heart Association, in its recommendation on the management of iliofemoral deep venous thrombosis, stated that, "The placement of iliac vein stents to reduce post-thrombotic syndrome (PTS) symptoms and heal venous ulcers in patients with advanced PTS and iliac vein obstruction is reasonable" (Class IIa; Level of Evidence C)[14]. Moreover, Guidelines of the European Society of Vascular Surgery (to be published in 2014) state that "Clinically relevant central venous obstruction or stenosis might be eligible for interventional treatment with a self-expandable stent with a sufficient large diameter" (Class I; Level of evidence B).

Prior conservative therapies, such as chronic extended anticoagulation and compression, have been shown to be ineffective. Surgical bypass procedures are invasive with significant complication rate and have been exclusively performed as an end-stage procedure in the most severely compromised patients. Today open surgery is offered only to surgically fit patients with severe symptoms after unsuccessful or failed stenting.[15] There are no, randomized or multicenter studies on venous stenting, but multiple single center large (over 50 patients) registries cohort studies [9 16 17 18] have reported technical success rates superior to 90% and patency rates of 79-98% at 5 years.[18] It is difficult to determine the exact expected patency rates from these studies, as these studies included different etiologies, extent of the disease, concomitant reflux and clinical status, typically do not state the degree of obstruction prior to procedure, have variability in inflow to the stent system and often base the definition of patency on duplex-scan. (There is no reported comparison between duplex ultrasound scanning and venography in the assessment of stent patency. Venography is, therefore, still considered the gold standard.) However, given the very high rate of recurrence of thrombotic disease or clinical deterioration after non-stenting approaches, even a patency rate of 50-60% would offer significant improvement over current approved therapy.

The data available indicate that stenting for chronic obstructive iliofemoral lesions comes with a very low risk. So far, in the published literature, neither death nor pulmonary embolism nor life-threatening complications have occurred. In the largest single-center report on 953 stented limbs with ultrasound guided venous access[16], there were only four access-related adverse events: three femoral artery pseudoaneurysms treated with thrombin injection alone, and one arteriovenous fistula[5]. In addition to the access complications, there was one case where the guidewire became trapped in the stent and the stent/guidewire was removed via a cutdown of the femoral vein. In this large series, there were 47 thrombotic events that occurred over a 5-year period (5%).

The benefits to patients with a decompression of the lower limb after stenting such as alleviation of clinical symptoms, improvement of quality of life and less venous disability, far outweigh the potential risks associated with the stenting procedure. The results of clinical reports demonstrate the safety and potential benefits of vascular stents as a treatment of adults with symptomatic CVD and venous outflow obstruction.

4.3 Assessment of Current Venous Stents

All stents used in the venous system in the United States currently are used off-label. In Europe, there are available stents developed for placement in the venous outflow, however, none have undergone rigorous assessment of efficacy or safety for use in the venous system. The stent most commonly used in the iliofemoral venous outflow system is the Wallstent Stent (Boston Scientific, Minneapolis, MN), with well-recognized deficiencies. This stent,

designed for use in the arterial system, has moderate radial force and is subject to significant foreshortening during its deployment (40%) with balloon dilation, leading to problems with lesion coverage or separation of contiguous stents. Stents specifically designed for the unique environment of the venous system need to be tested in controlled and scientific prospective studies. There are no randomized multicenter studies on venous stenting. The difficulty is to find an adequate control group. The natural alternative to stenting would be to perform open invasive surgery. However, multiple studies reporting results of open bypass surgery of the outflow of the lower limb total only about 400 patients in the literature and show variable results often with poor bypass-related endpoints.[21] Already, thousands of patients have had percutaneous stent placement with uniformly better clinical and stent-related outcome than bypass surgery and adequate stent related follow-up with minimal morbidity.[22] It is generally considered that the surgical alternative in a randomized study is unethical due to the significant invasiveness and poorly documented outcome. Another alternative would be a comparison between stenting of the chronic venous outflow versus conservative treatment. However, the patients scheduled for stenting are those that already had optimal conservative treatment, which has failed. Thus, a carefully controlled prospective cohort study with well-defined inclusion criteria and critical clinical and stent-related follow-up needs to be performed showing no inferiority to results achieved in previous reports of less stringent studies.

5 INVESTIGATIONAL PRODUCT

5.1 Device Description

One such stent, designed specifically for use in the venous system, is the Veniti Vici Venous Stent System (Veniti, St. Louis, MO). The Vici Venous Stent System, manufactured by Veniti, is comprised of two components: the implantable prosthesis and the stent delivery system. The stent is a laser cut self-expanding stent composed of a nickel titanium alloy (nitinol). The stent has closed-cell segments and flexible interconnections designed specifically for use in venous anatomy. It is available in 60-, 90- and 120-mm lengths and 12-, 14- and 16-mm diameters. The delivery system is a coaxial design with an exterior shaft to protect and constrain the stent prior to deployment. The delivery system is an Over-The-Wire system compatible with 0.035 in. (0.89 mm) guidewires, and a 9French sheath introducer which allows delivery via either a jugular, femoral or popliteal vein approach.

The Veniti Vici Venous Stent System has the CE mark. In the United States, the Veniti Vici Venous Stent System will be studied under an Investigational Device Exemption (IDE), upon approval/conditional approval of an IDE submission.

5.2 Intended Use

The Veniti Vici Venous Stent System is intended for improving luminal diameter in the iliofemoral veins for the treatment of symptomatic venous outflow obstruction in symptomatic adult patients (age 18 and older).

6 POTENTIAL RISKS AND BENEFITS

6.1 Potential Risks

The potential risks of venous stenting are those associated with any intra-vascular procedure up to and including death, although at lower rates than those typically seen for arterial procedures.

- Access complications
  - Access bleeding or hematoma
  - Arterial or venous injury
  - Arterial pseudoaneurysm
  - Retroperitoneal hematoma
  - Pain
- Procedure related
  - Mis-deployment of the stent
  - Stent migration
  - Stent embolization
  - Thrombus formation (femoral vein, iliac vein, inferior vena cava)
  - Distant thrombo-embolism (pulmonary)
  - Pain
- Anticoagulation: although many of these patients are on long-term anticoagulation, those that are not may be required to be anticoagulated for a limited period of time; the risks of this study include bleeding related to anticoagulation. (See Appendix 2.)

6.2 Potential Benefits/Advantages of Treatment/Product

Prior therapies, such as chronic anticoagulation or surgical bypass procedures, are either ineffective, or significantly invasive. The potential risks of venous stenting are those associated with any intra-vascular procedure up to and including death, although at lower rates than those typically seen for arterial procedures. With demonstrated primary patency rates of 60-90% through 12 months, and demonstrated serious adverse event rates of <1%, the benefits of the proposed study outweigh the potential risks.

Currently marketed venous stents have sufficient clinical data regarding their use in veins of the lower extremities and pelvis for the treatment of venous outflow obstruction in adults and their risk profiles are not known or considered to be different from the Veniti Vici Venous Stent.

7 STUDY OBJECTIVE AND DESIGN

The VIRTUS trial is a prospective, multicenter, single arm, non-randomized study to define safety and efficacy of the Veniti Vici Venous Stent System in relation to pre-defined Objective Performance goals. The objective of this study is to assess the safety and efficacy of the Veniti Vici Venous Stent System in achieving patency of the target venous lesion in patients who present with clinically significant chronic non-malignant occlusion of the iliofemoral venous outflow tract.

7.1 Primary Endpoint – Efficacy:

The primary efficacy endpoint for this study will be the primary patency rate at 12 months post-intervention, defined as freedom from occlusion by thrombosis AND freedom from surgical or endovascular intervention on target vessel which are found to have re-stenosis or stent occlusion to maintain patency AND freedom from in-stent stenosis more than 50% by venogram. For patients refusing the venographic assessment at 12 months, DUS-determined patency will be used instead.

7.2 Primary Endpoint – Safety:

The primary safety endpoint for this study will be a composite endpoint of any Major Adverse Event within 30 days, as adjudicated by a Clinical Events Committee. Major Adverse Events are listed in Section 11.1.4.

7.3 Secondary Endpoint – Efficacy:

The formal secondary endpoint of this study is a binary response variable based on whether or not a subject achieves at least 50% improvement on the Venous Clinical Severity Scoring (VCSS) scale at 12 months post-intervention.

7.4 Ancillary Outcomes:

Procedural Endpoints

1. *Procedural technical success*, defined as achievement of a final residual target vessel diameter stenosis of ≤50% as measured on the post-procedural venogram, without skipped lesion regions, with placement of the study device alone with or without post-stenting balloon dilation as needed
2. *Lesion success* defined as achievement of ≤50% residual diameter stenosis using any percutaneous method (including the use of non-study devices)
3. *Procedural success* defined as procedural technical success without the occurrence of major adverse event between the index procedure and discharge
4. *Late technical success* (through 12 months) defined as:
   a. Absence of migration
   b. Absence of stent embolization
   c. Achievement of primary patency
   d. Structural integrity, defined as the absence of:
      i. Pinching, defined as focal compression of the stent with > 50% diameter reduction of the stent

ii. Kinking, defined as >50% diameter reduction of the stent with the stent doubling or bending on itself
iii. Recoil, defined a poor radial resistance to diffuse collapse, which results in >50% diameter reduction of the stent (i.e., stent diameters obtained throughout the study period as compared to the final stent diameter after insertion measured by DUS or venogram).
iv. Absence of fractures, which will be assessed as per Jaff, et al.1 (See Appendix 3.) Data to be collected for each fracture identified includes:
Limb (right or left)
Venous segment(s) where fractures are located
Overlapping versus non-overlapping
Type of fracture (Type I, II, III, IV)

5. *Subgroup* analysis to evaluate device performance across genders.

Clinical Endpoints

6. Improvement in Venous Clinical Severity Scoring (VCSS) at 6 and 12 months
7. Improvements in Quality of Life (CIVIQ-2) at 12 months (See Appendix 5.)
8. Minor outcomes: complications occurring within 30 days of the procedure that do not meet the definition of an MAE, do not require hospitalization and do not delay discharge.

8 PATIENT POPULATION

A maximum of 200 patients at 45 centers worldwide will be enrolled. Thirty feasibility patients will be enrolled at approximately 7 – 10 centers and 170 pivotal patients will be enrolled at approximately 45 centers worldwide. A minimum of 114 pivotal patients will be enrolled at US centers.

The 12-month data from at least 156 evaluable pivotal patients, as well as detailed summary data on the 30 feasibility patients will be submitted to FDA to support a Pre-Market Approval (PMA) application.

Patients will include symptomatic adults ≥18 years of age with clinically significant chronic non-malignant obstruction of the iliofemoral venous outflow tract.

8.1 Initial DSMB Safety Evaluation

Thirty (30) patients will be enrolled at approximately 7 centers. These patients will not be included in the pivotal study population, but will be evaluated separately for the primary safety and efficacy endpoints as well as for all secondary endpoints. When these 30 patients have completed their 30-day follow-up, a Data Safety Monitoring Board (DSMB) will review the safety data and will determine if the study can proceed with enrollment of the pivotal population. The DSMB report will be submitted to FDA for reference.

