VIVID

Venous stent for the **I**liofemoral **V**ein **I**nvestigational clinical trial using the **DUO™** Venous Stent System (VIVID)

Investigational Device:	DUO™ Venous Stent System
Protocol Number:	V-CA-0001
Protocol Version:	Rev. E
Effective Date:	April 23, 2021
Study Sponsor:	Vesper Medical, Inc. 640 Lee Road, Suite 101 Wayne, Pennsylvania 19087 United States of America 484-892-6340

This investigational protocol contains confidential information for use by the principal investigators and their designated representatives participating in this clinical investigation. It should be held confidential and maintained in a secure location. It should not be copied or made available for review by any unauthorized person or firm.

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Table 1. List of Acronyms

Acronym	Definition
ADE	Adverse Device Effect
AE	Adverse Event
aPTT	Activated Partial Thromboplastin Time
AT	Acute Thrombotic
BfArM	Federal Institute for Drugs and Medical Devices
BMI	Body Mass Index
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CD-TLR	Clinically Driven Target Lesion Reintervention
CD-TVR	Clinically Driven Target Vessel Reintervention
CEAP	Clinical-Etiology-Anatomy-Pathophysiology
CEC	Clinical Events Committee
CFV	Common Femoral Vein
CIV	Common Iliac Vein
COVID-19	Coronavirus Disease of 2019
CPT	Chronic Post Thrombotic
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Computed Tomography
CVD	Chronic Venous Disease
CVI	Chronic Venous Insufficiency
DSA	Digital Subtraction Angiography
DSMB	Data Safety and Monitoring Board
DUS	Duplex Ultrasound
DVT	Deep Vein Thrombosis
EC	Ethics Committee
eCRF	Electronic CRF
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EIV	External Iliac Vein
EU	European Union
FAS	Full-Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act

Acronym	Definition
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IFU	Instructions for Use
INR	International Normalized Ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
IVC	Inferior Vena Cava
IVUS	Intravascular Ultrasound
LTFU	Lost to Follow-up
MAE	Major Adverse Event
NSAID	Nonsteroidal anti-inflammatory drug
NT	Nonthrombotic
OUS	Outside the United States
PE	Pulmonary Embolism
PG	Performance Goal
PI	Principal Investigator
PIC	Subject Implant Card
PP	Per-Protocol
PT	Prothrombin time
PTA	Percutaneous Transluminal Angioplasty
PTS	Postthrombotic Syndrome
QOL	Quality of Life
RO	Radiopaque
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
TLR	Target Lesion Reintervention
TVR	Target Vessel Reintervention
UADE	Unanticipated Adverse Device Effect
VCSS	Venous Clinical Severity Score
WBC	White Blood Cell

1. INVESTIGATOR PROTOCOL SIGNATURE PAGE

STUDY TITLE: **V**enous stent for the **I**liofemoral **V**ein **I**nvestigational clinical trial using the **DUO**™ Venous Stent System (**VIVID**)

CLINICAL TRIAL CENTER: _____

(Print name of study center)

I, the undersigned, have read and understand the protocol specified above. As an Investigator, I understand that I am responsible for adhering to the terms of this protocol by ensuring the safety of clinical trial subjects enrolled under my supervision and by providing the Sponsor with complete and timely information. In addition, I understand that all information pertaining to this clinical trial shall be held strictly confidential and I will ensure that the requirement for confidentiality is understood by all staff involved in this clinical trial. I agree to abide by the terms of this protocol and to maintain the procedures required to conduct this clinical trial in accordance with the Investigator Agreement, Good Clinical Practice, Declaration of Helsinki, 21 CFR Parts 50, 54, 56, and 812, ISO 14155, and any applicable local regulations.

_____

SITE INVESTIGATOR – Print Name

_____

SITE INVESTIGATOR – Signature

_____

DATE

2. CLINICAL TRIAL SYNOPSIS

Study Title:	**V**enous stent for the **I**liofemoral **V**ein **I**nvestigational clinical trial using the **DUO™** Venous Stent System (**VIVID**)
Study Design:	This is a prospective, multi-center, single-arm, non-blinded clinical trial.
Study Objective:	To investigate the safety and efficacy of the Vesper DUO Venous Stent System in the treatment of subjects presenting with iliofemoral occlusive disease as compared to a pre-defined performance goal (PG) established from published, peer reviewed scientific literature related to stenting of iliofemoral venous outflow obstructions.
Study Device:	The DUO Venous Stent System is manufactured by Vesper Medical, Inc. and consists of a primary hybrid stent designed for treating the iliac vein and an extension stent designed for extending treatment into the common femoral vein. Subjects may be treated with the hybrid stent alone or the hybrid stent and extension stent together.
Intended Use:	The DUO Venous Stent System is intended for use in the iliac and common femoral veins for improving luminal diameter in symptomatic venous outflow obstructions.
Subject Population:	Subjects with nonmalignant iliofemoral venous outflow obstruction presenting with nonthrombotic (NT), acute thrombotic (AT) or chronic postthrombotic (CPT) disease pathogenesis will be selected for study participation. At least 20% of the total population must be enrolled in each group. Subjects must meet all inclusion criteria and not meet any of the exclusion criteria to be enrolled in the study.
Regulatory Status:	The DUO Venous Stent System will be limited by U.S. (Federal) law to investigational use only.
Enrollment and Follow-up:	Up to 160 subjects will be enrolled at up to 45 U.S. and International investigative sites. Each site can enroll a maximum of 32 subjects, establishing an enrollment cap at 20% of the total subject sample size. The follow-up period for enrolled subjects that receive at least one DUO Stent is 36 months. Subjects that are enrolled but do not receive at least one DUO Stent will be followed for 30 days and then exited from the study.
Primary Endpoints:	**Safety:** Freedom from major adverse events (MAEs) at 30 days post index procedure, as adjudicated by the Clinical Events Committee (CEC) or Core Laboratory, including: ▪ Device or procedure-related death ▪ Device or procedure-related bleed at the target vessel and/or the target lesion or at the access site requiring surgical or endovascular intervention or blood transfusion of ≥2 units

	▪ Device or procedure-related venous injury occurring in the target vessel and/or the target lesion or at the access site requiring surgical or endovascular intervention ▪ Major amputation of the target limb ▪ Clinically significant pulmonary embolism (PE), confirmed by CT angiography ▪ Stent embolization outside of the target vessel ▪ Presence of new thrombus within the stented segment **Efficacy:** Primary patency of stented segment at 12 months defined as freedom from: ▪ Duplex Ultrasound (DUS) core laboratory adjudicated occlusion or stenosis >50% within the stented segment. If site reported or core laboratory adjudicated DUS shows >50% stenosis or occlusion, confirmation by diagnostic intravascular ultrasound (IVUS) is required. ▪ CEC adjudicated clinically driven target lesion reintervention (CD-TLR) defined as endovascular or surgical procedure for new, recurrent, or worsening symptoms and core lab adjudicated >50% stenosis or occlusion within the stented segment confirmed by diagnostic IVUS
Secondary Efficacy Endpoints:	▪ Subject symptom relief via VCSS pain score at 12 months ▪ Primary assisted patency at 12 months o Defined as freedom from DUS core laboratory adjudicated occlusion or stenosis >50% within the stented segment following a reintervention due to a >50% but <100% stenosis. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS is required. ▪ Secondary patency at 12 months o Defined as freedom from DUS core laboratory adjudicated occlusion or stenosis >50% within the stented segment following a reintervention due to 100% occlusion. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS is required.
Observational Endpoints:	▪ Device Success defined as:

(*Core Laboratory Adjudicated)	○ Successful deployment of the DUO Stent(s) at the intended target site, AND ○ Successful withdrawal of the delivery catheter(s) from the introducer sheath, AND ○ The DUO Stent remaining at the intended deployment location through completion of the index procedure as determined by the Principal Investigator (PI) ▪ Lesion success defined as target lesion patency of ≤50% residual diameter or area stenosis of the stented segment at the completion of the procedure* ▪ Procedural success defined as lesion success without the occurrence of CEC adjudicated major adverse events (MAEs) from the time start of the index procedure through discharge ▪ Stent fracture via X-ray through 36 months* ▪ Stent migration via X-ray through 36 months* ▪ Stent embolization via X-ray or venogram through 36 months* ▪ Primary patency of the stented segment via DUS at 24 and 36 months. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS may be required.* ▪ Primary assisted patency of the stented segment via DUS at 24 and 36 months. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS may be required.* ▪ Secondary patency of the stented segment via DUS at 24 and 36 months. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS may be required.* ▪ Changes in the clinical CEAP Classification through 36 months ▪ Changes in the EQ-5D-3L through 36 months ▪ Changes in the Villalta Score through 36 months ▪ Changes in the VCSS Pain Score at 24 and 36 months ▪ Changes in the VEINES QOL/Sym Score through 36 months ▪ CEC adjudicated MAEs post 30 days through 36 months

	▪ CEC adjudicated CD-TLR through 36 months ▪ CEC adjudicated clinically driven target vessel reintervention (CD-TVR) through 36 months ▪ Venous Ulcer Assessment through 36 months
Inclusion Criteria:	1. Males or non-pregnant, non-breastfeeding females ≥18 years of age at the time of consent 2. Subject is able and willing to provide written informed consent prior to receiving any non-standard of care, protocol specific procedures 3. Female subjects of childbearing potential must have a negative pregnancy test within 7 days prior to treatment and must use some form of contraception (abstinence is acceptable) throughout the time of clinical trial exit 4. Willing and capable of complying with all required follow-up visits 5. Estimated life expectancy ≥1 year 6. Subject is ambulatory (use of assistive walking device such as a cane or walker is acceptable) 7. Body mass index (BMI) <45 8. Clinically significant symptomatic venous outflow obstruction in one iliofemoral venous segment (one limb) per subject, is indicated for venoplasty and stenting, and meets at least one of the following clinical indicators: a. CEAP score ≥3 b. VCSS pain score ≥2 c. Suspected deep vein thrombosis (DVT) with symptoms occurring prior to receiving a DUO Stent 9. Subject is willing and able to comply with PI recommendation for compression therapy, if required 10. Presence of unilateral, non-malignant venous obstruction of the common femoral vein (CFV), external iliac vein (EIV), common iliac vein (CIV), or any combination thereof, defined as a ≥50% reduction in target vessel lumen diameter and confirmed by venographic or IVUS imaging. The cranial point of the obstruction may extend to the iliac vein confluence of the inferior vena cava (IVC) and the caudal point may be 2mm above either the inflow of the deep femoral (or profunda) or the lesser trochanter, whichever is most cranial 11. Obstructive lesion(s) able to be treated with continuous stent coverage

	12. Adequate inflow to the target lesion(s) involving at least a patent femoral or deep femoral vein and a landing zone in the CFV free from significant disease requiring treatment 13. Reference vessel diameter is of adequate size to accommodate the appropriate size stent as measured by IVUS 14. All vessels from insertion site through target vessel can accommodate a 9F or 10F sheath, depending on the stent size used 15. Ability to cross interventional devices through target lesion(s) 16. In DVT subjects, successful treatment of acute thrombus must have occurred prior to receiving any DUO Stents for an underlying obstructive lesion. Successful treatment of acute thrombus is defined as reestablishment of antegrade flow with ≤30% residual thrombus (confirmed by venogram or IVUS) and freedom from bleeding and symptomatic pulmonary embolism (confirmed by imaging). After successful treatment of thrombus is confirmed, eligible obstructive lesion(s) can be treated with a DUO Stent during the same procedure. 17. All subjects must undergo a SARS-CoV-2 test and have a negative test result within 8 days prior to the index procedure. If a SARS-CoV-2 test is unavailable due to institution policy, a test shortage, or if there is a delay in test results, the subject must complete the COVID-19 questionnaire and must have answered NO to all questions to be eligible for enrollment. A SARS-CoV-2 test will not be required for enrollment if a subject has received a complete cycle of an authorized COVID-19 vaccine or has documented evidence of a positive COVID-19 antibody test and is asymptomatic and has no long-lasting effects (per PI discretion) from a prior COVID-19 infection. 18. A measured temperature less than 99.5°F (37.5°C) on the day of the index procedure and no history of fever or feeling feverish within 14 days of the index procedure 19. No prior history, within 60 days of the index procedure, of a SARS-CoV-2 positive test, or COVID-19 symptoms
Exclusion Criteria:	1. Target limb symptoms caused by peripheral arterial disease 2. Presence of unresolved significant PE prior to use of the DUO Venous Stent System confirmed by chest CT. If subject has documented history of significant pulmonary embolism within the last 6 months, a chest CT is required to confirm significant pulmonary embolism is not currently present.

	3. Presence of IVC obstruction or target venous obstruction that extends into the IVC 4. Presence of acute DVT located outside target limb 5. Contralateral venous occlusive disease of the CFV, EIV, and/or CIV, with planned treatment ≤390 days after the index procedure 6. Uncontrolled or active coagulopathy or known, uncorrectable bleeding diathesis 7. Coagulopathy causing INR >2 which is not amenable to medical treatment 8. Platelet count <50,000 cells/mm^3 or >1,000,000 cells/mm^3 and/or White blood cell (WBC) <3,000 cells/mm^3 or >12,500 cells/mm^3 9. Uncorrected hemoglobin of ≤9 g/dL 10. Subject is on dialysis or has an estimated glomerular filtration rate (eGFR) <30 mL/min. In subjects with diabetes mellitus, eGFR <45 mL/min. 11. History of Heparin Induced Thrombocytopenia 12. Presence of known aggressive clotting disorders such as Lupus Anticoagulant Disorder, Antiphospholipid antibody syndrome, homozygous gene Factor V Leiden or Prothrombin gene abnormalities, Protein C and S deficiency or Antithrombin deficiency 13. Known hypersensitivity or contraindication to antiplatelet therapy or anticoagulation, nickel, or titanium 14. Contrast agent allergy that cannot be managed adequately with pre-medication 15. Intended concurrent adjuvant procedure (except for venoplasty) such as creation of temporary arteriovenous fistula, femoral endovenectomy or saphenous vein ablation and/or saphenous vein stripping during the index procedure 16. Subjects who have had any prior surgical or endovascular procedures to the target vessel. Note that subjects who have had successful catheter-directed or mechanical thrombolysis in the target vessel for DVT at least 90 days prior to the index procedure may be included 17. Planned surgical or interventional procedures of the target limb (except thrombolysis and/or thrombectomy in preparation for the procedure or vena cava filter placement prior to stent implantation in subjects at high risk for pulmonary embolism) within 30 days prior to or 30 days after the index procedure

	18. Planned surgical or interventional procedures for other medical conditions (i.e., not associated with the target limb) 30 days prior to or 30 days after the index procedure 19. Previous venous stenting of the target limb, the IVC, or contralateral limb if stents extend into the IVC 20. Iliofemoral venous segment unsuitable for treatment with available sizes of DUO Stent implants 21. Lesions with intended treatment lengths extending into the IVC 22. No safe landing zone at or above the profunda femoral confluence 23. Participating in another investigational study in which the subject has not completed the primary endpoint(s) 24. Has other comorbidities that, in the opinion of the Investigator, would preclude them from receiving this treatment and/or participating in study-required follow-up assessments

3. STUDY MANAGEMENT CONTACT LIST

Please see **APPENDIX A – Study Management Contact List** located at the end of this document.

4. INTRODUCTION

4.1. Background and Rationale

Chronic venous insufficiency (CVI), an advanced stage of chronic venous disease, is a common problem occurring in approximately 1-5% of the adult population. CVI can be caused by a nonthrombotic (primary) or postthrombotic (secondary) stimulus that involves reflux, obstruction, or a combination of both.[1,2]

Initial treatment for CVI centers around wearing compression stockings or performing venous valve repair.[3] For subjects in which symptoms are not relieved, the dominant pathophysiologic component may be obstruction rather than reflux. Previous estimations that obstruction is a major contributor in only 10% to 20% of subjects with severe chronic venous disease are probably low.[4] One study reported that 80% of subjects with iliofemoral thrombosis show extrinsic iliac compression on CT venography.[5]

The role of venous obstruction in the deep venous system is increasingly recognized as a major cause of CVI, with obstructive lesions in the iliocaval segment being much more relevant than lesions in the crural and/or femoral veins.[6,7] Venous obstruction can occur as a result of different causes, including extrinsic compression because of malignancy or anatomic variants (May-Thurner) and acute or chronic DVT.[8] Nonthrombotic iliac vein obstruction occurs where the iliac vein is crossed by the iliac or hypogastric artery, more commonly known as May-Thurner's syndrome.[9] Initial treatment for symptomatic acute DVT involves anticoagulation; 23-60% experience postthrombotic syndrome despite optimal anticoagulant therapy.[10]

Endovenous treatment of iliofemoral stenosis or occlusion with angioplasty and stent placement has emerged as the procedure of choice to establish and maintain venous outflow.[11] Venous stenting was first described in the late 1980s[12] and is now recommended by a number of international guidelines as treatment for subjects with iliac or common femoral vein obstruction.[13,14,15]

The American Venous and Lymphatic Society recommends venous balloon angioplasty and stenting for treatment of nonthrombotic and postthrombotic iliac and common femoral venous obstructions in subjects with lower extremity pain or edema affecting quality of life (QOL) that cannot be palliated by compression. Stenting is also recommended for subjects with impending or active lower extremity venous leg ulceration caused by obstruction.[16]

Stent placement has a high technical success rate and is effective at restoring patency.[17] Technical success of stent placement has been reported to be 84-93% in chronic postthrombotic iliac vein obstruction.[18] Clinical improvement appears to be long lasting.[19] Neglen reported on a group of 982 subjects with chronic nonmalignant obstructive lesions of the femoroiliocaval vein that were stented under IVUS guidance. Primary, assisted primary and secondary patency rates of 57%, 80%, and 86% were achieved at 6 years in thrombotic disease while nonthrombotic rates were 79%, 100%, and 100%, respectively.[20] Other smaller studies have reported similar results.[21,22,23,24,25,26] More recent data reported primary, assisted primary, and secondary patency rates of 93%, 96%, and 100%, respectively,

at 1 year, in the first 30 subjects treated with the Veniti Vici stent[27] and 85% primary patency in the first 20 subjects treated with the Zilver Vena stent.[28]

Adverse Events (AEs) associated with venous stenting have been minimal. The most common complications include early (<30 days) and late thrombosis (1.5-3% and 5%, respectively). Mortality is low, reported at 0-1%.[29] Extension of the stent into the IVC is associated with contralateral iliac vein occlusion 1% of the time. However, failure to extend the stent into the IVC when needed may result in an ipsilateral restenosis or occlusion rate of 36%.[30] Absolute contraindications listed for iliocaval stenting include uncorrectable coagulopathy and local or systemic infection.[31]

In summary, stenting in chronic iliocaval obstruction is safe and effective. Excellent long-term results with respect to revascularization and symptom relief have been achieved. Recanalization to treat venous claudication with venous stents suggests the highest probability of success.[32,33]

The Vesper DUO™ Venous Stent System is a new purpose-built stent system that will be studied for use in treating iliac and common femoral vein obstructions due to either nonthrombotic or postthrombotic etiology.

4.2. Report of Prior Investigations

This is the first investigation of the DUO Venous Stent System in humans.

5. INVESTIGATIONAL DEVICE

5.1. Description

The *Vesper DUO Venous Stent System* consists of a portfolio of self-expanding venous stent configurations mounted on disposable delivery systems for improving luminal diameter in symptomatic venous outflow obstructions. The portfolio approach includes delivery systems with either a hybrid venous stent implant or an extension venous stent implant, enabling the clinician to custom tailor treatment in the iliofemoral venous anatomy based on disease patterns and severity. The hybrid stent design has varying mechanical characteristics such as radial force/crush resistance and flexibility along its length to target the varying dynamic loading conditions in the iliofemoral venous system related to the treatment of disease states including nonthrombotic iliac vein compression, May-Thurner syndrome, deep venous thrombosis and postthrombotic venous occlusion. The extension stent consists of a highly flexible region with reinforcement rings at both ends. The hybrid stent can be used independently or in conjunction with the extension stent to personalize the treatment region. The Extension stent shall only be used in conjunction with the Hybrid stent.

5.2. Full Portfolio of DUO Venous Stent System Sizes

Stent Type	Stent Diameter	Stent Lengths Available	Delivery System Size
Extension	12mm	40mm, 60mm, 80mm, 100mm, 120mm, 140mm	9F
Extension	14mm	40mm, 60mm, 80mm, 100mm, 120mm, 140mm	9F
Extension	16mm	40mm, 60mm, 80mm, 100mm, 120mm, 140mm	10F
Hybrid	12mm	60mm, 80mm,100mm, 120mm, 140mm, 160mm	9F
Hybrid	14mm	60mm, 80mm, 100mm, 120mm, 140mm, 160mm	9F
Hybrid	16mm	60mm, 80mm, 100mm, 120mm, 140mm, 160mm	10F
Hybrid	18mm	60mm, 80mm, 100mm, 120mm, 140mm, 160mm	10F

5.3. Principles of Operation

FIGURE 1 below provides an overview of the *Vesper DUO Venous Stent System*.

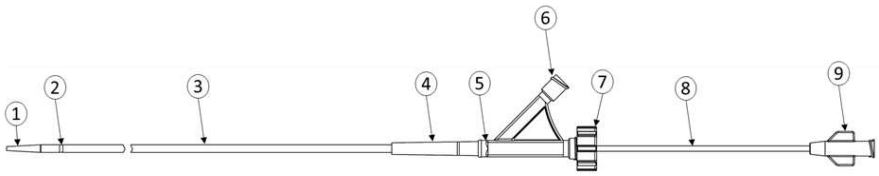

Figure 1. Duo Venous Stent System

The delivery catheter has an effective length of 120cm. The Outer Braided Sheath (3), which constrains the stent implant, is bonded proximally to the Bifurcation Luer (5) within the Transition sleeve (4). The Hemostatic Valve (7) is integrated proximally to the Bifurcation Luer. The Inner Core Shaft (8) slides within the Hemostatic Valve. A soft, tapered Distal Tip (1) is bonded to the distal end of the Inner Core Shaft for ease of advancement in the blood vessel. Constrained within the Outer Braided Sheath the self-expanding Stent implant is positioned on the Inner Core between two radiopaque (RO) Distal Inner Core Markers. A radiopaque Target Band (2) is located on the distal end of the Outer Braided Sheath.

The catheter is flushed prior to the procedure through the side port (6) of the Bifurcation Luer and the Guidewire Port (9). Stent implant positioning is achieved prior to deployment by using the RO Markers on the Stent implant (**FIGURE 2** and **FIGURE 3**) and the Target Band on the outer sheath. During Stent implant deployment, the Hemostatic Valve is unlocked by rotating the valve counterclockwise. The Stent implant is unsheathed by pinning the Proximal Inner Core Shaft and pulling back on the outer sheath.

FIGURE 2 and **FIGURE 3** below provide an overview of the *Vesper DUO Venous Stent System*, Hybrid and Extension Stents.

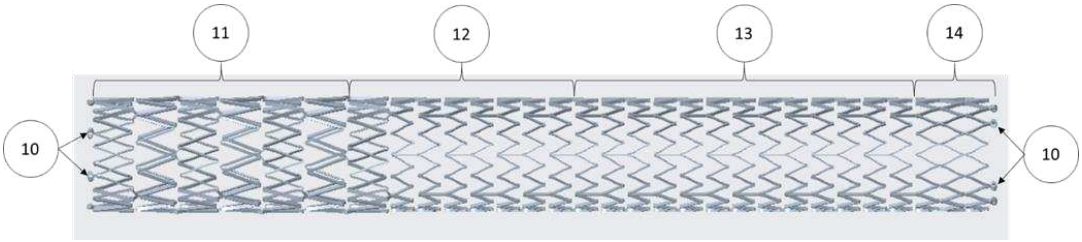

Figure 2. Hybrid Stent

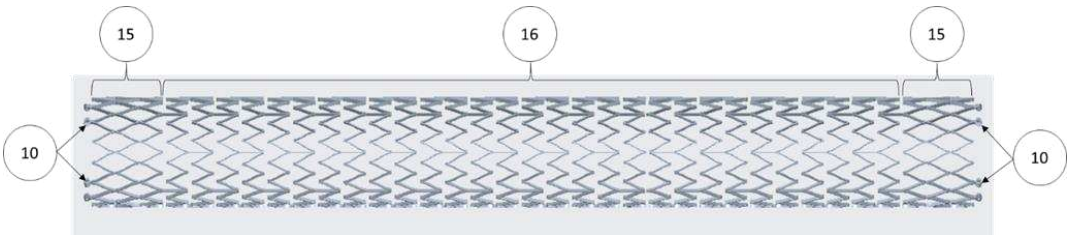

Figure 3. Extension Stent

The self-expanding Nitinol (nickel-titanium) Hybrid stent is designed with a "High Crush Resistance" segment (11) at the cranial end to resist local focal crush associated with May-Thurner Syndrome and other nonthrombotic iliac vein compressions, followed by a "Transition" segment (12) that transitions into a "Highly Flexible" segment (13) to mitigate kinks during knee and hip flexion. The caudal end of the Hybrid stent is designed with a "reinforcement ring" (14) to mitigate end crush of the stent. Both the cranial and caudal ends of the Hybrid stent include Gold radiopaque markers (10), 4 markers per end.

The self-expanding Nitinol (nickel-titanium) Extension stent is designed with a "Highly Flexible" (16) body to mitigate kinks during knee and hip flexion with "reinforcement rings" (15) on both ends to mitigate end crush of the stent. Both the cranial and caudal ends of the Extension stent include Gold radiopaque markers (10), 4 markers per end.

The Nitinol (nickel-titanium) stents self-expand upon deployment from the Delivery Catheter (**FIGURE 1**) into the target vessel. The self-expanding Nitinol (nickel-titanium) stents impart a radial outward force on the inner luminal surface of target vessel to establish patency.

5.4. Intended Use

The *Vesper DUO Venous Stent System* is intended for use in the iliac and common femoral veins for improving luminal diameter in symptomatic venous outflow obstructions.

5.5. Future Considerations

It is anticipated that the DUO Venous Stent System with a handle delivery system will become available during the clinical trial. Once available, a minimum of 5 subjects at up to 5 study sites will be treated using the handle delivery system, irrespective of disease state.

6. CLINICAL TRIAL OBJECTIVES

6.1. Primary Endpoints

Safety: Freedom from major adverse events (MAEs) at 30 days post index procedure, as adjudicated by the Clinical Events Committee (CEC) or core laboratory including:

- Device or procedure-related death
- Device or procedure-related bleed at the target vessel and/or the target lesion or at the access site requiring surgical or endovascular intervention or blood transfusion of ≥2 units
- Device or procedure-related venous injury occurring in the target vessel and/or the target lesion or at the access site requiring surgical or endovascular intervention
- Major amputation of the target limb
- Clinically significant pulmonary embolism, confirmed by CT angiography
- Stent embolization outside of the target vessel
- Presence of new thrombus within the stented segment

Efficacy: Primary patency of stented segment at 12 months defined as freedom from:

- Duplex Ultrasound (DUS) core laboratory adjudicated occlusion or stenosis >50% within the stented segment. If site reported or core laboratory adjudicated DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS is required.
- CEC adjudicated clinically driven target lesion reintervention (CD-TLR) defined as endovascular or surgical procedure for new, recurrent, or worsening symptoms and core lab adjudicated >50% stenosis or occlusion within the stented segment confirmed by diagnostic IVUS

6.2. Secondary Efficacy Endpoints

- Subject symptom relief via VCSS pain score at 12 months
- Primary assisted patency at 12 months
    - Defined as freedom from DUS core laboratory adjudicated occlusion or stenosis >50% within the stented segment following a reintervention due to a >50% but <100% stenosis. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS is required.
- Secondary patency at 12 months
    - Defined as freedom from DUS core laboratory adjudicated occlusion or stenosis >50% within the stented segment following a reintervention due to 100% occlusion. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS is required.

6.3. Observational Endpoints

- Device Success defined as:
  - Successful deployment of the DUO stent(s) at the intended target site, AND
  - Successful withdrawal of the delivery catheter(s) from the introducer sheath, AND
  - The DUO Stent remaining at the intended deployment location through completion of the index procedure as determined by the Principal Investigator (PI)
- Lesion success defined as target lesion patency of ≤50% residual diameter or area stenosis of the stented segment at the completion of the procedure*
- Procedural success defined as lesion success without the occurrence of CEC adjudicated major adverse events (MAEs) from the time start of the index procedure through discharge*
- Stent fracture via X-ray through 36 months*
- Stent migration via X-ray through 36 months*
- Stent embolization via X-ray or venogram through 36 months*
- Primary patency of the stented segment via DUS at 24 and 36 months. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS may be required.*
- Primary assisted patency of the stented segment via DUS at 24 and 36 months. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS may be required.*
- Secondary patency of the stented segment via DUS at 24 and 36 months. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS may be required.*
- Changes in the clinical CEAP Classification through 36 months
- Changes in the EQ-5D-3L through 36 months
- Changes in the Villalta Score through 36 months
- Changes in the VCSS Pain Score at 24 and 36 months
- Changes in the VEINES QOL/Sym Score through 36 months
- CEC adjudicated MAEs post 30 days through 36 months
- CEC adjudicated CD-TLR through 36 months
- CEC adjudicated CD-TVR through 36 months
- Venous Ulcer Assessment through 36 months

*Core Laboratory adjudicated

7. CLINICAL TRIAL DESIGN

This is a prospective, multi-center, single-arm, non-blinded clinical trial designed to investigate the safety and efficacy of the Vesper DUO Venous Stent System as compared to a pre-defined performance goal (PG) established from published, peer reviewed scientific literature related to stenting of iliofemoral venous outflow obstructions.

7.1. Anticipated Number of Subjects and Investigational Sites

Up to 160 subjects will be enrolled at up to 45 U.S. and International investigative sites. Each site can enroll a maximum of 32 subjects, establishing an enrollment cap at 20% of the total subject sample size.

7.2. Subject Population

Subjects with nonmalignant iliofemoral venous outflow obstruction presenting with nonthrombotic (NT), acute thrombotic (AT), or chronic postthrombotic (CPT) disease pathogenesis will be selected for study participation. At least 20% of the total population must be enrolled in each group. Subjects must meet all inclusion criteria and not meet any of the exclusion criteria to be enrolled in this clinical trial.

7.3. Clinical Trial Duration & Follow-up

The follow-up duration for each enrolled subject who receives a DUO Stent implant is 36 months. Any subject who is enrolled but does not receive at least one DUO Stent implant will be followed for 30 days and then exited from the study (see **Section 13.3.1**).