8.2 Inclusion/Exclusion Criteria

Patients meeting all pre-procedural inclusion and exclusion criteria will have the study presented to them. Patients giving informed consent will complete protocol-required testing, undergo baseline evaluation, and undergo the protocol-defined determination of binary stenosis, as measured by venogram. Patients meeting the venogram binary stenosis definition, as determined by the treating physician, will undergo the protocol-defined stenting procedure and all protocol-defined follow-up visits.

8.2.1 Inclusion Criteria – Pre-Procedural Criteria

1. Age ≥18 years
2. Willing and capable of complying with all follow-up evaluations at the specified times
3. Able and willing to provide written informed consent prior to study specific procedures
4. Presence of unilateral, clinically significant, chronic non-malignant obstruction of the common femoral vein, external iliac vein, common iliac vein, or any combination thereof, defined as a ≥50% reduction in target vessel lumen diameter (to be measured by venogram during procedure, per Exclusion 25).
5. Clinically significant venous obstruction defined as meeting at least one of the following clinical indicators:
   - Clinical severity class of CEAP classification ≥3 (See Appendix 4.)
   - VCSS Pain Score ≥2 (See Appendix 7.)
6. Negative pregnancy test in females of child-bearing potential
7. Intention to stent the target lesion only with the Veniti Vici Venous Stent

8.2.2 Exclusion Criteria - Pre-Procedural Criteria

8. Presence or history of clinically significant pulmonary emboli within 6 months prior to enrollment.
9. Venous obstruction that extends into the inferior vena cava
10. Contralateral disease of the common femoral vein, external iliac vein, common iliac vein, or any combination thereof with planned treatment within 30 days after subject enrollment
11. Life expectancy <12 months
12. Female of childbearing potential who is pregnant or plans to become pregnant during the duration of the clinical study
13. A. Uncontrolled or active coagulopathy OR
    B. Known, uncorrectable bleeding diathesis with the following definitions:
    - Uncorrected INR ≥2.0 or aPTT ≥1.5 X normal local lab value
    - Platelet count <80,000
14. Uncorrected hemoglobin of ≤9 g/dL

15. Patients with an estimated glomerular filtration rate (eGFR) <30 mL/min. In patients with diabetes mellitus, eGFR <45 mL/min.
16. Known hypersensitivity to nickel or titanium
17. Contrast agent allergy that cannot be managed adequately with pre-medication
18. Intended concurrent thrombolysis or thrombectomy procedure OR intended or planned (within 30 days) adjuvant procedure such as creation of temporary AV fistula, placement of IVC filter, endovenectomy or saphenous vein ablation
19. Current or recent (within 30 days) active participation in another drug or device clinical trial (Participation in observational studies is acceptable.)
20. Patient judged to be a poor candidate by the primary investigator
21. Patients who have had any prior surgical or endovascular intervention of the target vessel
    Note: Patients who have had catheter-directed or mechanical thrombolysis in the target vessel for DVT at least 3 month (90 days) prior to the VIRTUS index procedure may be included in the trial.

8.2.3 Exclusion Criteria – Intra-procedural Criteria

22. Patients in whom the lesions cannot be traversed with a guide wire. These patients will not count against the study sample size.
23. Patients where the obstruction extends into the inferior vena cava or below the level of the lesser trochanter. These patients will not count against the study sample size.
24. Patients whose vein diameters are not within limits stated in current Instructions for Use as determined by venogram. These patients will not count against the study sample size.
25. Patients who do not meet the venogram binary stenosis definition above, as determined by the treating physician. These patients will not count against the study sample size.

9 STUDY PROCEDURES AND DATA COLLECTION

9.1 Patient Screening Procedure

Patients who have been diagnosed with chronic nonmalignant obstruction of the iliofemoral venous segment of either extremity will undergo screening to determine their appropriateness for inclusion in the study.

- Patient medical history and physical examination
- Review of diagnostic investigations to ascertain diagnosis of chronic non-malignant venous obstruction (See Section 1.)
- The investigator must maintain detailed source documents on all patients who are enrolled or who undergo screening in the study. Investigators will maintain a screening log that must include at a minimum: screening date, enrollment status (enrolled/excluded) and the reason for exclusion for all screen failures.

9.2 Informed Consent

All patients who meet the pre-procedural inclusion criteria will have the study presented to them, as well as their family if possible. Patients must document consent to the study by signing the approved consent form. One copy of the informed consent will be placed in the patient's medical record, a second will be given to the patient or representative, and a third may be placed in the study records.

Patients that sign the informed consent will be considered enrolled in the study. These patients should also be entered into the electronic data capture (EDC) system and monitored for protocol deviations and adverse events until discharge from the hospital. Subjects that sign consent, but are found to not meet Inclusion/Exclusion criteria (i.e. screen failures) will not be included in the statistical analysis.

9.3 Baseline Evaluation (within 30 days of implant procedure)

Patients who sign an informed consent will undergo baseline testing:

- History and physical examination
- Laboratory evaluation (CBC and eGFR will be required for all patients; Patients on a Vitamin K antagonist or direct thrombin or Factor Xa inhibitors, prior to the intervention, require a PT with INR; subjects on heparin prior to the intervention require an aPTT. Patients with history of liver disease will require a PT with INR and an aPTT.)
- Medication review
- Pregnancy test in females of child-bearing age (within 48 hours of implant procedure)
- CEAP Assessment (See Appendix 4.)
- CIVIQ-2 Quality of Life questionnaire (See Appendix 5.)
- VAS pain score (See Appendix 6.)
- VCSS (See Appendix 7.)

9.4 Pre-Procedural Evaluation

Patients who consent, and who meet the pre-procedural inclusion and exclusion criteria, will undergo baseline venography to verify appropriateness for enrollment, as determined by the treating physician.

- Venography only to ascertain obstruction with at least a ≥50% in the target vessel lumen diameter compared to the normal vein lumen diameter immediately peripheral to the target lesion as measured by venogram. IVUS may not be used to fulfill this requirement.
- Absence of obstruction extending into the inferior vena cava (IVC) as determined by any imaging modality.

9.5 Venous Stent Implant Procedure

9.5.1 Procedure Guidelines

Patients who meet all of the inclusion and exclusion criteria will undergo the venous stenting procedure. During the venous stenting procedure, the current Veniti Vici Venous Stent System Instructions for Use will be followed.

- Patients will be monitored, per local institutional guidelines.
- Patients will receive appropriate sedation and anesthesia, per local institutional guidelines.
- Venography will be performed to determine sizing for venous stenting with the Veniti Vici Venous Stent System and to evaluate lesion characteristics.
- IVUS will be performed to confirm sizing for venous stenting with the Veniti Vici Venous Stenting System. Assessment of target lesion presence/absence, lesion severity (maximal binary stenosis), and lesion characteristics, per the case report form (location, length).
- Occluded veins will require guidewire recanalization before stenting.
- The lesion(s) must be adequately covered by the stent(s).
- If 2 or more stents are required to cover the target lesion, the stents will be overlapped by at least 1 cm to insure adequate stent cover without skipped areas.
- The diameter of the stent should be 2 mm greater than ("over") the measured diameter of the surrounding "normal" vessel. The stent should be at least 1 cm longer than the obstructive venous lesion (0.5 cm (peripherally) and 0.5 cm centrally. When selecting stent length, the expected foreshortening should be taken into account.

9.5.2 Perioperative Anticoagulation Regimen

- Patients on long-term warfarin therapy should be bridged prior to the intervention with LMWH or other anticoagulant per local institution guidelines, and will restart warfarin therapy within 24 hours.
- All patients will receive prophylactic LMWH or other anticoagulant prior to the intervention and following the procedure, per local institutional guidelines.
    - This applies to all patients, including those bridged, as described in Bullet 1 of Section 9.5.2 above.
- All patients should be appropriately anticoagulated during the procedure, per hospital protocol.
- SCD compression/early ambulation post-intervention will occur in all patients.

9.5.3 Post-Stent Placement Assessments

- Venography to assess post-procedural target vessel lumen diameter and to determine residual target lesion stenosis. This assessment will serve as the baseline for determining the primary efficacy

endpoint at the 12 month follow-up (or prior Interval Evaluation, when applicable). When venographic data is available at the 12 month visit, values from the venogram obtained at the Post-Stent Placement will serve as the subject's baseline.

- Adverse event assessment
- Extended Anticoagulation Protocol (See Appendix 2.)
  Anticoagulation or antiplatelet treatment for concomitant conditions should be continued at the discretion of the enrolling physician. Study patients should also receive anticoagulation or antiplatelet therapy, per the following guidelines. These guidelines apply through the 12 month visit.
  - Patients on extended Vitamin K antagonists or direct thrombin or Factor Xa inhibitors prior to enrollment should continue on warfarin post-procedure with a target INR of 2-3, or within the documented therapeutic range for INR per local guidelines.
  - Patients with a history of ≥2 thrombo-embolic event(s) and not on extended Vitamin K antagonists or direct thrombin or Factor Xa inhibitors prior to enrollment will be anticoagulated following the procedure and continue through the 12 month visit, as per ACCP guidelines[7] (Vitamin K antagonists such as warfarin to achieve an INR of 2-3 [or an INR within the documented therapeutic range for INR per local guidelines] or direct thrombin or Factor Xa inhibitors such as rivaroxaban per recommended dosing).
  - Patients with a history of <2 prior thrombo-embolic event OR patients with no history, but where the obstruction is determined to be caused by previous silent thrombotic event, will begin anticoagulation post-procedure and continue for 6 months in the case of non-occlusive obstruction (Vitamin K antagonists such as warfarin to achieve an INR of 2-3 [or an INR within the documented therapeutic range for INR per local guidelines], or direct thrombin or Factor Xa inhibitors such as rivaroxaban per recommended dosing). From 6 months through the 12 month visit, these patients should receive low-dose ASA.
    - Patients with occlusive obstruction should receive Vitamin K antagonists such as warfarin to achieve an INR of 2-3 (or an INR within the documented therapeutic range for INR per local guidelines), or direct thrombin or Factor Xa inhibitors such as rivaroxaban per recommended dosing through the 12 month visit.
  - Patients who were on clopidogrel or prasugrel pre-procedure will resume their baseline dose within 24 hours of the procedure and continue as required for the underlying condition UNLESS the enrolling physician believes that the

need for anticoagulation outweighs the need for anti-platelet drugs.
    - All patients not receiving anticoagulation therapy or anti-platelet therapy as noted above will receive low-dose ASA (i.e. 75 mg, 81mg, etc.) daily throughout the 12 month visit.
- IVUS to assess stent characteristics (apposition, webbing, coverage of target lesion, etc.)
- Physician evaluation of technical difficulty of implantation

9.6 Discharge or Three Days Post-Procedure (whichever comes first)

- Duplex ultrasound to determine post-procedural target vessel lumen diameter (For patients refusing the venographic assessment at 12 months [or prior Interval Evaluation, as applicable], DUS-determined patency will be used instead, with the DUS obtained at the Discharge or Three Days Post-Procedure visit serving as the baseline).
- Determination of discharge
- Anticoagulation Review, based on the Extended Anticoagulation Protocol (See Appendix 2.)
- Adverse event assessment
- Patients who do not meet intra-procedural inclusion criteria (and who do not receive the implanted study device) should be followed only through hospital discharge for protocol deviations and adverse events. This visit will conclude participation for these screen failed patients. These subjects will not be included in the statistical analysis.