7.4. Subject Selection

7.4.1. Inclusion Criteria

Subjects must meet all the following Inclusion Criteria. The response for each criterion below must be "Yes":

1. Males or non-pregnant, non-breastfeeding females ≥18 years of age at the time of consent
2. Subject is able and willing to provide written informed consent prior to receiving any non-standard of care, protocol specific procedures
3. Female subjects of childbearing potential must have a negative pregnancy test within 7 days prior to treatment and must use some form of contraception (abstinence is acceptable) throughout the time of clinical trial exit
4. Willing and capable of complying with all required follow-up visits
5. Estimated life expectancy ≥1 year
6. Subject is ambulatory (use of assistive walking device such as a cane or walker is acceptable)
7. Body mass index (BMI) <45

8. Clinically significant symptomatic venous outflow obstruction in one iliofemoral venous segment (one limb) per subject, is indicated for venoplasty and stenting, and meets at least one of the following clinical indicators:
    a. CEAP score ≥3
    b. VCSS pain score ≥2
    c. Suspected deep vein thrombosis (DVT) with symptoms occurring prior to receiving a DUO Stent
9. Subject is willing and able to comply with PI recommendation for compression therapy, if required
10. Presence of unilateral, non-malignant venous obstruction of the common femoral vein (CFV), external iliac vein (EIV), common iliac vein (CIV), or any combination thereof, defined as a ≥50% reduction in target vessel lumen diameter and confirmed by venographic or IVUS imaging. The cranial point of the obstruction may extend to the iliac vein confluence of the inferior vena cava (IVC) and the caudal point may be 2mm above either the inflow of the deep femoral (or profunda) or the lesser trochanter, whichever is most cranial
11. Obstructive lesion(s) able to be treated with continuous stent coverage
12. Adequate inflow to the target lesion(s) involving at least a patent femoral or deep femoral vein and a landing zone in the CFV free from significant disease requiring treatment
13. Reference vessel diameter is of adequate size to accommodate the appropriate size stent as measured by IVUS
14. All vessels from insertion site through target vessel can accommodate a 9F or 10F sheath, depending on the stent size used
15. Ability to cross interventional devices through target lesion(s)
16. In DVT subjects, successful treatment of acute thrombus must have occurred prior to receiving any DUO Stents for an underlying obstructive lesion. Successful treatment of acute thrombus is defined as reestablishment of antegrade flow with ≤30% residual thrombus (confirmed by venogram or IVUS) and freedom from bleeding and symptomatic pulmonary embolism (confirmed by imaging). After successful treatment of thrombus is confirmed, eligible obstructive lesion(s) can be treated with a DUO Stent during the same procedure.
17. All subjects must undergo a SARS-CoV-2 test and have a negative test result within 8 days prior to the index procedure. If a SARS-CoV-2 test is unavailable due to institution policy, a test shortage, or if there is a delay in test results, the subject must complete the COVID-19 questionnaire and must have answered NO to all questions to be eligible for enrollment. A SARS-CoV-2 test will not be required for enrollment if a subject has received a complete cycle of an authorized COVID-19 vaccine or has documented evidence of a positive COVID-

19 antibody test and is asymptomatic and has no long-lasting effects (per PI discretion) from a prior COVID-19 infection.

18. A measured temperature less than 99.5°F (37.5°C) on the day of the index procedure and no history of fever or feeling feverish within 14 days of the index procedure
19. No prior history, within 60 days of the index procedure, of a SARS-CoV-2 positive test, or COVID-19 symptoms

7.4.2. Exclusion Criteria

Subjects must not meet any of the following Exclusion Criteria. The response for each criterion below must be "No":

1. Target limb symptoms caused by peripheral arterial disease
2. Presence of unresolved significant pulmonary emboli prior to use of the DUO Venous Stent System confirmed by chest CT. If subject has documented history of significant pulmonary embolism within the last 6 months, a chest CT is required to confirm significant pulmonary embolism is not currently present.
3. Presence of IVC obstruction or target venous obstruction that extends into the IVC
4. Presence of acute DVT located outside target limb
5. Contralateral venous occlusive disease of the CFV, EIV, and/or CIV, with planned treatment ≤390 days after the index procedure
6. Uncontrolled or active coagulopathy or known, uncorrectable bleeding diathesis
7. Coagulopathy causing INR >2 which is not amenable to medical treatment
8. Platelet count <50,000 cells/mm^3 or >1,000,000 cells/mm^3 and/or White blood cell (WBC) <3,000 cells/mm^3 or >12,500 cells/mm^3
9. Uncorrected hemoglobin of ≤9 g/dL
10. Subject is on dialysis or has an estimated glomerular filtration rate (eGFR) <30 mL/min. In subjects with diabetes mellitus, eGFR <45 mL/min.
11. History of Heparin Induced Thrombocytopenia
12. Presence of known aggressive clotting disorders such as Lupus Anticoagulant Disorder, Antiphospholipid antibody syndrome, homozygous gene Factor V Leiden or Prothrombin gene abnormalities, Protein C and S deficiency or Antithrombin deficiency
13. Known hypersensitivity or contraindication to antiplatelet therapy or anticoagulation, nickel, or titanium
14. Contrast agent allergy that cannot be managed adequately with pre-medication

15. Intended concurrent adjuvant procedure (except for venoplasty) such as creation of temporary arteriovenous fistula, femoral endovenectomy or saphenous vein ablation and/or saphenous vein stripping during the index procedure
16. Subjects who have had any prior surgical or endovascular procedures to the target vessel. Note that subjects who have had successful catheter-directed or mechanical thrombolysis in the target vessel for DVT at least 90 days prior to the index procedure may be included
17. Planned surgical or interventional procedures of the target limb (except thrombolysis and/or thrombectomy in preparation for the procedure or vena cava filter placement prior to stent implantation in subjects at high risk for pulmonary embolism) within 30 days prior to or 30 days after the index procedure
18. Planned surgical or interventional procedures for other medical conditions (i.e., not associated with the target limb) 30 days prior to or 30 days after the index procedure
19. Previous venous stenting of the target limb, the IVC, or contralateral limb if stents extend into the IVC
20. Iliofemoral venous segment unsuitable for treatment with available sizes of DUO Stent implants
21. Lesions with intended treatment lengths extending into the IVC
22. No safe landing zone at or above the profunda femoral confluence
23. Participating in another investigational study in which the subject has not completed the primary endpoint(s)
24. Has other comorbidities that, in the opinion of the PI, would preclude them from receiving this treatment and/or participating in study-required follow-up assessments

8. TREATMENT PLAN

8.1. Time and Events Schedule

All subjects will receive the assessments at specific time points as listed below:

Assessment	Baseline[1]	Index Procedure	Post-Procedure/ Pre-Discharge*	30-day (-2 days/+14 Days)[14]	6 Month (±30 Days)[14]	12 Month (± 30 Days)[14]	24 Month (± 30 Days)[14]	36 Month (± 30 Days)[14]	Unscheduled[9,10]
Informed Consent	X[2]								
Inclusion/Exclusion Criteria	X	X							
SARS-CoV-2 Test/COVID-19 Questionnaire[4]	X[3]			X	X	X	X	X	X
Demographics, Medical History and Risk Factors	X								
Brief Physical Exam (Height, Weight, Temp)	X								
Serum Creatinine, eGFR, WBC, Platelet Count, Hemoglobin	X								
Prothrombin Time (PT)/ International Normalized Ratio (INR)[5]	X		X						
Activated Partial Thromboplastin time (aPTT)[6]	X		X						
Urine or Blood Pregnancy Test[7]	X								
Venous Ulcer Assessment	X			X	X	X	X	X	X
CEAP Classification	X				X	X	X	X	X
Villalta Score	X				X	X	X	X	X
VCSS Pain Score	X				X	X	X	X	X
VEINES-QOL/Sym Questionnaire	X				X	X	X	X	X
EQ-5D-3L Questionnaire	X				X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Duplex Ultrasound (DUS)[8,11]				X	X	X	X	X	X
Venogram[11]		X[15]				X[12]	X[16]	X[16]	X
Intravascular Ultrasound (IVUS)[11]		X[15]				X[12]	X[16]	X[16]	X
X-ray of Implanted Stent[11]						X	X	X	X

Adverse Event (AE) Assessment[13]		X	X	X	X	X	X	X	X

[*] Assessments are to be completed post-index procedure and prior to the subject being discharged from the hospital/clinic.

[1] Assessments may be done up to 30 days prior to the index procedure, except for a pregnancy test and SARS-CoV-2 test

[2] Informed Consent may be obtained up to 30 days prior to index procedure.

[3] All subjects must undergo a SARS-CoV-2 test and have a negative result within 8 days of the Index Procedure to be eligible for study inclusion. COVID-19 questionnaire is only required under certain circumstances when SARS-CoV-2 testing is not possible.

[4] If a SARS-CoV-2 test is unavailable due to institution policy, a test shortage, or if there is a delay in test results, the subject must complete the COVID-19 questionnaire and answer NO to all questions to be eligible for study treatment. If a SARS-CoV-2 test is unavailable due to institution policy or a test shortage at the time of any follow-up or unscheduled visits, the COVID-19 questionnaire must be completed. A SARS-CoV-2 test will not be required if a subject has received a complete cycle of an authorized COVID-19 vaccine or has documented evidence of a positive COVID-19 antibody test, is asymptomatic, and has no long-lasting effects (per PI discretion) from a prior COVID-19 infection.

[5]PT/INR to be obtained only if a subject is on chronic warfarin therapy.

[6] aPTT to be obtained only if a subject is on chronic heparin therapy.

[7] Negative urine or blood pregnancy test is required for female subjects of childbearing potential within 7 days of the index procedure.

[8] All scheduled DUS exams should be performed per the protocol established by the core laboratory. If a DUS is non-diagnostic (per the imaging protocol), the site should make every effort to obtain a repeat exam within the visit window.

[9] Unscheduled tests and assessments should be completed prior to any interventional procedures to target limb.

[10] Unscheduled tests and assessments to be performed as clinically indicated.

[11] All imaging of the target limb acquired during scheduled visits or an interventional procedure to the target limb (such as venogram, IVUS, DUS, or X-ray) should be submitted to the respective core laboratory within 3 business days.

[12] Required if DUS suggests >50% stenosis or occlusion of the stented segment, or if the DUS is non-diagnostic or sub-optimal (i.e., due to obesity). If a follow-up venogram and/or IVUS is refused by the subject, this must be documented and will not be considered a protocol deviation.

[13] For the purposes of this study, all AEs, regardless of relatedness to the study device and/or study device procedure, target limb, or underlying venous disease are required to be reported on the AE eCRF and are considered “protocol reportable”. Please see **Section 17** for more information on safety events and reporting requirements.

[14] Follow-up assessments (required at the 30-day visit and beyond) that cannot be performed due to a subject’s medical condition (i.e., amputation) will not be considered protocol deviations if documentation of the medical condition is present in the subject’s medical records.

[15] To be performed both pre-and post-study device treatment as outlined in **Sections 9.5** and **9.6** and as described in the core laboratory manuals.

[16] May be required if DUS suggests >50% restenosis or occlusion of the stented segment **and** if the subject is presently symptomatic requiring a reintervention. If a follow-up venogram and/or IVUS is refused by the subject, this must be documented and will not be considered a protocol deviation.

9. REQUIRED TESTS AND ASSESSMENTS

The tests and assessments described in this section are required at baseline and/or at various follow-up visits according to the Time and Events Schedule in **Section 8.1**.

9.1. Laboratory Testing

Laboratory blood samples must be drawn pre-procedure but may not exceed 30 days prior to the index procedure.

Laboratory samples include:

- Serum Creatinine, eGFR, WBC, Platelet Count, Hemoglobin
- PT/INR (only if a subject is on chronic warfarin)
- aPTT (only if a subject is on chronic heparin)
- Pregnancy test (if female of childbearing potential) within 7 days prior to index procedure
- SARS-CoV-2 test and/or COVID-19 questionnaire within 8 days prior to index procedure (not required if subject has received a COVID-19 vaccination or shows positive for COVID-19 antibodies per Inclusion 17)

9.2. SARS-CoV-2 Testing

It is required that all subjects undergo testing for the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that results in the Coronavirus Disease 2019 (COVID-19) within 8 days prior to the index procedure. The result of this test must be negative for the subject to be eligible for enrollment in this clinical trial. If the test is positive, the subject must be documented as a screen failure.

A SARS-CoV-2 test will not be required if a subject has received a complete cycle of an authorized COVID-19 vaccine or has documented evidence of a positive COVID-19 antibody test and is asymptomatic and has no long-lasting effects from a prior COVID-19 infection.

If a SARS-CoV-2 test is unavailable due to institution policy, a test shortage, or if there is a delay in test results, the subject must complete the COVID-19 questionnaire. If the subject answers NO to all questions on the questionnaire and meets all other inclusion/exclusion criteria, the subject may be enrolled in this clinical trial. In the event that a subject is enrolled in this clinical trial without a SARS-CoV-2 test, the reason must be documented in the subject's study records and be able to be verified by the Sponsor in order to avoid a protocol deviation.

All enrolled subjects that receive a DUO Venous Stent(s) must undergo a SARS-CoV-2 test at every follow-up visit as well as all unscheduled visits. If at any time a SARS-CoV-2 test is unavailable, the COVID-19 questionnaire must be administered. If the results of this test are positive at any time throughout the duration of the clinical trial, this must be documented as an adverse event. If at any time a subject does test positive, no further SARS-CoV-2 testing is required. Please see **Section 17** for more information on safety events and reporting requirements.

A SARS-CoV-2 test will not be required at follow-up if one of the following have occurred:

1. Subject was enrolled under the vaccination and/or antibody requirements for Inclusion 17
2. Subject has received a full cycle of an authorized COVID-19 vaccination
3. Subject has documented evidence of a positive COVID-19 antibody test and is asymptomatic and has no long-lasting effects from a prior COVID-19 infection

9.3. Clinical Assessments

9.3.1. Venous Disease State Classification

Subjects will be grouped and analyzed based on their pre-treatment disease etiology. The PI will determine Venous Disease State Classification by classifying the subject as nonthrombotic, acute thrombotic, or chronic postthrombotic based on the criteria outlined below. The Venous Disease State Classification will be documented accordingly in the subject's source records and in EDC.

1. Nonthrombotic group:
    - Symptomatic subjects with iliofemoral venous obstruction and no history of DVT
    - If complete obstruction/occlusion extends into the EIV or CFV without involvement of iliac veins, subject should be classified as chronic postthrombotic
2. Acute thrombotic group:
    - First episode of acute symptomatic ipsilateral DVT ≤ 14 days old with venographic or IVUS evidence of acute clot and iliofemoral obstruction requiring stent placement
    - Successful clot removal required prior to stent placement
    - Prior to stent placement, if target lesion shows evidence of a chronic component, subject will be classified as chronic postthrombotic

3. Chronic postthrombotic group:

- Total occlusion or stenosis of iliofemoral segments requiring stent placement with onset of symptoms more than 14 days ago
- Any obstruction of iliofemoral segments with history of ipsilateral DVT within 2 years regardless of onset of symptoms

9.3.2. Venous Ulcer Assessment

An assessment of existing and/or new venous ulcers is to be performed according to the Time and Events Schedule in **Section 8.1**. Any pre-existing venous ulcers documented at Baseline will be followed until they are resolved or until the subject completes/is exited from the study. Any new venous ulcers that develop during follow-up will be documented and followed in the same manner. For all documented venous ulcers, the PI or Sub-Investigator (Sub-I) will classify them as Healed, Improving, Unchanged, or Worsening as well as the location of each. If, at the time of any follow-up visit, a subject's venous ulcer is dressed and it is not advisable to remove the dressing per PI discretion, this should be clearly documented and will not be considered a protocol deviation.

9.3.3. Clinical-Etiology-Anatomy-Pathophysiology (CEAP) Classification

The Clinical aspect of the CEAP classification will be used to categorize venous disease. The 'Clinical' signs of venous disease are those that are visible and used to categorize the subject from C0 to C6.

Clinical CEAP Classification	
Clinical Classification	**Description**
C0	No visible or palpable signs of venous disease
C1	Telangiectasia or reticular veins
C2	Varicose veins
C2r	Recurrent varicose veins
C3	Edema
C4	Changes in skin and subcutaneous tissue secondary to chronic venous disease
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C4c	Corona phlebectatica
C5	Healed
C6	Active venous ulcer
C6r	Recurrent active venous ulcer

9.3.4. Venous Clinical Severity Score (VCSS) – Pain Score

The VCSS system is a scoring system used to categorize nine attributes of venous disease into levels of severity ranging from 0 (absent) to 3 (severe). For this study, only the Pain Score will be collected.