9.7 1 Month Evaluation (30 days -7/+14 days)

- Physical examination (to assess for the presence of Adverse Events)
- Anticoagulation Review, based on the Extended Anticoagulation Protocol (See Appendix 2.)

9.8 6 Month Evaluation (180 days ± 30 days)

- Physical examination (to assess for the presence of Adverse Events)
- Duplex ultrasound (required only for first 30 patients to assess patency)
- CIVIQ-2 Quality of Life questionnaire (See Appendix 5.)
- VAS pain score
- VCSS (See Appendix 7.)
- Anticoagulation Review, based on the Extended Anticoagulation Protocol (See Appendix 2.)

9.9 12 Month Evaluation (365 days ± 60 days)

Patients that refuse the venogram and IVUS at this visit should have all other assessments listed here performed:

- Physical examination (to assess for the presence of Adverse Events)
- Assessment of primary patency by venography

- Determination of residual external venous segment compression, stent recoil, and lesion coverage by IVUS
- Duplex ultrasound for all patients (For patients refusing the venographic assessment at this visit, DUS-determined patency will be used towards the primary efficacy endpoint instead.)
- Assessment of stent integrity by bi-plane X-Ray (See Appendix 3.)
- CIVIQ-2 Quality of Life questionnaire (See Appendix 5.)
- VAS pain score (See Appendix 6.)
- VCSS (See Appendix 7.)
- Anticoagulation Review, based on the Extended Anticoagulation Protocol (See Appendix 2.)

9.10 Interval Evaluation

At any point following the venous stenting procedure, the patient may present with symptoms of clinically significant obstruction of the target vessel. Patients with possible obstruction should undergo all medical examinations and interventions as deemed appropriate for medical care. All technical examinations (DUS, IVUS, or venograms) obtained during the course of the evaluation will be submitted as part of the case report form and will be submitted to the Core Laboratory for determination of primary endpoint.

Patients who undergo re-intervention, but who are found on Core Laboratory assessment to have vessel patency prior to the re-intervention will not be counted as a primary efficacy endpoint failure. Patients who undergo an interval evaluation but do not receive an intervention will have their status (patency/non-patency) determined by the Core Laboratory. Patients who are found to be patent by Core Laboratory analysis will continue in the study through 12 months.

Patients who undergo another intervention at any time prior to the 12 month evaluation, or who are found to have in-stent stenosis > 50%, by Core Laboratory assessment, will be considered to have failed the primary efficacy endpoint and will not be required to have further assessment of vessel patency or other secondary endpoints.

All patients will complete the 30-day safety assessment regardless of primary patency status.

9.11 24 Month Evaluation (730 days ± 90 days)

- Telephone follow-up for SAE assessment. May be performed in-person, at the discretion of the investigator.
- Duplex ultrasound to assess vessel patency. (Office or laboratory visit)

9.12 36 Month Evaluation (1,095 days ± 90 days)

- Telephone follow-up for SAE assessment. May be performed in-person, at the discretion of the investigator.
- Duplex ultrasound to assess vessel patency. (Office or laboratory visit)

9.13 48 Month Evaluation (1,460 days ± 90 days)

- Telephone follow-up for SAE assessment. May be performed in-person, at the discretion of the investigator.

9.14 60 Month Evaluation (1,825 days ± 90 days)

- Telephone follow-up for SAE assessment. May be performed in-person, at the discretion of the investigator.

10 SUMMARY OF PROCEDURES

Visit (window)	Description	Screening	Baseline Evaluation (30 days from implant)	Implant Procedure (Day 0)	Post-stent placement assessment	Discharge or 3 days post-procedure[a]	1 Month Evaluation (30 days -7/+14 days)	6 Month Evaluation (180 ±30 days)	12 Month Evaluation (365 ±60 days)	24 and 36 Month Evaluation (±90 days)	48 and 60 Month Evaluation (±90 days)	Interval Evaluation[b]
Assessment of Inclusion and Exclusion Criteria	Medical records	X	X	X[c]								
Informed Consent	IC		X[d]									
Assessment of baseline characteristics	H&P, labs, CEAP		X				Physical Exam Only	Physical Exam Only	Physical Exam Only			Physical Exam
Duplex Ultrasound	DUS					X		X[e]	X	X[i]		X
Venogram	VG			X	X				X[h]			X
IVUS	IVUS			X	X				X			X
AE Assessment				X	X	X	X	X	X			X
SAE Assessment										X[i]	X[j]	
Anticoagulation Regimen				X		X	X	X	X			X
Pregnancy Test (women of child bearing years)			X[f]									
CIVIQ-2			X					X	X			
VAS			X					X	X			
VCSS			X					X	X			
Biplane X-ray[g]									X			

a: Discharge or 3 days post-procedure, whichever comes first
b: Performed if patients present with symptoms of clinically significant obstruction of the target vessel. (See Section 9.10.)
c: Evaluate intra-procedural exclusion criteria prior to implant (See Section 8.2.3.)
d: Informed consent may be collected before or at the Baseline Evaluation visit.
e: Required only for the first 30 study patients to assess patency
f. Pregnancy test in females of child-bearing age must be collected within 48 hours of implant procedure
g: To assess stent integrity.
h: To assess primary patency
i: To assess patency
j: SAE Assessment may be performed via telephone.

11 ADVERSE EVENTS

11.1 Event Definitions

11.1.1 Adverse Event

All Adverse Event (AE) data will be collected and recorded on the Adverse Event Form. At each evaluation, the Investigator or Investigator's designee will determine whether an AE has occurred.

An AE will be defined as any untoward medical occurrence in a subject that does not necessarily have a causal relationship with the investigational treatment. This will include any new undesirable experience (signs, symptoms, illness or other medical event), or worsening of a pre-existing condition. An AE may or may not be related to the medical (investigational) product.

If a pre-existing condition (any clinically significant abnormality) is present at the start of the study, it must be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the Investigational Plan-defined surveillance.

Alterations in laboratory parameters will not be considered AEs unless such alteration is qualified as medical condition. For example, decrease in hemoglobin will not be considered an AE unless it meets the definition of anemia.

11.1.2 Serious Adverse Event

All **serious adverse events** (SAEs) must be reported immediately to the Sponsor or Sponsor Designee. For the purposes of this Investigational Plan, when an AE or complication meets the definition for a SAE as noted below, it will be considered as such and reported within ***24 hours*** of becoming aware of the event to the Sponsor or Sponsor's designee. These events may also need to be reported per requirements of the reviewing EC.

Serious Adverse Events are defined according ISO 14155 and are adverse events that:

1. Led to death
2. Led to a serious deterioration in the health of a patient that:
    a. Resulted in a life-threatening illness or injury
    b. Resulted in a permanent impairment of a body structure or a body function
    c. Required in-patient hospitalization or prolonged hospitalization
    d. Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function
3. Resulted in fetal distress, fetal death or a congenital abnormality or birth defect

11.1.3 Device Deficiency

Device deficiency is inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

In addition to reporting qualifying event(s) (as described above) the study Investigator and Sponsor must each determine (in writing) whether device deficiency could have led to a serious adverse device effect (see definition below) if:

a. suitable action had not been taken or
b. intervention had not been made or
c. if circumstances had been less fortunate.

11.1.4 Major Adverse Event (MAE)

All **major adverse events (MAEs)** must be reported within 24 hours of knowledge of the event to the Sponsor or Sponsor Designee. A subcategory of SAEs include any of the following primary safety endpoints occurring within 30 days of the study procedure:

- Device or procedure-related death
- Device or procedure-related bleeding at the target vessel and/or the target lesion or at the access site requiring surgical or endovascular intervention or blood transfusion ≥2 units
- Device or procedure-related arterial or venous injury occurring in the target vessel segment and/or target lesion location or at the access site requiring surgical or endovascular intervention
- Device or procedure related acute DVT outside of the target vein segment
- Clinically significant pulmonary embolism defined as being symptomatic with chest pain, hemoptysis, dyspnea, hypoxia etc… AND be documented on CT
- Embolization of stent

These events may also need to be reported per requirements of the reviewing EC.

11.1.5 Adverse Device Effects (ADE)

Adverse event related to the use of an investigational medical device. This includes any event resulting from: insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

11.1.6 Serious Adverse Device Effects (SADE)

ADE that has resulted in any of the consequences and characteristic of a SAE.

11.1.7 Unanticipated Serious Adverse Device Effects (USADE)

SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

11.2 Reporting of Adverse Events

The event is considered to be reported to the Sponsor once the site completes an AE eCRF in electronic data capture (EDC) system.

The information provided for each AE on Adverse Event eCRF must include:

- Description of the event
- Date of event onset
- Date of event outcome
- Date of discovery by site
- Seriousness of the event (e.g., SAE vs. non-SAE)
- Severity of the event
- Relationship of the event to the study procedure, study device
- Actions taken as a result of the event
- Outcome of the event

Every effort should be made to gather as much information as possible regarding reporting serious or unanticipated event within 24 hours. As additional information regarding reporting event becomes available, it should be entered in EDC and source documents should be sent to the Sponsor or Sponsor's designee.

11.3 Relatedness to the Study Procedure, Study Device

Relationship Assignment: Relationship assessment of AEs to the study procedure, study device will be made by the Investigator using the following definitions:

Definitely Related
The clinical event occurs in a plausible time relationship to study procedure/study device and cannot be explained by any concurrent disease or other devices, drugs or chemicals.

Probably Related
The clinical event occurs within a reasonable time sequence to study procedure/study device and the possibilities of factors other than the study procedure/study such as concurrent disease or other devices, drugs or chemicals can be probably excluded.

Possibly Related
The clinical event occurs within a reasonable time sequence to study procedure/study device and there is some evidence to "possibly" suggest a causal relationship. However, the influence of other factors such as underlying disease, concomitant medications, or concurrent treatment may have contributed to the event.

Not related
The clinical event is completely independent of study procedure/study device and/or evidence exists that the event is definitely related to another etiology.

11.4 Reporting a Death

If a site becomes aware of a subject's death, phone or electronic notification to the Sponsor or Sponsor's designee is expected within 24 hours of site learning of the death. Completed appropriate CRF(s) should be submitted to the sponsor within 48 hours of learning of the event.

In addition, the following materials must be submitted to the Sponsor or Sponsor's designee as soon as possible:

- A copy of the subject's death certificate.
- Any additional requested information if available (e.g., hospital records and autopsy reports).

11.5 Protocol Deviations

Each Investigator should conduct the study in compliance with the Study Protocol. Any deviation from the Study Protocol will be documented on appropriate CRFs by explaining the deviation and corrective actions taken to prevent possible re-occurring deviations. Any emergency deviations (deviations from the study protocol to protect the life or physical wellbeing of a subject) must also be reported to the Sponsor within 48 hours and the site EC per their local guidelines.

11.6 Device Malfunctions

A device malfunction is defined as any inadequate performance of the study device when used per the most current IFU. Each device malfunction will be reported on the appropriate CRF by the site. Every effort must be made by the site to return the suspected device to the Sponsor for analysis. All device performance issues/malfunctions will be reported in the clinical results (e.g., final report). Device malfunction by itself should not be reported as AE unless it led to the new medical condition or worsening of pre-existing condition or met the definition of an Adverse Device Effect in Section 11.1.5.