Venous Clinical Severity Score (VCSS) – Pain Score		
Attribute	**Score**	**Description**
Pain (presumes venous origin)	Absent = 0	None
	Mild = 1	Occasional, not restricting activity or requiring analgesics
	Moderate = 2	Daily, moderate activity limitation, occasional analgesics
	Severe = 3	Daily, severe limiting activities or requiring regular use of analgesics

9.3.5. Villalta Score

The Villalta Scale for post thrombotic syndrome (PTS) is a scoring system in which five symptoms and six clinical signs are categorized by severity ranging from 0 (absent) to 3 (severe) as well as presence or absence of venous ulcer. A total score of 0 through 4 indicates no PTS, a score of 5 through 14 indicates mild/moderate PTS and a score of 15 or greater or presence of venous ulcers indicates severe PTS.

The Villalta Scale	
Symptoms	**Score** (Absent=0, Mild=1, Moderate=2, Severe=3)
Pain	
Cramps	
Heaviness	
Pruritus	
Paraesthesia	
Clinical Signs	**Score** (Absent=0, Mild=1, Moderate=2, Severe=3)
Pretibial edema	
Skin induration	
Hyperpigmentation	
Redness	
Venous ectasia	
Pain on calf compression	
Venous Ulcer	Present or Absent
Total Score*	

*The total score is the sum of all scores for each symptom and clinical sign. A score of 0 through 4 indicates no PTS, a score of 5 through 14 indicates mild/moderate PTS and a score of 15 or greater or presence of venous ulcers indicates severe PTS.

9.4. Questionnaires

9.4.1. VEnous INsufficiency Epidemiological and Economic Study Quality of Life/Symptoms (VEINES-QOL/Sym)

The VEINES-QOL/Sym scale is a 26-item subject-reported measure that generates 2 separate summary scores for symptoms (VEINES-Sym) and quality of life (VEINES-QOL).

- The VEINES-QOL summary score (25 items) is an estimate of the disease effect on a subject's quality of life
- The VEINES-Sym summary score (10 items) measures the severity of physical symptoms.

This questionnaire must be completed by the subject. Responses are evaluated on a 2-point to 7-point scale that rates intensity, frequency, or agreement.

9.4.2. EQ-5D-3L

The EQ-5D-3L instrument includes five dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. They each have three levels of categorization. This questionnaire must be completed by the subject.

9.5. Intravascular Ultrasound Imaging

IVUS is a very important imaging modality used in conjunction with venography. To some, this is considered the new gold standard in venous imaging. IVUS allows for direct imaging of the vein from an inside-out vantage point with high resolution reproduction of the vessel lumen, vessel wall, and importantly, the extravascular structures in close proximity to the vein. This is particularly useful for detecting iliofemoral compression syndrome, often caused by overriding iliac arteries or mass-effect from other nearby structures (tumors, aneurysms, etc.). Intraluminal filling defects such as acute or chronic thrombus, webs, or spurs are better imaged and identified with IVUS. Additionally, accurate and reproducible direct measurements of vessel diameter (long and short axis) and cross-sectional areas can readily be obtained using IVUS. The typical technique is to insert the IVUS catheter though the lesion and then acquire images as the catheter is pulled back. IVUS runs generally should begin in a normal segment of the vessel cranial to the lesion of interest and terminate in a normal segment caudal to the lesion. It is important to perform a slow and steady pull back of the IVUS catheter.

An IVUS run of the IVC, CIV, EIV, and CFV must be acquired both pre-treatment and post-treatment. Images must be acquired in DICOM format directly from the IVUS equipment for core laboratory analysis.

IVUS is required at the index procedure, for any reinterventions, and if the 12-month site reported or core laboratory adjudicated DUS shows >50% stenosis or occlusion of the stented segment. In addition, IVUS may be required for the 24 or 36-month DUS shows >50% stenosis or occlusion of the stented segment **and** the subject is symptomatic requiring a reintervention. Operators will be trained on the IVUS protocol provided by the core laboratory. No test cases are required for IVUS. A comprehensive overview for IVUS acquisition requirements can be found in the core laboratory manual.

9.6. Venographic Imaging

Venography is an important modality for the assessment and treatment of iliofemoral compression syndrome. A lower extremity vein caudal to the lesion, typically the popliteal vein or mid femoral vein, is accessed and radiopaque iodinated contrast is injected. Images are then captured as the dye flows cranially under digital subtraction angiography (DSA). This allows for the assessment of stenosis of the veins from extrinsic compression/obstruction, and for the detection of acute thrombus and intrinsic vein defects (webbing, spurs, etc.). Angiographic images are typically acquired in the AP view. However, angulated views from the LAO or RAO projections are essential to add additional information about vessel narrowing or “pancaking”, especially when the stenosis is eccentric. This is also useful if the AP view does not demonstrate a narrowing of the vessel. A lack of dye in a venous segment usually represents an occlusion. In the presence of occlusion there are typically numerous collaterals clearly visualized on venography.

A full venographic run of the IVC, CIV, EIV, and CFV must be acquired both pre-treatment and post-treatment. For all venography runs, a radiopaque or marker pigtail catheter should be utilized. This allows for accurate lesion length determination by the core laboratory. Images must be acquired in DICOM format with and without DSA. Full venographic runs, not only still frames, are required for core laboratory assessment.

Full venographic assessment must include the femoral vein, iliac veins, renal veins, and IVC at the index procedure, for any reinterventions, and if the 12-month site reported or core lab adjudicated DUS shows >50% stenosis or occlusion of the stented segment. In addition, venography may be required for the 24 or 36-month DUS shows >50% stenosis or occlusion of the stented segment **and** the subject is symptomatic requiring a reintervention. Operators will be trained on the venography protocol provided by the core laboratory. No test cases are required for venography.

A comprehensive overview for abdominal venography acquisition requirements can be found in the core laboratory manual.

9.7. Duplex Ultrasound Assessment

Abdominal/pelvic venous DUS is accepted as an effective method for diagnosis and follow up of iliofemoral obstruction syndrome and DVT. DUS combines spectral Doppler technology in addition to B-mode imaging to allow visualization of blood flow pattern abnormalities within the Iliofemoral veins in the presence of DVT or obstruction. Increased velocities associated with lumen narrowing can be visualized with spectral and color Doppler. B-mode cross-sectional and longitudinal imaging of diameters can also assess obstruction and extrinsic compression. A lack of color fill and B-mode visualization of thrombus can indicate DVT.

B-Mode, Color Doppler, and Spectral Doppler are required at the target vessels: IVC, CIV, EIV, and CFV. Color and Spectral Doppler B-Mode diameters are required at the narrowest point (lesion) of the target vessel and at a normal reference level taken caudal to the lesion. Velocity measurements are required at the narrowest point (lesion) of the target vessel and at a normal reference level taken caudal to the lesion.

Abdominal Venous DUS is required at the 30-day, 6-month, 12-month, 24-month, and 36-month follow up visits. Operators will be trained on the DUS protocol provided by the core laboratory. Each site is required to submit a test DUS exam to the core laboratory prior to performing any study related DUS exams.

A comprehensive overview for DUS acquisition requirements can be found in the core laboratory manual.

9.8. X-ray Assessment

An X-ray assessment will be performed at the 12-month, 24-month, and 36-month follow-up visits to assess the DUO Stent(s)' implant integrity for all subjects in whom at least one DUO Stent was placed during the index procedure.

A comprehensive overview of procedural requirements for X-ray assessments can be found in the core laboratory manual.

In Europe, the only medical procedure that may be considered a deviation from routine medical care are the X-rays performed during the 12, 24, and 36-month follow-up visits. The X-rays are performed to assess stent fracture and migration rates.

10. SCREENING PROCEDURES

All subjects presenting to the institution with a suspected iliofemoral venous outflow obstruction will be screened for initial eligibility. A trained member of the research team shall perform a preliminary evaluation of the potential subject's medical history and screen for initial eligibility. Only assessments consistent with the institution's standard of care may be performed prior to obtaining a signed consent form. If during pre-screening, a subject is found to meet one or more exclusion criteria, or does not meet one or more inclusion criteria, the subject would be considered a pre-screen failure. The reason for pre-screen failure must be documented in the screening log and no further action is required.

If a subject is not a pre-screen failure, the subject is eligible to move forward with the screening and informed consent process. Qualified and trained research staff listed on the Site Delegation of Authority Log will approach the subject and initiate the informed consent process.

10.1. Obtaining Informed Consent

All sites shall comply with 21 CFR 50, provisions of International Conference on Harmonization (ICH) E6 Good Clinical Practices (GCPs), local institutional review board (IRB)/ethics committee (EC) policies and all applicable local regulations for obtaining informed consent. Prior to obtaining informed consent, the PI or designee will thoroughly explain the nature and purpose of the study to the subject. The PI or designee will document the informed consent process in the subject's source records and use the most current IRB/EC approved informed consent form (ICF) for each subject **prior** to any study-specific screening/baseline tests or procedures being performed. This does not include those procedures or tests that are completed in the normal course of the subject's non-study related care and that are done prior to undergoing the study procedure, but shall include previously performed tests that may need to be repeated to determine eligibility.

All subjects shall possess the ability to understand the information contained in the informed consent form. Subjects will have the study procedures explained in a manner as non-technical as possible, including the risks, benefits, and follow-up requirements. If the subject agrees to participate in this study, the subject will be required to sign and date the ICF. If a subject possesses the ability to understand the informed consent process and participation in study, but due to physical inability cannot sign the ICF, an impartial witness may sign the ICF on behalf of the subject. Non-English-speaking subjects may only be enrolled if they sign an IRB/EC approved and certified translated informed consent form that has been IRB/EC approved and is reflective of his/her spoken language.

Once all required parties have signed the ICF, the subject will receive a copy of their signed informed consent form for his/her records.

10.2. Screening Success and Failure Criteria

Final eligibility of a subject will be confirmed during the Index Procedure. Subjects must provide prior informed consent no greater than 30 days prior to the index procedure. If 30 days have passed since the subject signed an informed consent form, the subject should be re-consented. Every effort will be made to ensure subject eligibility prior to enrollment. If the subject meets all the inclusion criteria and none of the exclusion criteria after pre-enrollment angioplasty, the subject will be considered eligible for

enrollment. If at any point prior to or just after pre-enrollment angioplasty, but prior to the DUO stent system being advanced through the introducer sheath, an exclusion criterion is met and/or an inclusion criterion is not met, the subject will be deemed a screen failure. No further follow-up will be required for these subjects; however, the following details will be documented in the subject's source records:

- Documentation that the subject is a screen failure
- Documentation of the inclusion/exclusion criteria that was met and/or not met, with clarification provided as necessary

11. BASELINE EVALUATION

11.1. Baseline Assessments

The following assessments will be performed during baseline evaluation. These examinations and tests will be used both to screen for eligible subjects and to provide baseline information for those subjects who meet study criteria. All assessments must be completed no more than 30 days prior to the subject undergoing the index procedure, except for the urine or blood pregnancy test and the SARS-CoV-2 test and/or COVID-19 questionnaire.

The urine or blood pregnancy test is required for female subjects of childbearing potential and must be completed no more than 7 days prior to the index procedure. The SARS-CoV-2 test may be required (See Inclusion 17) and must be completed no more than 8 days prior to the index procedure. The result of both tests must be negative for the subject to be eligible for enrollment in this clinical trial. A COVID-19 questionnaire may be used in place of a SARS-CoV-2 Test under certain conditions. See **Section 9.2 SARS-CoV-2 Testing** for more details.

- Informed Consent
- SARS-CoV-2 Test, if required per Inclusion 17
- Assessment of Inclusion/Exclusion Criteria
- Demographic information and medical history including risk factors
- Brief physical examination
    - Including height and weight
- Serum Creatinine, eGFR, WBC, Platelet Count, Hemoglobin
- PT/INR (only if a subject is on chronic warfarin)
- aPTT (only if a subject is on chronic heparin)
- Urine or blood pregnancy test (required for females of childbearing potential only) within 7 days prior to index procedure
- Venous Ulcer Assessment
- CEAP Classification
- VCSS Pain Score
- Villalta Score
- VEINES-QOL/Sym Questionnaire
- EQ-5D-3L Questionnaire
- Review of Concomitant medications

12. CONCOMITANT MEDICATIONS

In addition to the procedural medications described in the sections below, reportable medications to be recorded in the electronic Case Report Form (eCRF) are medications taken by the subject to treat their cardiovascular disease, including antithrombotics (antiplatelets, anticoagulants), antibiotics, NSAIDs, steroids, diuretics, calcium channel blockers, and statins. These medications will be captured at baseline through study completion and include prior ongoing or new use of the medications mentioned in this section (either prescription or over the counter).

In addition, all COVID-19 vaccinations received (prior to or after enrollment) will be recorded in the eCRF.

The following antiplatelet and anticoagulation regimen described in **Sections 12.1, 12.2, and 12.3** below, is required, unless otherwise dictated by Institution or PI standard of care. If an alternative antiplatelet and anticoagulation regimen is required per Institution or PI, the regimen must be documented prior to the first subject being enrolled. This alternative antiplatelet and anticoagulation regimen will be used to monitor pre-procedure, peri-procedure, and post-procedure medication compliance. Non-compliance with the documented antiplatelet and anticoagulation regimen will be considered a protocol deviation. If non-compliance is deemed medically necessary for the patient's safety and/or well-being, the reason must be documented, and the non-compliance will not be considered a protocol deviation.

12.1. Pre-Procedural Medications

Pre-procedural anticoagulation should be stopped if required by the PI or Institution.

Subjects taking warfarin prior to the index procedure with a pre-procedural INR >2 due to coagulopathy (on the day of the index procedure) are still eligible for study device treatment subject to the approval of the PI. Subjects on antiplatelet therapy should stop, if required by the Institution or PI.

12.2. Peri-Procedural Medications

Full therapeutic anticoagulation is required for all subjects for the duration of the index procedure. The anticoagulation regimen should follow the site's standard anticoagulation protocol and must be documented in the subject's study records.

12.3. Post-Procedural Medications

For all subjects, institute full anticoagulation within 4 hours following the completed index procedure and follow the below regimen. Start time of full anticoagulation should be documented.

Enoxaparin for the first 30 days post-procedure. After this time, continue full anticoagulation with an oral anticoagulant. If warfarin is used, an INR of 2.0-3.0 with appropriate bridging therapy is required. A direct oral anticoagulant, such as apixaban, dabigatran, rivaroxaban, or edoxaban can be used instead of warfarin.

The minimum anticoagulation treatment durations are:

- 3 months for nonthrombotic subjects
- 12 months for thrombotic subjects
- Long-term for subjects with thrombophilia

Concomitant antiplatelet therapy with aspirin or thienopyridine class drugs may also be used at the discretion of the PI. Due to the high risk of bleeding, dual antiplatelet therapy in addition to anticoagulation is not recommended unless deemed appropriate by the PI. Antiplatelet therapy can be considered after anticoagulation therapy is discontinued.

13. INDEX PROCEDURE

All imaging-related inclusion/exclusion criteria are based on the PI's assessment at the time of the Index Procedure.

13.1. Index Procedure Baseline IVUS

Final eligibility of all subjects will be confirmed using the Index Procedure Baseline IVUS. The Index Procedure Baseline IVUS must be performed during the index procedure in order to assess baseline imaging-related eligibility for inclusion as described in **Section 13.1.3** below. Both the baseline venogram and IVUS are to be performed as per guidelines established by the independent core laboratory. Baseline venograms performed for all enrolled subjects will be reviewed by the core laboratory as outlined in the venographic core laboratory protocol.

All data that are required to be recorded during the index procedure are reflected in the index procedure interval eCRFs within the EDC. Required measurements and data listed in the following sections are not exhaustive of all data that is required. Therefore, the required data should be reviewed in advance of the procedure to ensure it is understood and captured appropriately. The electronic Case Report Form (eCRF) Completion Guidelines contain instructions for data entry and should be referenced, as necessary.

13.1.1. Preparation

Procedural techniques will be in accordance with the institutional standard of care for iliofemoral venoplasty and stenting.

All subjects should receive the appropriate anticoagulant therapy per **Section 12**.

13.1.2. IVC Filter Placement

IVC filter placement is not recommended but is ultimately at the discretion of the PI in circumstances such as floating thrombus in iliocaval segments or if there is planned use of mechanical thrombectomy in the presence of acute thrombus. In all cases, the IVC filter should be removed as soon as deemed safe by the PI. Confirmation of successful placement and removal of the IVC filter should be documented in the source documents and the eCRF.