12 CLINICAL EVENTS COMMITTEE (CEC)

The purpose of the CEC is to complete unbiased reviews and classification of adverse events. The CEC will consist of physicians who are not Investigators in the Veniti Trial and who do not have any significant investment in Sponsor's or any of their entities. Committee membership will be limited to the specialties of interventional cardiology, vascular surgery, or interventional radiology.

13 DATA SAFETY MONITORING BOARD (DSMB)

The purpose of the DSMB committee is to complete unbiased review of all safety data in comparison to the established criteria in order to determine if the rate of SAEs is acceptable, to evaluate interim data analysis results, to provide related advice on study

management and progress, and to make any recommendations regarding the study protocol. Members of the DSMB will be comprised of a multidisciplinary group of physicians and a biostatistician, they will not be employees or shareholders of Veniti, Inc., and they will not be participating VIRTUS Investigators.

The DSMB will be responsible to communicate any safety, scientific concerns, or other perceived concerns to Veniti or Veniti's designee as soon as possible. The DSMB will provide, after each scheduled meeting, written recommendation regarding the continuation of the trial, early stopping, or any suggested changes for the conduct of the trial. Veniti is responsible for informing the IEC if the DSMB has advised them of any major safety concerns and has recommended the study be stopped or if they have made any recommendations to alter the study.

DSMB decisions are final and non-negotiable by the sites.

14 INVESTIGATIONAL DEVICE DISTRIBUTION AND TRACKING

Investigators are prohibited from providing an investigational device to any person not authorized to receive it (21 CFR 812.110(c)). Investigators must also maintain complete, current, and accurate records of the receipt, use, or disposition of investigational devices (21 CFR 812.140(a)(2)) that relate to:

- The type and quantity of the devices received at the site, dates of receipt, and lot numbers (or other reference numbers) for each received device,
- The type and quantity of the devices received returned to the Sponsor or disposed at the site,
- Name of person who received or dispose each device,
- Subject number(s) correlated to each used device.

Upon completion or termination of the study (or the Investigator's part of the study), or at the Sponsor's request, an Investigator is required to return to the Sponsor any remaining supply of the device or otherwise to dispose of the device as the Sponsor directs (21 CFR 812.110(e)).

15 STATISTICAL METHODS

15.1 Overview of Study Design

This study will be a single-arm trial compared to performance goals developed from the medical literature (See Section 15.5). Enrollment will be stratified according to etiology of disease. A total of 125 subjects (approximately 74% of enrollees) enrolled in the pivotal arm will have obstruction associated with thromboembolic disease (post-thrombotic, PT). A total of 45 subjects (approximately 26% of enrollees) enrolled in the pivotal arm will have iliofemoral venous segment obstruction without previous thrombo-embolic disease without intraluminal disease (non-thrombotic, NT). The feasibility stage will aim to acrue approximately the same relative proportion of NT:PT subjects.

15.2 Missing Data

Every effort will be made to collect all data points in the study. The sponsor plans to minimize the amount of missing data by appropriate management of the prospective clinical trial, proper screening of study subjects, and training of participating investigators, monitors and study coordinators. The sponsor will provide a list of patients who do not complete the trial along with the best information available on why the each left the trial prematurely.

15.3 Primary Analysis: Per-protocol

All patient data that is available on subjects who drop out during the course of the study will be included. In the primary analysis of the primary endpoints, we will assume that data are missing at random (i.e., it is not the study treatment that is causing the data to be missing) and ignore missing values in the analyses.

15.3.1 Sensitivity Analyses: Worst-case and Tipping point

Supportive, sensitivity analyses will be performed to assess the impact of missing endpoint data. In the worst-case analysis, subjects with missing primary endpoints will be analyzed as failures with regard to that endpoint. For the primary efficacy endpoint, patients with missing data will be treated as clinical failures, i.e., re-stenosed or occluded stents. For the tipping-point analysis, the number of subjects with missing data required to be failures in order to reverse the trial conclusion will be determined.

15.4 Poolability Analysis

This study will be conducted such that 1) the same protocol will be used at each site; 2) site investigators and personnel will receive uniform training; and 3) central data management and monitoring will be applied with equal rigor at all sites. The diversity of settings will add to the scientific validity and generalizability of the findings.

Two types of poolability analyses will be performed to assess whether the data from the centers can be treated as one population: 1) on the patient demographic variables, and 2) on the endpoint data. Centers with fewer than 10 implants will be treated as a single center.

For the assessment of patient demographic variables, centers will be compared using a random-effects ANOVA for continuous variables such as age, or a random-effects logistic regression for categorical variables such as sex.

For the assessment of the primary endpoints, both of which are binary (Y/N or S/F) variables, a random-effects logistic regression will be used to assess the comparability of results across centers.

15.5 Development of the Performance Goal (PG) – Primary Efficacy Endpoint

15.5.1 Rationale

The FDA has indicated that venous stent trials should establish a performance goal to be met in the study, as described in Rocha-Singh et al.[8] In that article, the authors performed a literature search and identified 11 controlled studies of femoropopliteal stenting in *arterial* stenotic lesions where the patency rate of the control arm was described. The studies were all prospective, with clearly defined enrollment criteria and with pre-specified patency definitions (all using quantitative rather than qualitative criteria). Independent investigators performed the review of the anatomic endpoints in four of the five included studies (core laboratories).

The historical literature for venous stenting is considerably different. A total of 6 studies (See Table 15.5.2.a and Table 15.5.2.b) have been included in our review, all of which are retrospective, single arm, uncontrolled, and with variable populations. The endpoint of "primary patency" is qualitative in some studies, i.e., based on absence of symptoms in most cases, and quantitative in others, using an assessment of in-stent stenosis by an imaging modality such as venography or Doppler ultrasound (DUS). None of the studies used an outside, objective independent core laboratory assessment of pre-defined patency. Without independent core laboratory assessment of patency, there is an inherent, if subconscious bias to report higher patency rates, as authors are biased to report the best results possible.

Despite these issues, a clinical evaluation based on a performance goal is the best available approach in the absence of an already marketed comparator. These issues support a delta of 10% from the literature-based patency rate in the determination of the performance goal. This conclusion is supported by the variability in primary patency rates reported, ranging from 61%-80% (19% delta) for PT and 83-98% (15% delta) for NT patients (See Table 15.5.2a and Table 15.5.2b).

15.5.2 Historical Patency Rates

A literature search was performed to identify peer-reviewed articles with original data about patency rates at 12 months in patients with chronic venous obstruction who underwent iliofemoral stenting. Two separate searches were conducted: the first one had been done previously (10/9/2011) for company review; the second one was repeated July 31, 2013. Both searches used the terms listed below with limits of English, after 2000, and

- "human",
- "venous stenting"

- (("May-Thurner syndrome" OR "May Thurner syndrome") AND stent)
- "Iliac vein" AND stent
- (("venous occlusion" OR "venous insufficiency" OR "post-thrombotic syndrome" OR "venous thrombosis" OR "venous obstruction" OR "iliac vein compression syndrome" OR "iliofemoral vein" OR "iliocaval vein" OR "femoral vein") AND stent).

A total of 36 articles (31 in the original search, and 5 in the update search) were identified for further review, and 6 were included in development of the Performance Goal. Only papers that reported primary patency data at 12 months for adult patients who underwent stenting for chronic venous obstruction without adjuvant procedures were included.

The exclusion criteria for the articles we used for the historical control were based on our intended study population. Studies were excluded from the control if the study included:

- Patients who had thrombolysis, thrombectomy, or creation of an AV fistula during the index procedure, or other adjuvant procedures (endovenous laser ablation)
- Patients who did not have stenting of the iliofemoral tract
- Adolescents or pediatric patients
- Patients with acute venous thrombosis

A weighted average of qualitative patency, i.e., patients free from reintervention *and* free from occlusion (flow present on DUS) *and* free from ≥50% stenosis (per venogram or DUS lumen diameter) was created.

Table 15.5.2.a. NT Patients (no prior history of thromboembolic event)

Author, date	Limbs studied at 1 yr	≥50% stenosis N (%)	Limbs occluded	Quantitative patency rate	Limbs with quantitative patency
Meng, 2011[6]	143	1	2	(97.9%)	140
Neglén, 2007[5]	132	(1%)	(6%)	(93%)	123
Total	**275**			**(95.5%)**	**262.8**

Table 15.5.2 b. PT Patients (history of prior thromboembolic event)

Author, date	Limbs studied at 1 yr	≥50% stenosis N (%)	Limbs occluded	Qualitative patency rate	Limbs with qualitative patency
Rosales, 2009[9]	34[a]	Not eval		(75%)	25.5
Neglén, 2007[5]	135	(3%)	(17%)	(80%)	108
Kölbel, 2009[10]	40			(78)[b]	31.2
Wahlgren, 2010[11]	11	(1 pt, in PP)		(61%)[b]	6.7
Kurklinsky, 2011[12]	91	Not eval	(17%)	(81%)	73.7
Total	**311**			**(78.8%)**	245.1

a Patients were only studied if symptomatic.

b Authors made note of patients in the re-intervention group who had stenosis, so we concluded some evaluation of in-stent stenosis was included in assessment of primary patency. Possibly, it could represent only those patients with in-stent stenosis with symptoms.

In addition to these data, we used evidence from Neglén[3] and Neglén and Raju[13] that there are patients with greater than 50% restenosis who are asymptomatic, and therefore unlikely to be evaluated for flow under usual clinical practice. These studies estimated that approximately 3% of asymptomatic patients had re-stenoses of 50% or greater. Table 15.5.2.c shows this adjustment to the rates in Table 15.5.2.b. (This phenomenon was noted only in PT patients, hence no adjustments were made to Table 15.5.2.a.)

Table 15.5.2.c. Table 15.5.2.b Revised to Include In-stent Restenosis of 3%

Author, date	Limbs studied at 1 yr	≥50% stenosis N (%)	Limbs occluded	Quantitative patency rate	Limbs with quantitative patency
Rosales 2009[9]	34	(3%)		(72%)	24.5
Neglén 2007[5]	135	(3%)	(17%)	(80%)	108
Kölbel, 2009[10]	40			(78%)	31.2
Wahlgren 2010[11]	11	No chg		(61%)	6.7
Kurklinsky 2011[12]	91	(3%)	(19%)	(78%)	71
Total	**311**			**(77.9%)**	**242.1**

15.5.3 Enrollment in the VIRTUS Study

Historically, about 50% of patient reported in mixed series are patients without thrombotic history[5]. The mix of thrombotic and non-thrombotic obstruction in those with chronic venous insufficiency is not known (varies from zero to approximately 50%). At the present time,

we expect that approximately 74% (n=148 of our enrolled subjects will have a history of thrombo-embolic disease (i.e., be PT patients), and 26% (n=52) will not (i.e., be NT patients).

Though the specified hypothesis test and corresponding sample size calculation utilizes different performance goals for the PT and NT populations, Table 15.5.3 shows the combined patency rate in a control group adjusted to 74% PT and 26% NT patients. The overall or pooled patency rate is approximately 85%.

Table 15.5.3. Combined Estimates of Tables 15.5.2.a and 15.5.2.c.

Author, Date	Weight	Limbs studied at 1 yr	Quantitative patency rate
Non-thrombotic	.25	275	95.5%
Thrombotic	.75	311	77.9%
Total using Weights	**1.00**	**302**	**(85.3%)**

15.6 Hypotheses and Sample Size Estimate

The minimum required sample size is calculated based on the hypothesis-driven primary efficacy objective.

15.7 Primary Efficacy Endpoint

The minimum required sample size was determined using a Monte Carlo power simulation, conducted in R, testing the following hypothesis:

$$H_O: q_{NT} * (p_{NT} - PG_{NT}) + q_{PT} * (p_{PT} - PG_{PT}) \leq 0$$

$$H_A: q_{NT} * (p_{NT} - PG_{NT}) + q_{PT} * (p_{PT} - PG_{PT}) > 0,$$

where p_{NT} and p_{PT} are the observed 12-month patency rates for NT and PT subjects, respectively; PG_{NT} and PG_{PT} are pre-specified fixed performance goals for NT and PT subjects, respectively; and q_{NT} and q_{PT}, both are fixed weights for NT subjects (0.26) and PT subjects (0.74), respectively. The sample weights will not be adjusted based on actual enrollment rates.

The literature-based patency rate for the PT population is assumed to be 0.779, with corresponding performance goal (PG_{PT}) of 0.779 – 0.10 = 0.679. The literature-based patency rate for the NT population is assumed to be 0.955, with corresponding performance goal (PG_{NT}) of 0.955 – 0.10 = 0.855. Sample size is calculated to achieve at least 85% power at the one-sided 2.5% significance level:

Characteristic	Value
Performance Goal	PG_{PT} = 0.679; PG_{NT} = 0.855
Confidence level α	0.025, one-sided
Power 1-β	≥85%
Estimated Vici patency rates	p_{PT}T = 0.779; p_{NT} = 0.955
RESULT: Sample Size	**156 evaluable subjects**

The estimated power is 84% for the primary efficacy endpoint (Patients who have a non-patent lesion prior to 12 months can be included in the analysis whether or not they are still being followed at 12 months because the 12-month patency status of their lesion is known).

In addition to rejecting the above hypothesis, overall success of the trial will also be determined based on whether a) the observed patency rate in the PT group is greater than 0.679, AND b) the *observed* patency rate in the NT group is greater than 0.855.

15.7.1 Primary Safety Endpoint

None of the case series in the literature used pre-specified adverse event definitions. The complication rate appears to be low, but there are no controlled studies to indicate what a true adverse event rate might be under controlled reporting conditions. It is expected that the true rate of the pre-specified safety endpoint will be approximately 1%. The primary safety evaluation will test the following hypothesis:

$$H_O: P_{Vici} \leq 0.94$$

$$H_A: P_{Vici} > 0.94,$$

where P_{Vici} is the freedom from event rate of pre-specified safety events associated with use of the Veniti Vici Venous Stent and 0.94 is the pre-specified performance goal. The hypothesis will be tested under a one-sided, one-sample exact binomial test. The hypothesis will be tested at the 2.5% significance level, and approximately 170 subjects provide greater than 90% power. Power was calculated using PASS 2008 software.

15.7.2 Primary Secondary Endpoint

The primary secondary endpoint is the binary response variable based on achieving at least 50% improvement in VCSS. In a review of manuscripts by Hartung[14], Rosales[9], and Wahlgren[11], information on VCSS improvements are provided, as follows:

Hartung[14]: Median VCSS from 8.5 to 2 (n=44)
Rosales[9]: Median VCSS from 9 to 1 (n=27) in group 1; median VCSS from 21 to 7 (n=7)
Wahlgren[11]: Mean VCSS from 9.1 to 6 (n=15)

However, distributional information (variance, specifically) is not provided. There also exists no generally agreed upon or accepted definition of a clinically meaningful improvement in VCSS to establish a performance goal. Therefore, Veniti will test a hypothesis test based on 50% of subjects improving by at least 50% as a means to demonstrate clinical benefit with the Veniti Vici Venous Stent. The formal hypothesis test takes the form:

$$H_O: P_{Vici} \leq 0.50$$

$$H_A: P_{Vici} > 0.50,$$

where P_{Vici} is the proportion of subjects achieving at least 50% VCSS improvement (success rate), and 0.50 is the pre-specified performance goal. Based on the literature cited above, it is reasonable to assume a 62% success rate. Assuming this underlying rate of success, at least 156 evaluable subjects provides greater than 80% power to evaluate this objective at the 2.5% significance level under a one-sided, one-sample exact binomial test. Power was calculated using PASS 2008 software.

15.8 Evaluation of Endpoints

15.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this study will be the primary patency rate at 12 months post-intervention. Stented limbs will be assigned the status of ***patency failure*** if they are known to have a patency failure event:

- Thrombosis including the stented area of the vein
- Re-intervention including the stented area
- Venous imaging study at any time through 12 months showing a restenosis of greater than 50%.

Patients will be assigned the status of ***patency success*** if their venous imaging study at 12 months showed no greater than 50% restenosis (and no prior study showed greater than 50% restenosis).

In the per-protocol (PP) analysis, only patients that meet either of these two criteria will be included. Patients with no imaging study at 12 months and no patency failure event will be ignored in the analysis.

In the worst-case and tipping point analyses, all patients will be included. Patients who were ignored in the PP analysis will be treated as patency failures.

Both the PP and worst-case analyses will test the following hypotheses:

$$H_O: q_{NT} * (p_{NT} - PG_{NT}) + q_{PT} * (p_{PT} - PG_{PT}) \leq 0$$

$$H_A: q_{NT} * (p_{NT} - PG_{NT}) + q_{PT} * (p_{PT} - PG_{PT}) > 0,$$

where p_{NT} and p_{PT} are the observed 12-month patency rates for NT and PT subjects, respectively; PG_{NT} and PG_{PT} are pre-specified fixed performance goals for NT and PT subjects, respectively; and q_{NT} and q_{PT}, both are fixed weights for NT subjects (0.26) and PT subjects (0.74), respectively. The sample weights will not be adjusted based on actual enrollment rates.

The hypothesis test for this endpoint will be tested using a one-sided weighted Z-test at the 0.025 significance level. The test statistic for this hypothesis test is:

$$Z = \frac{q_{NT} * (p_{NT} - PG_{NT}) + q_{PT} * (p_{PT} - PG_{PT})}{\sqrt{{q_{NT}}^2 * \frac{PG_{NT}(1 - PG_{NT})}{n_{NT}} + {q_{PT}}^2 * \frac{PG_{PT}(1 - PG_{PT})}{n_{PT}}}}$$

where p_{NT} is the proportion of successes in the NT population, PG_{NT} is the performance goal of 85.5% for the NT population, q_{NT} is the pre-defined weight of 0.266 for the NT population, p_{PT} is the proportion of successes in the PT population, PG_{PT} is the performance goal of 67.9% for the PT population, q_{PT} is the pre-defined weight of 0.74 for the PT population.

The p-value for the one-sided hypothesis test will be calculated as $\Phi(-Z)$, where Φ is the normal cumulative distribution function.

15.8.2 Primary Safety Endpoint

The primary safety events are listed in Section 8.2. Patients who experience any of these events will be counted as safety failures in the analysis. Detailed summaries of reported events will be provided, including calculated rates of events and corresponding 95% confidence intervals. The following hypothesis test will be evaluated under a one-sample, one-sided exact binomial test at the 0.025 significance level:

$$H_O: P_{Vici} \leq 0.94$$

$$H_A: P_{Vici} > 0.94,$$

where P_{Vici} is the freedom from event rate of pre-specified safety events associated with use of the Veniti Vici Venous Stent System and 0.94 is the pre-specified performance goal.

15.8.3 Secondary Efficacy Endpoint

In order to control the overall type I error rate, the formal secondary efficacy endpoint will only be assessed if the primary endpoint objective is met. The secondary efficacy endpoint is a binary response variable based on achieving at least 50% improvement in VCSS. The following hypothesis test will be evaluated under a one-sample, one-sided exact binomial test at the 0.025 significance level:

$$H_O: P_{Vici} \leq 0.50$$

$$H_A: P_{Vici} > 0.50,$$

where P_{Vici} is the VCSS success rate, and 0.50 is the pre-specified performance goal.

15.9 Evaluation of Ancillary Endpoints

General Considerations
None of the evaluations of ancillary endpoints will include hypothesis tests. Instead, the mean or proportion of each will be estimated along with the 95% confidence interval (CI). Only the PP analysis will be performed on secondary endpoints (i.e., patients or limbs who contribute data will be included; those without data on a particular endpoint will be ignored).

15.9.1 Procedural Endpoints

Procedural technical success. The proportion of limbs with procedural technical success and the 95% CI will be reported.

Lesion success. The proportion of limbs with lesion success and the 95% CI will be reported.

Procedural success. The proportion of limbs with procedural success and the 95% CI will be reported.

Late technical success. The proportion of limbs with late technical success and the 95% CI will be reported.

Subgroup analysis. A subgroup analysis will be performed to evaluate device performance across genders.

15.9.2 Clinical Endpoints

Change in Venous Clinical Severity Scoring System (VCSS). Each limb's change VCSS will be calculated; the mean of the changes and its 95% CI will be reported.

Change in Quality of Life (CIVIQ-2). Each patient's area under the curve (AUC) will be calculated for the CIVIQ-2; the mean AUC and its 95% CI will be reported.

Minor outcomes. The proportion of patients with minor outcomes and the 95% CI will be reported.

16 CORE LAB ASSESSMENTS

16.1 Venogram Core Laboratory

A copy of all venographic studies collected in the study will be sent to the angiographic core laboratory for review. Venographic site assessment guidelines and shipping requirements will be provided by angiographic core lab (e.g., during the site training).

16.2 Duplex Ultrasound Core Laboratory

All duplex ultrasound examinations collected through the 36 month follow-up of the study will be sent to the duplex ultrasound core laboratory for review and assessment. Duplex assessment guidelines, technician training (if required), and data submitting guidelines will be provided by the duplex ultrasound core laboratory (e.g., during the site training).

Pre-enrollment DUS is considered an investigator-determined inclusion criterion, and does not require Core Laboratory confirmation.

16.3 IVUS Core Laboratory

All IVUS evaluations will be analyzed by the independent core laboratory.

17 INSTRUCTIONS FOR USE

See the Instructions for the Veniti Vici Venous Stent System.

18 INVESTIGATOR TRAINING

Investigators responsible for delivering the Veniti Vici Venous Stent will receive sufficient training to ensure competence in the execution of all aspects of the procedures required to deliver the Veniti Vici Venous Stent. Training may include hands on experience with demonstration devices, didactic presentations, or observing placement procedures performed by another physician and will include an extensive review of this study protocol and the Veniti Vici Venous Stent System Instructions for Use.