13.1.3. Baseline Venographic and IVUS Requirements

Baseline venographic and IVUS measurements of the target lesion and target vessels (visual estimate) shall be captured to determine eligibility and include, but are not limited to, the following:

- Target lesion(s) details including vessel location(s), lesion length(s), and pre-PTA % reduction in target vessel lumen diameter
- Indication for stenting and final disease state classification (acute DVT, nonthrombotic, chronic postthrombotic)
- Reference vessel diameter(s)

- Inflow venous patency (if patency of profunda cannot be confirmed by venogram or IVUS, pre-operative DUS findings may be used to confirm)
- Absence of thrombus and/or successfully treated thrombus for acute DVT subjects

13.2. Pre-Dilation

Please refer to the Instructions for Use (IFU) for detailed instructions regarding Pre-dilation inflation recommendations. It is recommended that pre-dilation equivalent to the size of the intended stent be performed.

Pre-dilation balloon-related details will be recorded and include, but are not limited to, the following: balloon name/manufacturer and balloon size, max pressure, inflation duration at max pressure, and max inflation diameter across all inflations.

13.3. Study Device Treatment

Subjects who meet all inclusion criteria, and who do not meet any exclusion criteria will be deemed eligible for Study Device Treatment.

13.3.1. Enrollment (Intent-to-Treat)

A subject is defined as intent-to-treat (ITT) and officially enrolled in the study once the DUO Venous Stent System is advanced through the introducer sheath.

Subjects in whom no DUO Stent implant is placed will be exited after 30 days. Subjects in whom at least one DUO Stent implant is placed will be followed for 36 months.

The per-protocol (PP) population will be defined as ITT subjects with evaluable data that have met the definition for device success, excluding subjects with major deviations, such as those who meet criteria for a protocol violation(s), as determined by the Sponsor**.**

13.3.2. Treatment Recommendations

Please refer to the IFU for detailed instructions regarding recommended criteria for use of the study device and stent sizing. IVUS is required for stent sizing.

NOTE: When overlapping study devices, there should be no more than 2mm of diameter difference between devices.

13.3.3. Post-Study Device Treatment Measurements

The following information should be recorded Post-Study Device Treatment:

- Assessment of successful introduction, deployment, and withdrawal with the stent remaining in the intended location through completion of the procedure
- Number and type of DUO Venous Stent Systems used to treat subject and associated lot number(s) as well as number of stents deployed

- Vessel location and size of each deployed DUO Stent

13.3.4. Final Treatment Results

The following information should be recorded after post-dilation and upon completion of index procedure and includes but is not limited to:

- Adjunctive procedures performed and outcomes
- Study Device Procedure Time (defined as the time the first DUO Venous Stent System is advanced through the introducer sheath to the time of withdrawal of the last balloon catheter)
- Adverse event/device event occurrence

14. POST-PROCEDURE/PRE-DISCHARGE

All subjects will be assessed post-procedure prior to discharge (Pre-Discharge) and shall receive a medical regimen for the medications required post-procedure per **Section 12**. All study medications shall be captured in the eCRF.

14.1. Required Assessments

Assessments required post-procedure/pre-discharge include the following:

- Adverse event assessment
- Concomitant medication review
- PT/INR (only for subjects on chronic warfarin)*
- aPTT (only for subjects on chronic heparin)*

* If a subject is on chronic warfarin or chronic heparin, they may be discharged before lab results from PT/INR or aPTT tests are obtained.

All subjects receiving treatment with a DUO Stent implant should be provided with the DUO Stent System Subject Implant Card (PIC). The PIC is designed for the subject to carry along with their insurance cards. This PIC is to be completed by the designated research personnel to include information pertaining to the DUO Stent(s) including the model, lot number and vessel location of the implanted DUO Stent(s) and the date of the index procedure. The card also provides manufacturer information and MRI Compatibility.

15. REQUIRED FOLLOW-UP VISITS AND ASSESSMENTS

All subjects will be required to return for clinic follow-up visits as outlined in **Section 8.1** and in the sections below.

In the event of a public health crisis, a global pandemic, a natural disaster, or any other event which would preclude research sites from conducting research or restrict subjects' ability to attend follow-up visits, guidance will be provided by the Sponsor regarding visit windows.

15.1. 30-day Follow-up Visit (-2 days / +14 days post-Index Procedure)

The following assessments are required to be performed at the 30-day follow-up visit:

- SARS-CoV-2 Testing (if required per Section 9.2)
- DUS
- Venous Ulcer Assessment
- Adverse event assessment
- Review of concomitant medications

15.2. 6-month Follow-up Visit (±30 days post-Index Procedure)

The following assessments are required to be performed at the 6-month follow-up visit:

- SARS-CoV-2 Testing (if required per Section 9.2)
- Venous Ulcer Assessment
- CEAP Classification
- Villalta Score
- VCSS Pain Score
- DUS
- VEINES-QOL/Sym Questionnaire
- EQ-5D-3L Questionnaire
- Adverse event assessment
- Review of concomitant medications

15.3. 12-month Follow-up Visit (±30 days post-Index Procedure)

The following assessments are required to be performed at the 12-month follow-up visit:

- SARS-CoV-2 Testing (if required per Section 9.2)
- Venous Ulcer Assessment
- CEAP Classification

- Villalta Score
- VCSS Pain Score
- DUS
- X-ray of implanted stent(s)
- VEINES-QOL/Sym Questionnaire
- EQ-5D-3L Questionnaire
- Adverse event assessment
- Review of concomitant medications
- Follow-up venogram and IVUS are required if DUS suggests >50% stenosis or occlusion of the stented segment, or if the DUS is non-diagnostic or sub-optimal (i.e., due to obesity). If a follow-up venogram/IVUS is refused by the subject, this must be documented and will not be considered a protocol deviation and the DUS will be used if available.

15.4. 24-month Follow-up Visit (±30 days post-Index Procedure)

The following assessments are required to be performed at the 24-month follow-up visit:

- SARS-CoV-2 Testing (if required per Section 9.2)
- DUS
- X-ray of implanted stent(s)
- Venous Ulcer Assessment
- CEAP Classification
- Villalta Score
- VCSS Pain Score
- VEINES-QOL/Sym Questionnaire
- EQ-5D-3L Questionnaire
- Adverse event assessment
- Review of concomitant medications
- Follow-up venogram and IVUS may be required if DUS suggests >50% stenosis or occlusion of the stented segment, **and** if the subject is symptomatic requiring a reintervention. If a follow-up venogram and/or IVUS is refused by the subject, this must be documented and will not be considered a protocol deviation and the DUS will be used if available.

15.5. 36-month Follow-up Visit (±30 days post-Index Procedure)

The following assessments are required to be performed at the 36-month follow-up visit:

- SARS-CoV-2 Testing (if required per Section 9.2)
- DUS
- X-ray of implanted stent(s)
- Venous Ulcer Assessment
- CEAP Classification
- Villalta Score
- VCSS Pain Score
- VEINES-QOL/Sym Questionnaire
- EQ-5D-3L Questionnaire
- Adverse event assessment
- Review of concomitant medications
- Follow-up venogram and IVUS may be required if DUS suggests >50% stenosis or occlusion of the stented segment, **and** if the subject is symptomatic requiring a reintervention. If a follow-up venogram and/or IVUS is refused by the subject, this must be documented and will not be considered a protocol deviation and the DUS will be used if available.

There is no follow-up or observation planned after the subject completes the 36-month follow-up visit and is exited from the study.

15.6. Unscheduled Visit

An Unscheduled visit will be documented when a subject presents to the hospital or clinic between study-required follow-up visits and is seen by study personnel for a limb-related event, including reinterventions. The assessments below should be performed prior to any interventional procedures to the target limb. In addition, all imaging studies performed should follow the guidelines set forth by the respective core laboratory. This imaging should be submitted to the respective core laboratories within 3 business days for review and analysis.

- SARS-CoV-2 Testing (if required per Section 9.2)
- Venous Ulcer Assessment (if applicable)
- CEAP Classification
- Villalta Score

- VCSS Pain Score
- VEINES-QOL/SYM Questionnaire
- EQ-5D-3L Questionnaire
- DUS (as clinically indicated)
- Venogram and/or IVUS (as clinically indicated)
- X-ray assessment (as clinically indicated)
- Adverse event assessment
- Review of concomitant medications

  Note: Any change in concomitant medications, including any loading dose provided during an unscheduled procedure, should be recorded in the eCRF.

15.7. Follow-up Visit Compliance

As part of the informed consent process, all reasonable efforts will be made to obtain complete data for all subjects according to the follow-up visit schedule. PI and research staff will be expected to maintain continuous and open communication with study subjects regarding their participation in this study.

Three attempts via telephone will be made to contact subjects who do not return for a study follow-up visit. If after three telephone attempts the subjects cannot be contacted, a certified letter should be sent by the PI or designated study coordinator to the subject's last known address. If possible, public records should be searched to ascertain survival status. If efforts to reach the subject are unsuccessful after three telephone contacts and a certified letter, and there is no evidence of subject expiration, or the site has not been notified of a subject's wish to withdraw consent, a protocol deviation for a visit not done must be documented in the subject's source records and reported in the EDC system. A detailed record of all contact attempts should be maintained in the subject's file. This process should be repeated for all subsequently missed follow-up visits and documented accordingly. After required contact attempts are unsuccessful for at least 2 consecutive missed follow-up visits and the 12-month visit window (or any later subsequent visit window) has passed, only then should a subject be considered lost-to-follow-up (LTFU) and exited from the study.

In the event of a public health crisis, a global pandemic, a natural disaster, or any other event which would preclude research sites from conducting research or restrict subjects' ability to attend follow-up visits, guidance will be provided by the Sponsor and may include performing follow-up visits via alternative methods, extending visit windows, etc.

15.8. Subject Discontinuation and Replacement

A subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. In addition, a subject may be discontinued if in the PI's opinion it is in the subject's best interest. If a subject prematurely discontinues from the study, the reason will be recorded in the eCRF with supporting documentation. These results will be tabulated by number and percent for each category for discontinuation.

Subjects who prematurely exit the study after treatment will have their data maintained and evaluated up until the time of withdrawal. Subjects who are voluntarily or involuntarily (per PI discretion or if LTFU) withdrawn cannot re-enter the study. These subjects will not be replaced. There is no follow-up or observation planned for subjects who withdraw voluntarily or who are involuntarily withdrawn by the PI.

16. RISK/BENEFIT ASSESSMENT

16.1. Risks

The use of the DUO Venous Stent System in treating venous obstructions may result in anticipated potential risks or complications similar to other available endovascular implant devices (such as stents) used in these procedures. Such risks are included in the DUO Venous Stent System IFU and are listed below:

- Access failure or abrupt closure
- Allergic/anaphylactoid reaction to anticoagulant and/or antithrombotic therapy or contrast medium
- Allergic reaction to Nitinol
- Amputation
- Aneurysm
- Angina/coronary ischemia/myocardial infarction
- Arrhythmia
- Arteriovenous fistula
- Death
- Embolism
- Emergent repeat hospital intervention
- Extravasation
- Fever
- Gastrointestinal bleed from anticoagulation/antiplatelet medication
- Hematoma/hemorrhage
- Hypotension/hypertension
- Incorrect positioning of the stent requiring further stenting or surgery
- Intimal Injury/dissection
- Ischemia/infarction or tissue/organ
- Infection/abscess at insertion site
- Inflammation
- Malposition of stent
- Multi-organ failure
- Open surgical repair
- Pain
- Pulmonary Embolism
- Pseudoaneurysm
- Renal insufficiency or failure
- Respiratory distress or failure
- Restenosis
- Rupture
- Septicemia/bacteremia (sepsis)
- Stent implant fracture
- Stent implant migration (device moves over time)
- Trauma to adjacent structures

- Vasospasm
- Venous occlusion/thrombosis, remote from puncture site
- Venous occlusion/thrombosis, near puncture site
- Venous occlusion/restenosis of the treated vessel

These risks are present in any endovascular treatment procedure for which the study subjects would be indicated because of their disease and will be reviewed with all subjects during the informed consent process.

16.2. Potential Benefits

- The DUO Stent may help improve the blood flow in the leg vein.
- Participation in this study may yield information that is necessary for the development of better or new treatments for this disease and may benefit other people who have the same blockages in the leg veins.

16.3. Justification for Clinical Trial

The safety of the DUO Venous Stent System has been established through extensive design verification testing, including animal testing, and through a detailed risk analysis process per ISO 14971. The results of non-clinical testing have demonstrated safety and therefore it is anticipated that the assessment of risk and benefit is appropriate for the intended use of the study device and the initiation of this study.

This study is being conducted in to collect safety and efficacy data on the DUO Venous Stent System to support an FDA Premarket Approval application. All efforts will be made to minimize the occurrence of risk to study subjects through PI/institution qualification, PI training on the safe and proper use of the device in accordance with the IFU, PI/site training on the protocol, and clearly defining subject eligibility requirements (inclusion/exclusion criteria) and contraindications as described in the IFU.

17. SAFETY EVENTS AND REPORTING REQUIREMENTS

The PI at each participating site is ultimately responsible for the timely review and reporting of AEs per respective IRB/EC policy and in accordance with FDA and ISO 14155 (OUS sites) requirements.

The safety reporting period will begin at the time of enrollment into the study (See **Section 13.3.1** for details on what constitutes subject enrollment) and will continue through study completion.

All protocol reportable AEs will be monitored from the time of enrollment through the follow-up period for this study. A description of the event, including the start date, resolution (or date of final outcome assessment) date, action taken, and the outcome should be provided, along with the PI's assessment of the relationship between the event and the study device or study device procedure. Pain, neurological status, and functional impairment should be considered AEs when a subject's complaint of any of these symptoms is outside the normal pattern for the illness treated.

All protocol-reportable events reported during the safety observation period described above should be followed until the event is resolved or judged to be chronically stable. Follow-up information will be submitted to the Medical Monitor and/or the Sponsor as it becomes available.

In the event that the subject undergoes a SARS-CoV-2 test within 8 days of the index procedure and there is a delay in obtaining test results the subject may still be enrolled if they meet all of the other SARS-CoV-2 inclusion criteria, including successful completion of a COVID-19 questionnaire. If, when test results are received, the test result is positive, this must be recorded as an adverse event. **This is the only adverse event that will be captured prior to enrollment, as the start date of the adverse event will be the date of the SARS-CoV-2 testing, which occurred before the subject was enrolled.**

The Sponsor or its designee will include relevant adverse event information in annual Investigational Device Exemption (IDE) progress reports. Additionally, the Sponsor or its designee will report all applicable serious adverse events as vigilance reports per MEDDEV 2.12.1, Rev 8 (2013) "Guidelines on a Medical Devices Vigilance System" and as clinical trial reportable events per MEDDEV 2.7/3 "Clinical Investigations: Serious Adverse Event Reporting". The Sponsor will determine whether all the local PIs need to be informed immediately of a serious adverse event (SAE) or unanticipated adverse device effect (UADE), or whether this can be postponed until the next regularly scheduled study update.

17.1. Adverse Events

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects whether or not related to the investigational device/procedure.

If a pre-existing condition is present at enrollment, it must be recorded as an adverse event only if the frequency, intensity, or the character of the condition worsens during the study.

For the purposes of this study, all AEs, regardless of relatedness to the study device and/or study device procedure, target limb, or underlying venous disease are **required** to be reported on the AE eCRF and are considered "protocol-reportable".

All protocol-reportable AEs will be evaluated by the PI using his/her clinical judgement to determine whether the event further meets the criteria for adverse device effect (ADE), serious adverse event (SAE), serious adverse device effect (SADE), or unanticipated adverse device effect (UADE) and will be subject to the respective reporting requirements as outlined in the sections below. The PI or designee is also responsible for informing their IRB/EC of adverse events as required by their IRB/EC reporting requirements and in conformance with FDA and local regulatory reporting requirements. In addition, the PI shall provide documentation of the report submitted to the IRB/EC to Vesper Medical or its designee.

The following types of adverse events must be recorded on the AE eCRF by the PI (or designee):

- Serious Adverse Events
- Any adverse event, regardless of relatedness to the study device, study device procedure, target limb, or underlying venous disease.

The report will include: the AE term, seriousness, severity, action taken, treatment outcome, relationship of the adverse event to the study device and/or study device procedure, and the event status.

All events will be made accessible to the Sponsor and/or designee to review the need for FDA regulatory reporting.

Severity of adverse events will be classified according to the following criteria:

Mild: A mild adverse event is an AE usually transient in nature and generally not interfering with normal activities and not requiring intervention or treatment

Moderate: A moderate adverse event is an AE that is sufficiently discomforting to interfere with normal activities and may require intervention or treatment.

Severe: A severe adverse event is an AE that results in significant symptoms that prevent normal activities and may require hospitalization or invasive intervention.

The relationship of the AE to the device or study device procedure will be classified according to the following criteria:

Unrelated: The AE is clearly not related to the study device or study device procedure.

Possibly: Signs or symptoms of the AE may be related to the study device or study device procedure *and/or* the natural disease process or other injury/illness.

Definitely: The AE is clearly related to the study device or study device procedure. Signs and symptoms could not reasonably be related to the natural disease process or other injury or illness.

Unknown: Unable to determine the relationship between the study device, study device procedure, natural disease process and/or other injury/illness.

In addition, all AEs will be assessed and recorded in the eCRF by the PI or Sub-I for relatedness to COVID-19 by indicating:

- Yes, related to COVID-19
- No, not related to COVID-19
- Unknown

17.2. Adverse Device Effects

An ADE is defined as any untoward adverse event related to the use of an investigational device or unintended response to a medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device(See **Section 18**).

Note 2: This definition includes any event resulting from user error or from intentional misuse of the investigational medical device (See **Section 18**).

A list of events that may be associated with the study device and/or the study device procedure is provided in **Section 16.1**.

17.2.1. ADE Reporting

All ADEs must be evaluated to determine whether the event further meets criteria for a SADE (See **Section 17.5.1**) and would be subject to respective reporting requirements. Non-serious, anticipated ADEs must be reported by the PI (or designee) to the Sponsor and must also be submitted to the IRB/EC per the applicable reporting guidelines. If the event occurred as a result of a device event, respective reporting requirements must be followed as outlined in **Section 18**.

17.3. Serious Adverse Events

A SAE is defined as an adverse event that:

- led to death,
- led to a serious deterioration in the health of the subject, that either resulted in:
  - a life-threatening illness or injury, or
  - resulted in a permanent impairment of a body structure or a body function, or

- required in-patient hospitalization or prolongation of existing hospitalization, or
- resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function, or,
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the investigational plan without serious deterioration in health, is not considered a serious adverse event.

For study sites in Germany the following definition of a SAE according to article 3 MPSV (Ordinance on the Medical Device Safety Plan) shall be considered:

A serious adverse event is defined as "any untoward event that occurs during a clinical trial or performance evaluation requiring approval, which has led, could have led or might possibly lead, directly or indirectly, to the death or serious deterioration in the state of health of a subject, user or another person, whether or not the event is related to the medical device" (MPSV § 2 paragraph 5).

17.3.1. SAE Reporting

All SAEs must be evaluated to determine whether the event further meets criteria for a SADE (See **Section 17.5.1**) and would be subject to respective reporting requirements. All events that meet the criteria above for SAEs must be reported by the PI (or designee) to the Sponsor ***within 2 business days (Monday through Friday) from first knowledge of event*** and must also be reported to the IRB/EC per the applicable reporting guidelines.

In Germany, the investigator must report any SAE to the sponsor immediately according to MPSV § 3 paragraphs 4 through 6.

Any SAE with a potentially causal relationship between the event and the investigational medical device or procedures performed as part of the clinical trial or other conditions of the trial conduct will be reported to BfArM immediately. Such related/potentially related SAEs occurring in Germany will be reported via the BfArM SAE report form and on the MEDDEV 2.7.3 table. For all other SAEs, the reports will be submitted quarterly on MEDDEV 2.7.3 table.

SAEs with a causal relationship occurring in other countries will be reported via the MEDDEV 2.7.3 table to BfArM immediately after gaining knowledge and in accordance with the national requirements in the corresponding countries. For all other SAEs, the MEDDEV 2.7.3 table will be submitted quarterly on MEDDEV 2.7.3.

Further, a quarterly evaluation has to be provided to BfArM considering all SAEs occurred in the study. The BfArM template shall be used for this report.

17.4. Major Adverse Events

For this study, the definition of a MAE includes the following events that comprise safety and observational endpoints that require adjudication by the CEC:

- Device or procedure-related death
- Device or procedure-related bleed at the target vessel and/or the target lesion or at the access site requiring surgical or endovascular intervention or blood transfusion of ≥2 units
- Device or procedure-related venous injury occurring in the target vessel and/or the target lesion or at the access site requiring surgical or endovascular intervention
- Major amputation of the target limb
- Clinically significant pulmonary embolism, confirmed by CT angiography
- Stent embolization outside of the target vessel
- Presence of new thrombus within the stented segment

17.4.1. MAE Reporting

A major adverse event must be reported by the PI (or designee) to the Sponsor ***within 2 business days (Monday through Friday) from first knowledge of event*** and must also be reported to the IRB/EC per the applicable reporting guidelines.

17.5. Serious Adverse Device Effects

A SADE is defined as an ADE that results in any of the consequences characteristic of a SAE.

17.5.1. SADE Reporting

All events that meet the criteria above for a SADE must be reported by the PI (or designee) to the Sponsor ***within 2 business days (Monday through Friday) from first knowledge of event*** and must also be reported to the IRB/EC per the applicable reporting guidelines. If the event occurred as a result of a device event, respective device event reporting requirements must be followed as outlined in **Section 18**.

17.6. Unanticipated Adverse Device Effects

A UADE is defined as any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

17.6.1. UADE Reporting

Any event that is suspected of meeting UADE criteria should be reported in the same manner as a SAE or SADE and must be reported by the PI (or designee) to the Sponsor ***within 2 business days (Monday through Friday) from first knowledge of event*** and must also be reported to the IRB/EC per the applicable reporting guidelines. All SAEs will be reviewed by the Sponsor (or designee) to determine if UADE criteria is met, and if so, the Sponsor or designee will immediately conduct an evaluation and report the results of the evaluation to FDA, all reviewing IRBs/ECs, and participating PIs within 10 business days after the Sponsor first receives notice of the UADE.

17.7. Pregnancies

Female subjects of childbearing potential must use some form of contraception (abstinence is acceptable) throughout the duration of the study. Each pregnancy occurring while the subject is enrolled in the study should be reported to the study Sponsor upon learning of its occurrence. Thereafter, the pregnancy should be followed to determine its outcome.

17.8. Protocol Deviations and Protocol Violations

A protocol deviation occurs when, without significant consequence, the activities on a study diverge from the IRB-approved protocol. Any protocol-required test, assessment, or procedure that is not done or is done out of window is considered a protocol deviation. For example, a subject missing a protocol-required visit due to being away on vacation, or a DUS that is done out of window, would both be considered protocol deviations. All protocol deviations must be documented in EDC and reported to the Sponsor by the PI or designee upon first knowledge of the deviation.

A protocol violation is a divergence from the IRB-approved protocol that may reduce the quality or completeness of data, makes the ICF inaccurate, or impacts a subject's safety, rights, or welfare. Examples of protocol violations include, but are not limited to, the following:

- Inadequate or delinquent informed consent;
- Enrolled subject(s) who did not meet Inclusion/Exclusion criteria;
- Unreported SAEs, UADEs, SADEs;
- Multiple visits missed or visits that took place outside permissible windows;
- Materially inadequate record keeping;
- Intentional deviations from the protocol, GCP, or regulations by study personnel;
- Repeated noncompliance with study requirements;
- Events that may affect the outcome (endpoints) of the study, OR;

- Any other act or occurrence identified by the study Sponsor as constituting a violation from the protocol

18. STUDY DEVICE EVENT REPORTING

A Study Device Event refers to the performance of the study device and the occurrence of a deficiency or malfunction as defined in sub-sections below. Device events are to be reported on the Device Event eCRF and submitted to the Sponsor **within 2 business days (Monday through Friday) of first knowledge of occurrence.** Any AE suspected of resulting from a device event must be reported per the required timelines as outlined in **Section 17**.

18.1. Device Deficiency

Device deficiency is defined as inadequacy of a medical device related to its identity, quality, durability, reliability, safety, or performance, such as malfunction, misuse or not observing the IFU, and inadequate labeling.

18.2. Device Malfunction

A malfunction is defined as a failure of a device to meet its performance specifications or otherwise to perform as intended.

18.3. Device Returns

In the event that a device is suspected of deficiency or malfunction, the PI should make every effort to return the device to the manufacturer, Vesper Medical. The PI or designee shall contact Vesper Medical for a return manufacturer authorization number and for additional instructions for the return of potentially biohazardous material.

19. STATISTICAL METHODS AND CONSIDERATIONS

19.1. Introduction

Descriptive statistics for each variable will be calculated which will include the number of observations, mean, standard deviation, median, minimum and maximum for continuous variables and will also include the number and percent of observations for categorical variables.

When the mean is found not to be an appropriate measure of central tendency, alternative statistics will be considered (e.g. median). When the distribution of a variable does not support the use of parametric statistics, nonparametric approaches or data transformations may be implemented. If data transformations are used, they will be specified in the final clinical report.

19.2. Analysis Groups

A subject is defined as ITT and officially enrolled in the study once the DUO Venous Stent System is advanced through the introducer sheath.

Subjects in whom no DUO Stent implant is placed will be exited after 30 days. Subjects in whom at least one DUO Stent implant is placed will be followed for 36 months.

The full analysis set (FAS) are subjects who meet the ITT definition and have data evaluable for the primary endpoints.

The PP population will be defined as ITT subjects with evaluable data that have met the definition for device success, excluding subjects meeting criteria for a protocol violation(s) as outlined in **Section 17.8** and as determined by the Sponsor.

In addition, a SARS-CoV-2 positive population will be defined as:

1. Any documented confirmation of a SARS-CoV-2 positive test result or SARS-CoV-2 positive antibody test (at any approved testing site) from screening through study exit. Subjects will be grouped according to when they became SARS-CoV-2 positive based on the date that testing was performed as compared to the index procedure (i.e., within 30 days, greater than 30 days but within 12 months, greater than 12 months).
2. In the absence of a SARS-CoV-2 test, subjects will be required to complete a COVID-19 questionnaire. Any subject that completes a questionnaire after screening and answers YES to any question on the questionnaire will be included in the SARS-CoV-2 positive population.
3. Regardless of SARS-CoV-2 status or COVID-19 questionnaire results, all adverse events will be assessed by the PI for relatedness to a possible COVID-19 infection by indicating YES, NO, or UNKNOWN.

Any subject that has an adverse event where the PI indicates YES for relatedness will be included in the SARS-CoV-2 positive group.

Due to the unknown but possible risks associated with COVID-19 and hypercoagulability, once a subject is placed in the SARS-CoV-2 positive population, they will remain there regardless of future SARS-CoV-2 test results and or vaccination status. Any subject not meeting the above criteria will be placed in the SARS-CoV-2 Negative population.

19.3. Enrollment Sample Size

The maximum sample size for primary safety and efficacy is that of primary safety or 140 subjects required at 30 days. Conservatively, correcting that number for approximately 12.5% attrition at 30 days requires enrollment of 160 subjects. With 160 subjects enrolled and accounting for 20% attrition by 1 year, it is expected that 128 subjects will be evaluable for primary efficacy at 1 year providing 96 to 99% power depending on the proportion enrolled in each disease state.

19.4. Study Success

The study will be considered a success if the primary safety endpoint is met in either the SARS-CoV-2 negative subset or all subjects and the primary efficacy endpoint is met in either the SARS-CoV-2 negative subset or all subjects. The Type I error for testing in both the SARS-CoV-2 negative subset and all subjects will be controlled using the Hochberg correction.

19.5. Administrative Reports and Interim Reports

An administrative report will be completed upon completion of enrollment to fix the performance goal for primary efficacy. The study will enroll subjects from each of three disease states, i.e. nonthrombotic, acute thrombotic, and chronic postthrombotic. The study will require that at least 20% of the subjects are enrolled in each of the disease states. The PG for the primary efficacy objectives depends on the proportion of ITT subjects in each disease state. Once enrollment is completed, the proportion of ITT subjects with nonthrombotic, acute thrombotic, and chronic postthrombotic disease will be calculated. The proportions are the weights in the formula to calculate the PG. The calculation is described in **Section 19.11**, "Primary Efficacy Objective"**.** The PG for primary efficacy will be fixed in advance of or prospectively to the efficacy analyses. There is no Type I error adjustment for this report given that no hypotheses will be tested.

The study data may be summarized prior to the time at which all N=160 enrolled subjects complete 12 months of follow-up or exit the study early to fulfill an EU MDD post-market approval requirement for CE Mark. Since the interim look at the data set will *not* be used to claim early trial success with the FDA or to modify the study design, no correction to Type I error is required. Because of the potential to introduce bias into the study given knowledge of the interim results, Vesper Medical will create a standard operating procedure outlining the measures that will be taken to mitigate the risk of bias. Main measures will include: identifying the roles within the company who have visibility to the data, the security measures in place for storing the data, commitment

that no data will be shared with investigational sites until the full cohort is analyzed at 12 months and that the interim results will not be shared publicly via podium or publication.

19.6. Pooling Evaluation

The investigational sites will be tested for differences in the primary safety endpoint and primary efficacy endpoint in the FAS subset using Fisher's Exact test for both the SARS-CoV-2 negative subset and all subjects. Subjects will be stratified by disease state to evaluate pooling for primary efficacy and not stratified for primary safety. The Fisher's Exact test will be performed 4 times, once for each disease state for primary efficacy and once for primary safety.

Investigational sites with less than 10 subjects per disease state will be combined for the purpose of the pooling evaluation with respect to the primary efficacy endpoint. In chronological order of site participation, sites with less than 10 subjects per disease state will be aggregated until the pseudo-site reaches >10 subjects per disease state. Once that happens a second pseudo-site will be created, etc. If the final pseudo-site is less than 10 subjects per disease state it will be combined with the previous pseudo-site. Additionally, the poolability analysis will be conducted with ONLY sites with 10 or more subjects in each disease etiology.

Investigational sites with less than 10 subjects overall will be combined for the purpose of the pooling evaluation with respect to the primary safety endpoint. In order of site participation, sites with less than 10 subjects will be aggregated until the pseudo-site reaches >10 subjects. Once that happens a second pseudo-site will be created, etc. If the final pseudo-site is less than 10 subjects it will be combined with the previous pseudo-site. Additionally, the poolability analysis will be conducted with ONLY sites with 10 or more subjects.

If there are any investigational site effects (i.e., statistically significant results at two-sided $p < .15$), a random center effect will be included in a logistic regression model to assess the primary objective. If there are no differences, the data from all investigational sites will be pooled for the analyses.

Additionally, the primary safety and efficacy endpoints will be summarized by US and OUS centers. The study was not powered to demonstrate the primary efficacy and safety endpoints within the subgroups defined by geography and therefore it is not an expectation that the primary safety and efficacy endpoint will be statistically significant within the subgroups determined by geography.

19.7. Handling of Missing Data

A sensitivity analysis to the missing data in the ITT sample will be conducted for both the primary safety and efficacy endpoints in the SARS-CoV-2 negative subset and all subjects. The sensitivity analysis will include a best case, worst case and tipping point analysis. The best-case analysis will impute successes for the missing data. The worst-case analysis will impute failures for missing data. The tipping point analysis starts with the best-case analysis and continues until the worst-case analysis is completed, by increasing the number of missing cases imputed as failures by one in each analysis. The goal of the tipping point analysis is to determine at what point the imputation of

failures causes the statistical evaluation of the endpoint to lose statistical significance. If the worst-case analysis maintains statistical significance, the tipping point analysis is not necessary.