19 MONITORING PROCEDURES

19.1 Site Monitoring Plan

It is the responsibility of Veniti to ensure that proper monitoring of the investigation is conducted and that IRB/EC review and approval of the investigation is obtained. Monitoring visits will occur based on enrollment at the site, and at least annually. Adequately trained Veniti personnel or delegates appointed by the study sponsor will monitor in order to ensure that the investigation is conducted, recorded and reported in accordance with:

- The signed Investigator Responsibility Agreement

- The Investigational Plan
- Applicable laws and regulations
- Any requirements imposed by Veniti

All monitoring activities will be performed and/or supervised by the overall study manager, Karen Fraser, RN, MS, Senior Director of Clinical Affairs, Veniti. Monitoring will be planned periodically at the study site to assure compliance with the study protocol. The sponsor (or an appropriate designee) must therefore be allowed access to the patients' files as per the informed consent at the investigator's site when so requested. The monitoring visits may include but are not limited to the following:

19.2 Site Initiation Visit

Site Initiation visits will be conducted by Veniti personnel or delegates. The Veniti personnel or delegates will be responsible for the training of the investigators and other personnel. The Veniti personnel or delegates will review all documentation collected from the site and ensure that each site has met the regulatory requirements and has all the necessary documentation and training to begin the clinical study and assures that the Investigator/staff:

- Understands the investigational status of the device;
- Understands the Investigational Plan including the protocol, records and reports (as specified in section F);
- Understands the requirements for conducting a clinical study on medical devices;
- Submits the Investigational Plan and required supporting documentation to the study center's Institutional Review Board (IRB) or Ethics Committee (EC) for their review/approval;
- Submits all FDA and annual reports to their IRB/EC;
- Maintains all correspondence, the Investigational Plan, and all required records on file, and submits required reports in due time;
- Assumes responsibility for the investigation at his/her institution which may include supervision of some tasks.

19.3 Routine Monitoring

Routine monitoring visits are made periodically to assess the investigator's adherence to the Investigational Plan, IRB/EC review of study progress (if appropriate), maintenance of records and reports, continued acceptability of the facilities, and selected review of source documents to assess accuracy, completeness, legibility and omissions to the Case Report Forms. The monitors will acquire information to assess the progress of the study (toward meeting study objectives) and identify any concerns that stem from observation of device performance and/or review of the investigator's patient records, study management documents, device tracking and patient informed consent documents. Resolution of concerns and completion of assigned tasks may be documented by the monitors. Review of any ongoing findings may occur during monitoring visits.

19.4 Closeout Visit

Veniti personnel or delegates will schedule and conduct a Site Closeout Visit upon study or site closure. If the site has not enrolled any subjects in the study, the closeout visit can be done via phone. All investigational product will be returned to Veniti at the time of the closeout.

20 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE (IRB/EC)

The protocol, informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. In addition, any subject recruitment materials must be approved by the IRB/EC prior to use. This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice, ISO 14155-2011, and applicable regulatory requirements. The study must be conducted in accordance with the regulations of the United Stated Food and Drug Administration (FDA) as described in 21 CFR 50 and 56, applicable laws and the IRB requirements.

The sponsor must submit any change to the protocol to the IRB for review and approval before implementation. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the FDA and the reviewing IRB are notified within 5 working days.

It is the responsibility of the investigator to provide each subject with full and adequate verbal and written information, before inclusion in the study, using the IRB approved informed consent document, including the objective and procedures of the study and the possible risks involved. Informed consent must be obtained prior to performing any study-related procedures, including screening and changes in medications including any washout of medications. A copy of the signed informed consent document must be given to the study subject.

The investigators have been selected because of their medical qualifications, interest in participation, ability to conduct and document the results of the study, ability to accrue patients.

All investigators will provide their curriculum vitae to Veniti, Inc. and sign a Financial Disclosure and Investigator Agreement.

21 SUBJECTS' CONFIDENTIALITY

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The HIPAA regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the Investigator retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., fact whether the subject is alive) at the end of their scheduled study period.

All data used in the analysis and summary of this study will be anonymous. Access to subject files will be limited to authorized personnel involved in the study.

At time of enrollment, subjects will be assigned a trial-specific number identifier. This identifier will be used throughout the course of the study (instead of patient name, hospital ID, etc.) to ensure subjects confidentiality.

22 PUBLICATIONS

At the conclusion of all follow-up visits, a multi-site abstract reporting the preliminary results may be prepared and presented at a major endovascular meeting. A complete multi-center trial manuscript is the primary publication for the study. The publication of results from any single-site experience within the study must not be submitted for publication or presentation until a multi-center manuscript is published, unless otherwise approved by the Sponsor.

The Sponsor will establish a publication committee and policy. The committee membership may include the overall Principal Investigator, other investigators from the study, and representatives of Veniti (e.g. statistician, clinical research specialist, etc.). The committee will establish a publication strategy. The committee will be responsible for overseeing the development of any multi-site study manuscripts or abstracts. Any multi-site publications of study data must be reviewed and approved by at least two physician members of the publication committee prior to submission. Any previously unpublished information provided to the investigators by Veniti, such as patent applications, manufacturing processes and basic scientific data, is considered confidential and will remain the sole property of Veniti. The investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without Veniti's written consent.

In addition, all multi-site and single-site abstracts or manuscripts must be reviewed by Veniti prior to submission. Veniti will limit its review to a determination of whether or not confidential information is disclosed, and will not attempt to censor the data or conclusions made in the publication.

23 DATA MANAGEMENT

An electronic database capture (EDC) system (Mednet, Minneapolis, MN) will be used to record all subjects' data in the study. This secure EDC will be backed up regularly to ensure collected data storage. The server will be accessible by password for all approved users via the internet, and data analytical workstations will be used for data processing and management.

Conventional data verification sub-routines will be extensively programmed to test entry and logical errors, while all individual (subject-based) eCRFs will be linked for

cross-reference. Periodic analysis of each data field (across subjects) will be performed in order to examine the expected distributions of data, and to identify outliers for possible data mistakes. Corrections to data mistakes will be requested via queries.

All information and data concerning subjects or their participation in this study will be considered confidential. Only authorized personnel involved in the study will have access to these confidential files. As described in Section 21, each subject will be assigned unique identifier; therefore, all data used in the analysis and reporting of this evaluation will be without identifiable reference to the subject.

24 TERMINATION OF STUDY

Investigators will be notified by Veniti, Inc. of study termination for any reason. Investigators are required to submit all patient and study data in a timely manner and comply with Veniti, Inc.'s request regarding disposition of the outstanding investigational devices.

25 ADDITIONAL RECORDS AND REPORTS

25.1 Investigator Records

Records are subject to FDA inspection and must be retained for a period of two (2) years after the latter of the two dates:

- the date on which the investigation is terminated or completed; or
- the date that the records are no longer required for purposes of supporting an application to the FDA to market the device.
- the investigator is responsible for the preparation (review and signature) and retention of the records cited below.
- All correspondence which pertains to the investigation including required reports
- Device Disposition Record
- Screening Logs
- Subject's case history records, including:
- Signed Informed Consent document
- All relevant patient complaints
- Observations of adverse events
- Medical history
- All case report forms and supporting data
- Documentation of protocol deviations, including date(s) and reason(s) for deviation(s)
- Signed Protocol, Curriculum Vitae and Financial Disclosure (These must be submitted to Veniti and kept on file at the investigative center.)

25.2 Investigator Reports

The investigator is responsible for the preparation (review and/or signature) and submission of the reports cited in Table 25.2.1 as required by 21 CFR 812

Subpart G and sponsor. These are also subject to FDA inspection and the retention requirements described above for Investigator Records.

Table 25.2.1: Investigator Reports

REPORT TO	SUBMIT TO	DESCRIPTION/CONSTRAINTS
Unanticipated Adverse Device Effect	Monitor & IRB/EC	If an unforeseen complication is determined to be an unanticipated adverse device effect, then the investigator's report must be submitted within 10 working days after the investigator first learns of the effect.
Withdrawal of IRB/MEC Approval	Sponsor	The investigator must report a withdrawal of the reviewing IRB/MEC approval within 5 working days.
Progress Report	IRB/EC	The investigator must submit this report if the study lasts longer than one year.
Deviation from Investigational Plan	Sponsor & IRB/EC	If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects the deviation must be approved by Veniti, reviewing IRB/MEC, and the FDA. If the deviation does not affect these issues (study soundness, rights, safety, etc.) then only Veniti must approve it.
Failure to Obtain Informed Consent	Sponsor & IRB/EC	The Investigator must make notification within 5 working days after device use. The report must include a brief description of the circumstances justifying the failure to obtain informed consent and include written concurrence by a licensed physician not involved in the investigation.
Final Report	Sponsor & IRB/MEC	This report must be submitted within three months after termination or completion of the investigation.

Veniti Records

Veniti will maintain the following records and submit reports per Table 25.2.2:

1 All vital correspondence that pertains to the investigation including reports
2 Device Shipment/Disposition Record
3 Signed Protocol Cover Pages, Investigator Agreements Curriculum Vitae
4 IRB/EC Approval Letter
5 Adverse events and complaints
6 Case Report Forms
7 Clinical Investigation Plan
8 Monitoring Reports

Table 25.2.2: Veniti Reports

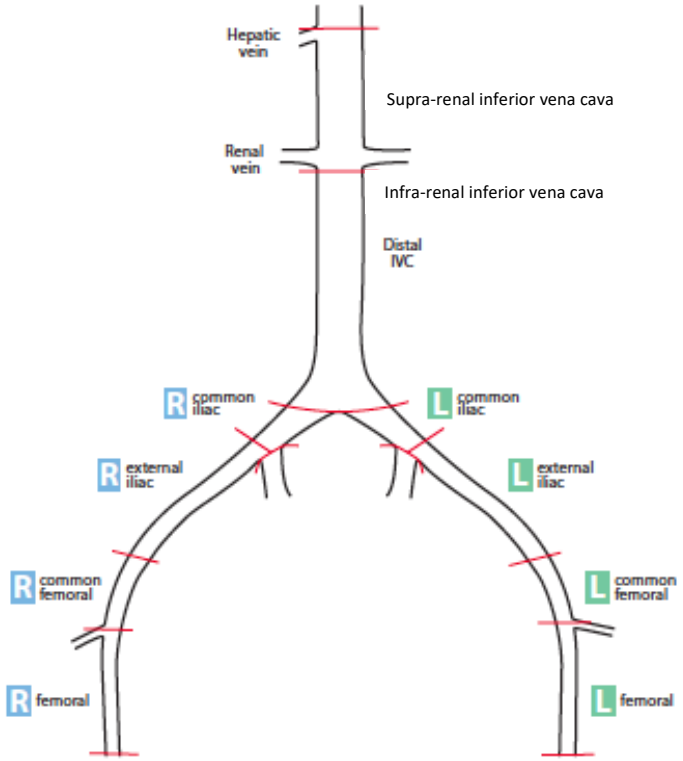
REPORT	SUBMIT TO	DESCRIPTION
Unanticipated Device Related Adverse Event	FDA, all IRBs/MECs and all Investigators	Veniti will report on any and all unanticipated device-related adverse event evaluation within 10 working days.
Withdrawal of IRB/MEC Approval	FDA, all IRBs/MECs and all Investigators	Notification will be made within 5 working days.
Withdrawal of FDA Approval	All IRBs/MECs and all Investigators	Notification will be made within 5 working days.
Current Investigator List	FDA	Veniti will submit a list of names and addresses of all participating investigators at 6 month intervals.
Progress Report	FDA, all IRBs/MECs and all Investigators	A progress report will be submitted at least yearly.
Recall and Disposition	FDA, all IRBs/MECs and all Investigators	Notification will be made within 30 working days and will include the reasons for any request that an investigator return, repair or otherwise dispose of any devices.
Final Report	FDA, all IRBs/MECs and all Investigators	Veniti will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted within 6 months after completion or termination.
Failure to Obtain Informed Consent	FDA/IRB/ MEC	A copy of the investigator's report will be submitted within 5 working days of notification.

25.3 IRB/EC Records

Each reviewing IRB/MEC must maintain the following records relating to the investigation:

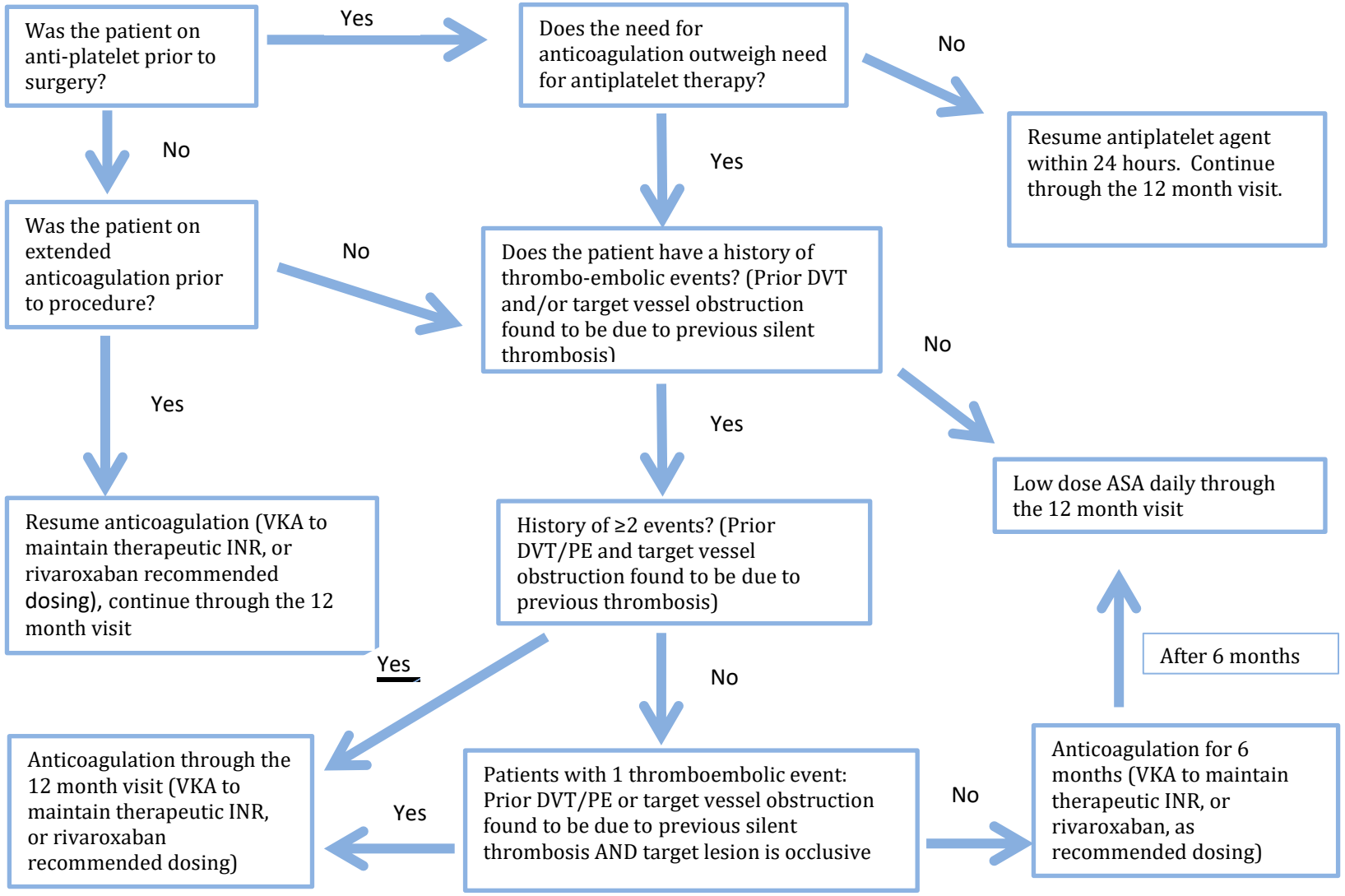
- Records of protocols and continuing review
- All pertinent correspondence between IRB and Investigator
- Statement of significant new finding provided to subjects
- All records of membership and affiliation
- Meeting minutes

26 APPENDIX 1: VENOUS ANATOMY DESIGNATIONS



- Supra-renal inferior vena cava
- Infra-renal inferior vena cava
- Left common iliac vein
- Left external iliac vein
- Left common femoral vein
- Left femoral vein
- Right common iliac vein
- Right external iliac vein
- Right common femoral vein
- Right femoral vein

27 APPENDIX 2: EXTENDED ANTICOAGULATION PROTOCOL

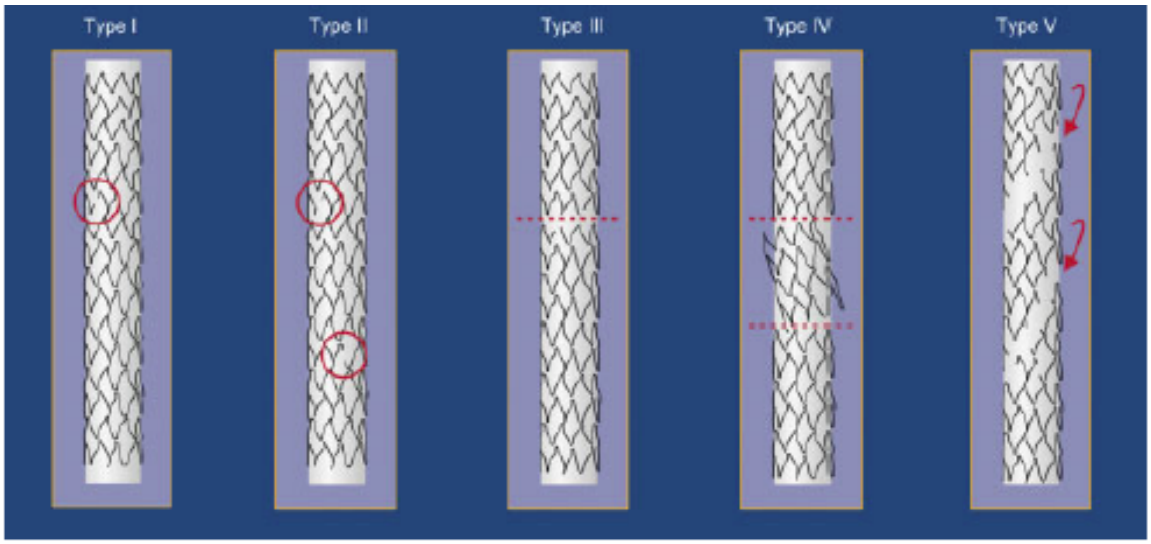


28 APPENDIX 3: FRACTURES

Assessment of the venous stents will be performed at 12 months, and at any interval evaluation, for analysis of strut fracture. High-resolution digital images should be obtained in a diagnostic X-Ray unit, or in an angiography suite (if performed as part of an interval evaluation). All images will be submitted to the Core Laboratory for assessment of strut fracture.

Fractures will be assessed as per Jaff, et al.[6] Data to be collected for each fracture identified includes:

- Limb (right or left)
- Venous segment(s) where fractures are located
- Overlapping versus non-overlapping
- Type of fracture (Type I, II, III, IV)



29 APPENDIX 4: ADDITIONAL STUDY DEFINITIONS

Allergic Reaction: A physical reaction to a substance that can cause wheezing, edema (swelling), induced thrombotic events, uticaria (rash), and/or shock.

Arterio-venous (AV) Fistula: A communication between an artery and a vein in which the arterial blood flows directly into a neighboring vein.

Bleeding: Blood loss resulting from the percutaneous interventional procedure or adjunctive drug therapy that may require transfusion of blood products.

Catheter-Directed pharmacologic thrombolysis: An image guided technique involving infusion of thrombolytic agents through a multi-side hole infusion catheter or wire placed directly into a venous thrombus through a remote puncture site.

CEAP Classification: A method for evaluating venous disease of the leg based on clinical, etiologic, anatomic, and pathophysiologic data.

Table 29.1: CEAP Classification of CVI

Class 0	No visible or palpable signs of venous disease (only symptoms)
Class 1	Telangiectasias or reticular veins
Class 2	Varicose veins
Class 3	Oedema
Class 4	Skin changes ascribed to venous disease (e.g. pigmentation, venous eczema, lipo-dermatosclerosis)
Class 5	Skin changes as defined above with healed ulceration
Class 6	Skin changes as defined above with active ulceration

Central: closer to the heart; antegrade to the flow

CIVIQ-2 (Chronic Venous Insufficiency Questionnaire): A self-administered questionnaire which explores four dimensions related to chronic lower limb venous insufficiency. The four dimensions are psychological, physical and social functioning and pain.[15]

Death: The termination of life.

Diabetes (History of): Defined as patients who have been diagnosed with either Type I or Type II diabetes and are currently taking oral hypoglycemics or insulin or have a hemoglobin A1C > 7%.

Discharge: The time point when the subject is released from the admitting hospital, transferred to another facility, or has expired.

Femoropopliteal DVT: A DVT involving the femoral or popliteal venous segments, or both without extension to the common femoral or iliac veins.

Fever: An increase in internal body temperature to levels that are above normal (37°C, 98.6°F).

Gastrointestinal (GI) bleeding: any bleeding that starts in the gastrointestinal tract, which may extend from the mouth to the anus.

Hematoma: Localized mass of extravasated blood ≥ 5 cm that prolongs hospitalization.

Hemorrhage: Bleeding requiring hospitalization, repeat procedure, operation or transfusion.

Hypertension: Increase in systolic blood pressure above 140 mm Hg or a diastolic blood pressure above 90 mm Hg.

Hypotension: Fall in systolic blood pressure that requires intravenous treatment with vasopressors or inotropic agents.

Iliofemoral DVT: DVT involving complete or partial thrombosis of the iliac vein or the common femoral vein, or both, with or without femoropopliteal DVT.

Index Procedure: The procedure in which the subject has the study procedure performed or attempted.

Infection: Inflammation caused by bacterial or viral sources, such as, urinary tract infection, puncture site infection, sepsis, endocarditis, and bacteremia from IV site.

Inflammation: An immunologic response to infection or trauma that can result in localized redness, swelling, heat, pain and dysfunction of the organs involved.

Invasive Assessment/Procedure: Any assessment, intervention or therapy that penetrates the skin, excluding administration of parenteral fluids or drugs.

Kidney Failure: Failure of the kidneys to perform essential functions that requires dialysis.

Myocardial Infarction (Non-Q wave): Post-treatment elevation of CK-MB more than 3 times the upper limit of lab normal value without evidence of pathologic Q-waves present on EKG. Elevated serum troponin levels are not sufficiently validated to be considered sole evidence of an MI in the absence of CK-MB elevations.

Myocardial Infarction (Q wave): Development/appearance of new pathological Q-waves in more than 2 contiguous leads per 12-lead electrocardiogram (EKG/ECG).

Peripheral: refers to a location away from the heart; retrograde to the flow

Physician-Directed Subject Withdrawal: Withdrawal of a subject from the study at the direction of the Principal Investigator. Reasons for physician-directed subject withdrawal include, but are not exclusive to: the subject is not adhering to the Study Protocol requirements, the subject has enrolled in another study that conflicts with the VIRTUS outcomes of interest, or the physician deems it in the best interest for the safety or welfare of the subject to withdraw.