19.8. Summary of Baseline Demographics, Index Procedure Measurements, and Subject Compliance

Baseline demographics including at a minimum gender, age, and selected medical history will be summarized for ITT subjects overall and in the SARS-CoV-2 – negative subset for primary safety and for primary efficacy. In addition, angiographic characteristics and measurements, as well as procedure characteristics will be summarized.

Subject follow-up and compliance with the protocol will be reported. The number and percent of subjects enrolled, completing study-required follow-ups, and completing the study will be summarized. The subjects who exit the study early will be summarized along with the reason for early study termination.

19.9. COVID-19 Statistical Considerations

Given that COVID-19 has been associated with a hypercoagulable state which has the potential to increase MAE occurrence and decrease patency, the study has been modified to test the primary safety and effectiveness hypotheses in both the SARS-CoV-2 negative subset and all subjects (regardless of SARS-CoV-2 status).

The performance goals for both primary safety and primary effectiveness were established based on research in a pre-COVID-19 era and therefore do not account for potential increases in MAEs or decreases in patency associated with SARS-CoV-2 or COVID-19. For each of the hypothesis tests, the current plan is to use the same performance goal in all subjects and in the SARS-CoV-2 negative subgroup given that the potential effects due to SARS-CoV-2 are not well understood. This decision will be revisited prior to analysis of the study data. In the event that additional information becomes publicly available regarding SARS-CoV-2, as related to the VIVID study primary endpoints, we may summarize the major event rate and primary patency in the subject population without and with SARS-CoV-2, and if possible, further based on the extent of COVID-19 illness. Should this information suggest that it may be reasonable to lower the performance goal for the all subject cohort, negotiation with FDA will be pursued given the FDA guidance document, “Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency” dated June 2020.

19.10. Primary Safety Objective

Subjects Included the Analysis: Subjects who meet the ITT definition.

Endpoint: The primary safety endpoint is freedom from major adverse events (MAEs) at 30 days post index procedure evaluated per subject. MAEs are defined in **Section 6.1** Primary Endpoints.

Performance Goal: Disease state specific PGs were calculated from the point estimates for major bleeding, pulmonary embolism and peri-procedural mortality from Razavi et al[1] converted to freedom from estimates and application of a 10% non-inferiority margin. For example, the expected freedom from the combined primary safety event for nonthrombotic subjects is 100 – (0.3 + 0.2 + 0.1) = 99.4%. Therefore, the PG for the nonthrombotic group is 99 – 10 = 89%. The same calculation for the acute-thrombotic group results in an 87% PG, 87%=100 – (1.1 + 0.9 + 0.7) – 10. Lastly, the PG for chronic postthrombotic is 88%=100 – (0.9 + 0.6 + 0.3) – 10. Given the similarity of the disease-state specific PGs, it was determined that a disease state specific goal was not necessary. A PG of 89% was adopted for the study in both the SARS-CoV-2 negative subset and overall.

Hypothesis and Performance Goal:

H_0: Proportion of subjects with freedom from MAE (p_{MAE}) is less than or equal to the (PG) at 30 days, $p_{MAE} \leq 89\%$

H_1: Proportion of subjects with freedom from MAE is greater than the (PG) at 30 days, $p_{MAE} > 89\%$

The freedom from MAE proportion will be calculated such that the numerator is the number of subjects in whom a MAE did not occur within 30 days of the index procedure. The denominator is the number of subjects with 30 days of follow-up plus the number of subjects with a MAE prior to 30 days who exited the study prior to 30 days, if any.

Sample Size Rationale: Using PASS 19, a one-sample Exact Test (binomial enumeration), power = 90%, one-sided Type I error controlled at 2.5%, and assumed freedom from MAE of 96.1% with a PG goal of 89%, the required evaluable sample size is 140 subjects.

Primary Statistical Analysis: The primary statistical analysis will be conducted in the FAS subset for the primary safety endpoint overall and in the SARS-CoV-2 negative subset. The primary statistical method is a one-sample exact test comparing the proportion of subjects free from a MAE to the PG using a two-sided $\alpha = 0.05$. The exact two-sided 95% confidence interval for the proportion of subjects free from MAE will be calculated.

The two-sided p-value in the SARS-CoV-2 negative subgroup and all subjects will be calculated and ordered from largest to smallest. If the largest p-value, is statistically significant at $p < 0.05$ then the hypothesis test is statistically significant in both the SARS-CoV-2 negative subset and all subjects. If not, testing continues to the smallest p-value. If the smallest p-value < 0.025 then the hypothesis test is statistically significant in the group for which the smallest p-value is associated with. If the

[1] Razavi MK, Jaff MR, Miller LE. Safety and Effectiveness of Stent Placement for Iliofemomral Venous Outflow Obstruction Systematic Review and Meta-Analysis. Circ Cardiovasc Interv. 2015;8:e002772. DOI: 10:1161/CIRCINTERVENTIONS.115.002772.)

smallest p-value ≥ 0.025, then the hypothesis test is not statistically significant in either the SARS-CoV-2 negative subset nor all subjects.

Additional Analysis: The evaluation for pooling analyses specified in **Section 19.6** will be completed. If there is missing data for the ITT subjects, the sensitivity to missing data analysis outlined in **Section 19.7** will be completed. Additionally, the primary statistical analysis will be conducted in the per protocol sample overall and in the SARS-CoV-2 negative subset.

19.11. Primary Efficacy Objective

Subjects Included the Analysis: Subjects who meet the ITT definition.

Efficacy: Primary patency of stented segment (confirmed by core laboratory) at 12 months evaluated per subject.

Hypothesis:

H_0: Proportion of subjects with primary patency (p_{p_pat}) is less than or equal to performance goal (PG) at 12 months, $p_{p\_pat} \leq PG$

H_1: Proportion of subjects with primary patency is greater than the performance goal at 12 months, $p_{p\_pat} > PG$

The primary patency proportion will be calculated such that the numerator is the number of subjects found to be patent at 12 months. The denominator is the total number of subjects found to be patent or not patent at 12 months.

Patency is:

- An in-window patent stenosis assessment with no reintervention per definition prior to the close of the 12-month window.
- In the absence of an in-window stenosis assessment, a subsequent patent stenosis assessment with no prior reintervention per definition can be used to declare patency at 12 months.

Lack of patency is:

- A reintervention per definition prior to the close of the 12-month visit window.
- A non-patent stenosis assessment within the 12-month visit window.

Performance Goal: The PG for primary efficacy will be set when all enrolled subjects complete the index procedure of this pivotal IDE trial based upon the proportions of ITT subjects in each of the disease states, i.e. nonthrombotic (p_{NT_ENROLL}), acute thrombotic (p_{AT_ENROLL}) and chronic postthrombotic (p_{CPT_ENROLL}). The disease state specific PGs were adopted as suggested in Razavi et al[1] that is, the lower 95% confidence limit minus 0.10. The disease state PGs are .83, .70 and .66 for nonthrombotic, acute thrombotic and chronic postthrombotic subjects respectively. The PG for the

pivotal study will be a weighted combination of these disease state specific PGs, where the weights are the proportion of subjects in each disease state in the ITT sample, i.e. study PG =(p_{NT_ENROLL})*0.83 + (p_{AT_ENROLL})*.70 + (p_{CPT_ENROLL})*0.66. The same PG will be used overall and in the SARS-CoV-2 negative subgroup. In order to have a minimum number of subjects from each disease condition in the ITT sample, the study will require that at least 20% of the ITT subjects are in each of the disease state.

Sample Size Rationale: With an expected FAS sample size of N=128, one-sided Type I error less than or equal to 2.5%, and assumed primary patency at 12 months equal to .96, .87, .79, i.e. the point estimates for primary patency from Razavi et al for nonthrombotic, acute thrombotic, and chronic postthrombotic respectively, the power for primary efficacy ranges from 96 – 99% depending on proportion in each disease-state given a minimum of at least 20% in each group. The table below provides the matrix of simulated power varying the ITT proportions for the disease states.

Power Calculations Using Simulation for the Primary Statistical Analysis

Proportion of Subjects Expected in Each Group			**Assumed Freedom from Primary Efficacy**				**Calculated Performance Goal**				**Power at N=128 Evaluable (20% attrition for N=160 enrolled**
NT	**AT**	**CPT**	**NT**	**AT**	**CPT**	**Pooled**	**NT**	**AT**	**CPT**	**PG**	**One-sided Type I error = 2.5%**
0.3333	0.3333	0.3333	0.96	0.87	0.79	**0.873**	0.83	0.7	0.66	**0.73**	98%
0.2	0.2	0.6	0.96	0.87	0.79	**0.84**	0.83	0.7	0.66	**0.702**	96%
0.2	0.6	0.2	0.96	0.87	0.79	**0.872**	0.83	0.7	0.66	**0.718**	99%
0.6	0.2	0.2	0.96	0.87	0.79	**0.908**	0.83	0.7	0.66	**0.77**	96%
0.3	0.3	0.4	0.96	0.87	0.79	**0.865**	0.83	0.7	0.66	**0.723**	97%
0.3	0.4	0.3	0.96	0.87	0.79	**0.873**	0.83	0.7	0.66	**0.727**	99%
0.4	0.3	0.3	0.96	0.87	0.79	**0.882**	0.83	0.7	0.66	**0.74**	98%
0.4	0.4	0.2	0.96	0.87	0.79	**0.89**	0.83	0.7	0.66	**0.744**	99%
0.4	0.2	0.4	0.96	0.87	0.79	**0.874**	0.83	0.7	0.66	**0.736**	98%
0.2	0.4	0.4	0.96	0.87	0.79	**0.856**	0.83	0.7	0.66	**0.71**	98%

Primary Statistical Analysis: The primary statistical analysis will be conducted in the FAS subjects overall and in the SARS-CoV-2 negative subgroup. The primary statistical comparison will use a one-sample Z-test comparing the proportion of subjects with primary patency to the PG using a one-sided α= 0.025 equivalent to a z-score of 1.96. The variation in the proportion will be estimated using the disease-specific performance goals themselves, i.e. under the null, rather than use the estimated patency rates, i.e. under the alternative.

The estimates that will be observed for primary patency in each disease etiology are noted as follows:

$\hat{p}_{p\_pat\_NT}$ = The primary patency observed in the NT subjects.
$\hat{p}_{p\_pat\_AT}$ = The primary patency observed in the AT subjects.
$\hat{p}_{p\_pat\_CPT}$ = The primary patency observed in the CPT subjects.

The percent of subjects in the FAS with each disease etiology are noted as follows:

p_{NT_FAS} = The proportion of FAS subjects with NT disease etiology.
p_{AT_FAS} = The proportion of FAS subjects with AT disease etiology.
p_{CPT_FAS} = The proportion of FAS subjects with CPT disease etiology.

The number of subjects in the FAS set with each disease etiology are noted as follows:

n_{NT_FAS} = The number of FAS subjects with NT disease etiology.
n_{AT_FAS} = The number of FAS subjects with AT disease etiology.
n_{CPT_FAS} = The number of FAS subjects with CPT disease etiology.

The primary patency for the hypothesis test is calculated as:

$$p_{p\_pat} = p_{NT\_FAS} * \hat{p}_{p\_pat\_NT} + p_{AT\_FAS} * \hat{p}_{p\_pat\_AT} + p_{CPT\_FAS} * \hat{p}_{p\_pat\_CPT}$$

with the variance of primary patency calculated as follows:

$$var(p_{p\_pat}) = ((p_{NT\_FAS})^2 PG_{NT}(1 - PG_{NT}))/ n_{NT\_FAS} + ((p_{AT\_FAS})^2 PG_{AT}(1 – PG_{AT}))/ n_{AT\_FAS} + ((p_{CPT\_FAS})^2 PG_{CPT}(1 – PG_{CPT}))/ n_{CPT\_FAS}$$

Such that the Z score is calculated as follows:

$$Z = (p_{p\_pat} – PG)/\text{square root}(var(p_{p\_pat}))$$

When Z >1.96, the primary patency is found to be significantly greater than the performance goal with two-sided Type I error held at 5%, i.e. two-sided p-value < 0.05.

The two-sided p-value in the SARS-CoV-2 negative subgroup and all subjects will be calculated and ordered from largest to smallest. If the largest p-value, is statistically significant at $p < 0.05$ then the

hypothesis test is statistically significant in both the SARS-CoV-2 negative subset and all subjects. If not, testing continues to the smallest p-value. If the smallest p-value < 0.025 then the hypothesis test is statistically significant in the group for which the smallest p-value is associated with. If the smallest p-value ≥ 0.025, then the hypothesis test is not statistically significant in either the SARS-CoV-2 negative subset nor all subjects.

Additional Analysis: As a supportive analysis to the primary patency analysis, a Kaplan-Meier analysis will also be performed using the patency data overall and in the SARS-CoV-2 negative subset. Time 0 is the index procedure and the event is lack of patency based on 1) reintervention per definition 2) a non-patent stenosis assessment within the 12 month visit window. For subjects who do not experience an event, the time of censoring is the date of the last follow-up whether scheduled or unscheduled.

The evaluation for pooling analyses specified in **Section 19.6** will be completed. If there is missing data for the ITT subjects, the sensitivity to missing data analysis outlined in **Section 19.7** will be completed. Additionally, the primary statistical analysis will be conducted in the per protocol sample overall and in the SARS-CoV-2 negative subset.

19.12. Subgroup Summaries for Primary Endpoints

Summary statistics for the following subgroups will be summarized. The study was not powered to demonstrate the primary efficacy and safety endpoints within the subgroups and therefore it is not an expectation that the primary safety and efficacy endpoint will be statistically significant within the subgroups defined by disease etiologies (NT, AT, CPT), gender, age, race and ethnicity. Age subgroups are defined by dichotomizing at the median.

19.13. Secondary and Observational Endpoints

The secondary endpoints are listed in **Section 6.2** and the observational endpoints are listed in **Section 6.3** and are supportive in nature. Descriptive statistics will be calculated and may be provided in labeling if deemed informative for the user. Descriptive statistics for the purposes of labeling are defined as N, mean, standard deviation, median, interquartile range, minimum and maximum for continuous variables, and number and percent of observations for categorical variables.

Standard statistical methods will be used and include the Kaplan-Meier product limit method for time to event endpoints and the Wilcoxon signed rank test for changes from baseline for endpoints compared to baseline. Statistical significance will be defined as two-sided $\alpha < 0.05$. Two-sided 95% confidence intervals may be calculated for estimates. P-values and 95% confidence intervals are not intended for the labeling.

Safety and efficacy endpoints will be evaluated in the sample of subjects meeting the ITT and PP definition in both the SARS-CoV-2 negative subgroup and all subjects.

20. REGULATORY AND ETHICAL OBLIGATIONS

As the study Sponsor, Vesper Medical is responsible for the overall conduct and quality of the study, including the assurance that the study complies with the regulations and guidance that apply to medical devices evaluated under an IDE and GCP guidance (FDA Regulations, ISO 14155, and ICH E6). Additionally, Vesper Medical will ensure that qualified monitors and designated personnel are monitoring the study and that the Informed Consent process is followed per each site's local and national requirements.

20.1. Institutional Review Board / Ethics Committee Approval

21 CFR Parts 50 & 56; ISO 14155

The PI at each participating site is responsible for securing IRB/EC approval for this study protocol and the informed consent documents. The IRB/EC for each specific institution must review and approve this study protocol, the specific informed consent form, and any written materials for subjects to be used at that site **prior** to enrollment of the first subject. The Sponsor **must** also review and approve the final informed consent documents prior to their use. The Sponsor must receive a copy of any IRB/EC correspondence as well as the final approval letter and the final approved informed consent form from each IRB/EC. The IRB/EC approval letter must be signed by the IRB/EC chair or designee, identify the IRB/EC name and address, the clinical trial protocol by name or number, and the date the approval was granted.