Principal Investigator: Physician responsible for overall clinical management of subjects enrolled at his/her institution. Assumes overall responsibility and accountability for the clinical team and for data obtained from each subject participating in the study. Ensures compliance with the Study Protocol, applicable laws, and applicable regulations; ensures

informed consents are signed, and reviews and signs eCRF indicating documents are accurate and complete.

Protocol Deviation: Any divergence from the Study Protocol.

Pseudoaneurysm: Perforation of the vessel with arterial blood flow outside of the vessel.

Sepsis: Systemic inflammatory response to infection.

Serious Adverse Device Effects: Any adverse device effects that result in any consequences characteristic of a serious adverse event or might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Serious Adverse Event: Any adverse events that led to a death or led to a serious deterioration in the health of the subject that 1) resulted in a life-threatening illness or injury, 2) resulted in a permanent impairment of a body structure or a body function, 3) required inpatient hospitalization or prolongation of existing hospitalization, or 4) resulted in medical or surgical intervention to prevent permanent impairment to a body structure or body function. This definition also includes any adverse event that led to fetal distress, fetal death or a congenital abnormality or birth defect.

Stroke: Neurological dysfunction caused by a brain disturbance or ischemia, with clinical symptoms lasting >24 hours or imaging of an acute clinically relevant brain lesion in patients with rapidly vanishing symptoms.

Study Coordinator: Employee at study site who assists Principal Investigator with study activities as delegated by the Principal Investigator, including tracking subjects involved in the study, scheduling testing and follow-up visits, maintaining study records, completing and providing eCRFs to the Sponsor in a timely manner.

Sub-Investigator(s): Physician(s) responsible for study activities in coordination with Principal Investigator and in accordance to the Study Protocol.

Systemic Infection: the bloodstream infection that affects a number of organs and/or tissues, or affects the body as a whole.

Transient Ischemic Attack (TIA): Brief episode of neurological dysfunction caused by a focal disturbance of brain or retinal ischemia, with clinical symptoms typically lasting less than 1 hour, and without evidence of infarction.

Vascular Complications: Adverse sequelae within the vasculature which can result from catheter-based interventions, including arterio-venous fistula, bleeding, hematoma, infection and pseudoaneurysm (see Access Site Complications), aneurysm, venous perforation, venous rupture, venous spasm, hemorrhage, hypertension, hypotension, sub-acute closure, and thrombosis.

Venous Clinical Severity Score (VCSS): An objective means to clinically assess venous disease[16]. (See Appendix 7.)

Visual Analog Scale (VAS): A scale for patients to report their pain level during activity or movement. (See Appendix 6.)

30 APPENDIX 5: CHRONIC VENOUS INSUFFICIENCY QUESTIONAIRRE (CIVIQ-2)

Many people in the country complain of heavy or aching legs. We are trying to find the frequency of these leg problems, and how they can affect the everyday life of the people suffering from them.

You will find hereafter a certain number of symptoms, sensations or discomforts that you may feel, and that can make everyday life more or less difficult.

For each **symptom, sensation or discomfort listed, we ask you to answer the corresponding question:**

Please indicate whether you have really experienced what is described in the sentence, and if so, to what intensity. Five answers are provided, please circle the intensity most suited to your situation.

1 If you do not feel concerned by the symptom, sensation of discomfort described

2, 3, 4, or 5 If you have felt it with more or less intensity.

1. In the past four weeks, if you have felt **pain** in the **ankles or legs**, what was *the intensity* of this pain? *(Circle the number corresponding to the right answer)*

No pain	Light pain	Moderate pain	Strong pain	Intense pain
1	2	3	4	5

2. During the past four weeks, to what extent did you feel bothered/limited in your **work** or your other **daily activities because of your leg problem**? *(Circle the number corresponding to the right answer)*

Not bothered/limited	A little bothered/limited	Moderately bothered/limited	Very bothered/limited	Extremely bothered/limited
1	2	3	4	5

3. During the past four weeks, did you **sleep badly** because of your leg problems, and how often? *(Circle the number corresponding to the right answer)*

Never	Seldom	Fairly often	Very often	Every night
1	2	3	4	5

During the past four weeks, to what extent did your **leg problems** bother/limit you **while doing the movement or activities** listed below?

(*For each of the sentences listed in the left hand column of the table below, indicate to what extent you are bothered/limited by circling the corresponding number.)*

	Not bothered / limited at all	A little bothered / limited	Moderately bothered / limited	Very bothered / limited	Impossible to do
4. To stand for a long time	1	2	3	4	5
5. To climb stairs	1	2	3	4	5
6. To crouch, to kneel	1	2	3	4	5
7. To walk briskly	1	2	3	4	5
8. To travel by car, bus, plane	1	2	3	4	5
9. To do housework such as standing about in the kitchen, carrying a child in your arms, ironing, cleaning floors or furniture, doing handy work	1	2	3	4	5
10. To go to discos, weddings, parties, cocktails	1	2	3	4	5
11. To do a sport, to make physically strenuous efforts	1	2	3	4	5

Leg problems can also have an effect on one's morale. To what extent do the following sentences correspond to the way you have felt during the past four weeks?

(*For each of the sentences listed in the left hand column of the table below, circle the number that best corresponds to the right answer.)*

	Not at all	A little	Moderately	A lot	Absolutely
12. I feel on edge.	1	2	3	4	5
13. I become tired quickly.	1	2	3	4	5
14. I feel I am a burden to people.	1	2	3	4	5
15. I must always take precautions (such as to stretch my legs, to avoid standing for a long time...).	1	2	3	4	5
16. I am embarrassed to show my legs.	1	2	3	4	5
17. I get irritated easily.	1	2	3	4	5
18. I feel handicapped.	1	2	3	4	5
19. I have difficulty to get going in the morning.	1	2	3	4	5
20. I do not feel like going out.	1	2	3	4	5

31 APPENDIX 6: VISUAL ANALOG SCALE (VAS PAIN SCALE)

Directions: Answer the following question by making a mark through the scale at the point which best describes your condition. Your mark should cross the line at only one point.

Example:

How bad is your pain with activity or movement?

No pain at all — Worst possible pain

32 APPENDIX 7: VENOUS CLINICAL SEVERITY SCORE (VCSS)

Right Leg (Please see below for definitions.) ☐ N/A

1. Pain	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
2. Varicose Veins	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
3. Venous Edema	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
4. Skin Pigmentation	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
5. Inflammation	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
6. Induration	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
7. Active Ulceration (Number)	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
8. Active Ulceration (Duration)	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
9. Active Ulceration (Size)	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
10. Compression	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
Left Leg (Please see below for definitions.)		☐ N/A		
11. Pain	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
12. Varicose Veins	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
13. Venous Edema	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
14. Skin Pigmentation	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
15. Inflammation	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
16. Induration	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
17. Active Ulceration (Number)	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
18. Active Ulceration (Duration)	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
19. Active Ulceration (Size)	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)
20. Compression	☐ 0 (Absent)	☐ 1 (Mild)	☐ 2 (Moderate)	☐ 3 (Severe)

32.1 VCSS Definitions

Pain		
The clinician describes the four categories of leg pain or discomfort that are outlined below to the patient and asks the patient to choose, separately for each leg, the category that best describes the pain or discomfort the patient experiences.		
0	Absent	None
1	Mild	Occasional pain or discomfort that does not restrict regular daily activity
2	Moderate	Daily pain or discomfort that interferes with, but does not prevent regular daily activities
3	Severe	Daily pain or discomfort that limits most regular daily activities

Varicose Veins		
The clinician examines the patient's legs and, separately for each leg, chooses the category that best describes the patient's superficial veins. Veins must be ≥3 mm diameter to qualify as "varicose veins".		
0	Absent	None
1	Mild	Few, scattered, varicosities that are confined to branch veins or clusters. Includes "corona phlebectatica" (ankle flare), defined as greater than 5 blue telangiectases at the inner or sometimes the outer edge of the foot.
2	Moderate	Multiple varicosities that are confined to the calf or the thigh
3	Severe	Multiple varicosities that involve both the calf and the thigh

Venous Edema		
The clinician examines the patient's legs and, separately for each leg, chooses the category that best describes the patient's pattern of leg edema. The clinician's examination may be supplemented by asking the patient about the extent of leg edema that is experienced.		
0	Absent	None
1	Mild	Edema that is limited to the foot and ankle
2	Moderate	Edema that extends above the ankle but below the knee
3	Severe	Edema that extends to the knee or above

Skin Pigmentation		
The clinician examines the patient's legs and, separately for each leg, chooses the category that best describes the patient's skin pigmentation. Pigmentation refers to color changes of venous origin and not secondary to other chronic diseases (i.e. vasculitis purpura).		
0	Absent	None, or focal pigmentation that is confined to the skin over varicose veins
1	Mild	Pigmentation that is limited to the perimalleolar area
2	Moderate	Diffuse pigmentation that involves the lower third of the calf
3	Severe	Diffuse pigmentation that involves more than the lower third of the calf

Inflammation		
The clinician examines the patient's legs and, separately for each leg, chooses the category that best describes the patient's skin inflammation. Inflammation refers to erythema, cellulitis, venous eczema, or dermatitis, rather than just recent pigmentation.		
0	Absent	None
1	Mild	Inflammation that is limited to the perimalleolar area
2	Moderate	Inflammation that involves the lower third of the calf
3	Severe	Inflammation that involves more than the lower third of the calf

Induration		
The clinician examines the patient's legs and, separately for each leg, chooses the category that best describes the patient's skin induration. Induration refers to skin and subcutaneous changes such as chronic edema with fibrosis, hypodermitis, white atrophy and lipodermatosclerosis.		
0	Absent	None
1	Mild	Induration that is limited to the perimalleolar area
2	Moderate	Induration that involves the lower third of the calf
3	Severe	Induration that involves more than the lower third of the calf

Active Ulceration - Number		
The clinician examines the patient's legs and, separately for each leg, chooses the category that best describes the number of active ulcers.		
0	Absent	None
1	Mild	One ulcer
2	Moderate	Two ulcers
3	Severe	Three or more ulcers

Active Ulceration - Duration		
If there is at least one active ulcer, the clinician describes the four categories of ulcer duration that are outlined below to the patient and asks the patient to choose, separately for each leg, the category that best describes the duration of the longest unhealed ulcer.		
0	Absent	No active ulcers
1	Mild	Ulceration present for less than 3 months
2	Moderate	Ulceration present for 3 to 12 months
3	Severe	Ulceration present for more than 12 months

Active Ulceration - Size		
If there is at least one active ulcer, the clinician examines the patient's legs, and separately for each leg, chooses the category that best describes the size of the largest active ulcer.		
0	Absent	No active ulcer
1	Mild	Ulcer of less than 2cm diameter
2	Moderate	Ulcer of 2 to 6cm diameter
3	Severe	Ulcer of greater than 6cm diameter

Compression		
Choose the level of compliance with medical compression therapy		
0	Absent	Not used
1	Mild	Intermittent use
2	Moderate	Wears stockings most days
3	Severe	Full compliance: stockings

33 APPENDIX 8: REFERENCES

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