The PI is also responsible for initiating and obtaining continuing review of the clinical trial. Continuing IRB/EC review and approval should not exceed intervals over one year but may occur at more frequent intervals as required by site specific IRB/EC policies. The PI must also provide the Sponsor with all correspondence and documentation of continued IRB/EC approval of the clinical trial.

20.2. Informed Consent

All sites shall comply with 21 CFR 50, provisions of ICH GCP, local IRB/EC policy, and all applicable local regulations (i.e. ISO 14155 for OUS Sites) for obtaining informed consent. Written informed consent is to be obtained for all subjects prior to treatment as described in **Section 10.1**.

Informed consent templates will be provided by the Sponsor to all participating clinical sites. Changes to this template made by the site based upon IRB/EC requirements must be provided to the Sponsor for review and approval prior to being submitted to the IRB/EC for review and approval. Any revisions required by a site's IRB/EC should also be provided to the Sponsor for review and approval prior to being submitted to the IRB/EC for final review and approval.

20.3. Protocol Amendment and Emergency Deviations

Changes to the research conducted under this protocol will be implemented with a formal protocol amendment. Amendments to the protocol may be initiated by the Sponsor or at the request of an PI. In either case, changes to the protocol must be approved by the Sponsor and submitted to the applicable

regulatory agency as appropriate. A protocol amendment cannot be implemented at the site without first being signed and acknowledged by the Investigator and approved by the IRB/EC.

Emergency deviations or modifications may be initiated without prior Sponsor or IRB/EC approval only in cases when the deviation is necessary to eliminate an immediate potential hazard to a subject. Emergency deviations or modifications implemented to protect the life or physical well-being of a subject must be reported to the Sponsor and site-specific IRB/EC **within 5 business days of occurrence.**

20.4. Subject Confidentiality

Confidentiality of subjects will be maintained throughout the study. A unique identification code will be assigned to each subject enrolled into the study. Access to the subject's medical records will be limited to authorized personnel of the Sponsor, their designated monitors, clinical site study staff, and authorized regulatory authorities as required by the IRB/EC and/or local or national agencies. Any data that may be published in abstracts or scientific journals and/or presented at medical meetings will at most reference the unique subject code and will not reveal any subject's identity. The Sponsor and their representatives will make every reasonable effort to protect the confidentiality of the subjects participating in the study.

All U.S. clinical trial sites must comply with the provisions of the Health Insurance Portability and Accountability Act (HIPAA) and in accordance with all applicable federal, local and institutional requirements. All European Union (EU) sites must comply with the provisions of the General Data Protection Regulation (EU) 2016/679) and in accordance with all applicable federal, local and institutional requirements.

21. CLINICAL TRIAL CONDUCT

21.1. Principal Investigator and Site Qualification

21 CFR 812.43; ISO 14155

All PIs and investigational sites will be selected by Vesper Medical through the PI and site qualification process. All selected PIs will be responsible for complying with all study-related and regulatory requirements and will be ultimately responsible for overseeing the conduct of the study at their respective investigational sites, per the Investigator Agreement.

All selected PIs will have the required training and expertise in performing peripheral vascular interventional procedures in a clinical research setting. The investigational sites where the study procedures and assessments are to be performed must have the adequate volume of the target subject population, experienced staff, as well as the appropriate facilities and equipment to meet the requirements of the study protocol and the expected enrollment time frames.

All PIs and research staff must be willing to undergo all study and device-related training and participate, assist, and comply with monitoring, audits, and inspections initiated by either the Sponsor and/or regulatory authorities.

21.2. Principal Investigator and Site Training

Training of the PI and clinical trial staff is the responsibility of the Sponsor and/or their designee. PIs and study staff will undergo site initiation visit training on the use of the study device, the study protocol, eligibility criteria, and device accountability prior to participating in the study. Training will also include, but is not limited to, instructions on timely and accurate eCRF completion, safety reporting timelines, as well as procedures for acquiring study-related images and associated timelines for submission to appropriate core laboratories. All training of the PIs and research staff must be documented on the site training log before performing any study-related function(s).

21.3. Clinical Monitoring

21 CFR 812.46; ISO 14155

Vesper Medical will designate qualified clinical monitors and oversee the conduct of this study. The clinical monitors will evaluate compliance with the protocol, GCP (FDA Guidance, ISO 14155, and ICH E6), any specific recommendations made by the site's IRB/EC, and the signed Investigator and Study Agreements.

The clinical monitor will conduct periodic monitoring visits to verify that the eCRFs agree with the source documentation and other records, that the rights and well-being of the subjects are being protected, and that the trial is being conducted in accordance with the approved protocol/amendments and GCPs. At the discretion of the Sponsor, periodic monitoring visits may occur either in-person or remotely. Periodic phone contact will also be conducted to ensure that the protocol is being followed and to assist the site with queries or other issues that may arise.

For record verification purposes during site monitoring visits, the clinical monitor and/or authorized Sponsor representative will be provided access to hospital records, original laboratory data, and other records and data as it relates to the study and as agreed to with the PI prior to the initiation of the trial. The PI will also make available to the clinical monitor all regulatory documents, all completed eCRFs, informed consent documents, source documentation, and other relevant records for all enrolled subjects at the site. It is important that the PI and other relevant site personnel are available for consultation with the clinical monitors during the monitoring visits and that sufficient time is devoted at the site to the monitoring process.

If the Sponsor and/or their authorized representative become aware that a PI is not complying with the study protocol, the PI Agreement, the Declaration of Helsinki, GCPs, applicable privacy standards, or any condition of the study imposed by the IRB/EC, the Sponsor or their authorized representative may immediately secure compliance, discontinue further shipments of the study devices and/or seize unused devices on-site. An inability to secure compliance and/or to complete an investigation into the factors that are inhibiting compliance may result in the PIs termination from the study by the Sponsor.

Study close-out visits will be conducted after the final follow-up visit is completed at each site. Following the resolution of any outstanding data discrepancies and adverse events, the remaining study devices will be the collected and returned to the Sponsor. A final study report will be generated and submitted to the PI and the appropriate study oversight authorities. Study document retention requirements will be reviewed with each site during the close-out visit.

21.4. Device Accountability

All study devices will be provided to the PI by the Sponsor after being tested, released, and shipped according to appropriate standards. The PI and/or designee is responsible for the secure storage of and controlled access to the study devices and accountability. The study device shall not be dispensed to any person who is not a consented study subject under this protocol.

21.5. Investigator Reports

21CFR Parts 50 & 56; ISO 14155:2011 Section 4

All PIs will be responsible for preparing and submitting the following complete, accurate, and timely reports:

To the Sponsor and the IRB/EC:

- Any unanticipated adverse device effect occurring during an investigation as soon as possible but no later than 2 business days after first learning of the effect.
- Assist Sponsor in generating progress reports on the investigation at regular intervals, but in no event less often than yearly. If there is a study monitor, a copy of the report will also be sent to the monitor.

- Any deviation from the investigational plan made to protect the life or physical well-being of a subject in an emergency, as soon as possible but no later than 5 working days after the emergency occurs. Except in emergency situations, a protocol deviation may require prior Sponsor approval. If the deviation may affect the scientific soundness of the plan or the rights, safety, or welfare of subjects, prior FDA and IRB/EC approvals are required.
- Any use of the device without obtaining informed consent must be reported within 5 working days after such use.
- Assist Sponsor in generating a final report within 3 months following termination or completion of the investigation or an individual PI's part of the investigation.
- Any further information requested by FDA or the IRB/EC about any aspect of the investigation.

To the Sponsor:

- Withdrawal of IRB/EC approval of the PI's part of an investigation. (Due within 5 working days of such action). If the PI's IRB/EC withdraws their approval to conduct this study for any reason, the PI must notify the Sponsor as soon as possible, but no later than five working days after the withdrawal of the approval.

In addition, the PI is responsible for the reporting of all safety and device events per the timelines specified in **Section 17** and **Section 18**.

21.6. Data Collection and Management

Standardized eCRFs will be used to collect complete and accurate records of the clinical data required by the study in accordance with GCP guidelines. The PI and/or study staff under his/her direction is responsible for accurately recording the clinical data for this study within five (5) business days after each visit.

Continuous review of the data will be performed by qualified data managers to ensure accuracy and consistency. Data review will persist until the data are clean and ready for approval and locking.

21.7. Safety Monitoring

21.7.1. Data Safety Monitoring Board

To meet the ethical responsibilities and standards for research subjects, an independent board of multi-disciplinary physicians and subject matter experts shall serve as the Data Safety and Monitoring Board (DSMB) for the study. In order to enhance objectivity and reduce the potential for bias, the DSMB shall be independent of the Sponsor as well as the investigational sites/ PIs.

The DSMB shall serve as an independent body conducting a review and oversight of all key safety events to monitor the rate of occurrence (both site reported and CEC adjudicated events) as part of their mission to protect the rights and safety of research subjects. The DSMB will define the types of events that may require real-time reporting and the format and frequency of interim data reviews for aggregate event rates. The DSMB will conduct systematic interim safety reviews at pre-specified intervals as outlined in the DSMB charter. The committee will be responsible for making any recommendations to the Sponsor it deems necessary to protect subjects enrolled in the trial.

At the close of each meeting, deliberation will occur and each DSMB member will vote in favor of continuation of the study as designed, or modification of the study to protect the welfare of subjects enrolled into the study. The result of this vote will be recorded in the meeting minutes.

The methodology for performing these responsibilities shall be developed and outlined in the DSMB Charter.

21.7.2. Clinical Events Committee

An independent CEC consisting of a team of clinical experts with experience in the conduct of clinical trials shall be formed to review clinical events reported by the PIs, or at the request of the Sponsor to determine if they meet the pre-specified endpoint definitions. The CEC may also be called upon to review relevant SAEs to assess the relationship to the study device and/or study procedure. The CEC's determination of whether a clinical event meets the study-defined endpoint will be considered the primary determination for the purpose of reporting study results with the exception of endpoints derived from core laboratory analysis.

Operational provisions shall be established to minimize potential bias (i.e., the physicians serving on the CEC shall be blinded to the clinical site to the extent possible during adverse event review and adjudication). The methodology for performing these responsibilities will be outlined in the CEC Charter. The CEC will define the minimum required information necessary to facilitate their review of an event. This may include information from original source documentation and imaging media.

21.8. Medical Monitoring

The Sponsor will be responsible for identifying a Medical Monitor who possesses the appropriate expertise and medical knowledge to oversee all adverse events reported during the study. All adverse event reports will be directed to the Sponsor as well as the Medical Monitor. The Medical Monitor will be responsible for first-line and timely review of all adverse events in order to identify the seriousness, severity, causality, and expectedness (anticipated vs. unanticipated) of the event to the study device and/or study procedure. The Medical Monitor will also have responsibilities including but not limited to:

- Reviewing all reported AEs for UADE potential and notifying the Sponsor of the need for regulatory reporting;
- Determining the need for additional information or supporting documentation from the site regarding an adverse event to facilitate complete assessment;

- Providing thorough review and assistance, as needed, for generating documents (i.e., subject event narratives) subject to CEC review and adjudication;
- Providing answers to the sites, IRBs/ECs, and/or Sponsor to questions requiring medical expertise that pertain to the protocol (i.e., subject eligibility) or any other medical aspect of the study;
- Identifying potential need for an amendment to the protocol;
- Providing a review of safety information included in regulatory reporting, as needed.

The Medical Monitor will review all adverse events throughout the duration of the study until study completion.

21.9. Central Core Laboratories

To ensure that the clinical data and images are analyzed in a controlled, non-biased manner and that the results are analyzed using a standardized process, all venograms, intravascular ultrasounds, duplex ultrasound studies and X-rays obtained during this study will be submitted to a respective central core laboratory for analysis. Any core laboratories used during the conduct of this study will be identified and selected by the Sponsor.

The core laboratories will be responsible for analyzing the venograms, intravascular ultrasounds, duplex ultrasounds, and X-ray images according to the study eligibility criteria, the study endpoints, and requirement measurements according to the study protocol. Feedback will be provided to the sites and Sponsor regarding the quality of the tracings and images.

21.10. Record Retention

The PI is responsible for maintaining the following accurate, complete, and current records relating to his/her participation in this investigational study:

- Correspondence with another PI, an IRB/EC, the Sponsor, a monitor, or FDA;
- Records of receipt, use, or disposition of a device that relate to:
    - The type and quantity of the device, dates of receipt, and batch numbers or code marks;
    - Names of all persons who received, used, or disposed of each device;
    - The number of units of the device returned to the Sponsor, repaired, or otherwise disposed of, and the reason(s) therefore.
- Records of each subject's case history and exposure to the device, including:
    - Documents evidencing informed consent and, for any use of a device without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent;

- All relevant observations, including records concerning adverse device effects (whether anticipated or not), information and data on the condition of each subject upon entering and during the course of the investigation, including information about relevant previous medical history and the results of all diagnostic tests;
- A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy;

- The protocol, with documents showing the dates of and reasons for each deviation from the protocol; and
- Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

In addition, all PIs and Sub-Is shall disclose to the Sponsor sufficient and accurate financial information to allow the Sponsor to submit certification or disclosure of financial interests under 21 CFR 54. All PI(s) and Sub-I(s) shall update the information if any relevant changes occur during the course of the investigation and for one year following completion of the study.

The Sponsor, core laboratories, and clinical sites will maintain the study records until two (2) years after the last marketing application and until there are no pending or contemplated marketing applications or at least two (2) years have elapsed since formal discontinuation of clinical development of the investigational product. These records may be retained for a longer period of time if required by applicable regulatory agencies or by the Sponsor. In such an instance, it is the responsibility of the Sponsor to inform the PI/institution as to when these documents no longer need to be retained. The Sponsor will notify each site regarding the regulatory requirements for record retention during the study close-out visit.

Per regulations in Germany § 10 (7) MPKPV, the record retention period for the study documents shall be at least ten (10) years after the end of the study. These records may be retained for a longer period of time if required by applicable regulatory agencies or by the Sponsor.

21.11. Audits/Inspections

In accordance with GCP requirements, the Sponsor and/or designee may request access to all study records, including source documents, for inspection and duplication at any time. In the event that a PI is contacted by an applicable regulatory body in relation to this study, the PI will notify the Sponsor as soon as possible.

The PI and/or designees must be available to respond to reasonable requests by the authorized Sponsor, Clinical Research Organization (CRO) and regulatory agency representatives during the monitoring and inspection process. The PI must provide the Sponsor with copies of all correspondence that may affect the review of the current study (i.e. inspection observations) or their qualification as a PI in clinical studies conducted by the Sponsor. The Sponsor will provide any needed assistance to the clinical site for regulatory audits.

21.12. Study Termination (Stopping Rules)

The Sponsor, IRBs/ECs, or regulatory authorities may terminate the study if the safety and well-being of study subjects is in jeopardy. If the PI terminates the study at his/her site without prior approval by the Sponsor, all details must be provided promptly to the Sponsor and IRB/EC.

The Sponsor reserves the right to terminate or reevaluate a site for continued participation in the study at any time for any of the following reasons:

- Unsatisfactory enrollment with respect to eligibility criteria
- Failure to obtain Informed Consent
- Failure to report SAEs within 2 business days of knowledge
- Loss of or unaccountable device inventory
- Repeated protocol violations or safety concerns
- Repeated failure to complete Case Report Forms (or inaccurate/incomplete eCRF completion)
- Failure to enroll an adequate number of subjects
- The potential benefits are unlikely to outweigh the risks (Futility)
- Or any other reason the Sponsor deems serious enough to require site reevaluation/termination.

If the study is terminated by the Sponsor, the PI(s) will be promptly informed and must then promptly inform the IRB/EC. If the IRB/EC terminates the study, the PI will promptly notify the Sponsor. This notification to the Sponsor must include the explanation for study termination.

21.13. Coverage of Subject Expenses

Subjects will not be compensated for their time during the trial. The Sponsor may provide reimbursement for reasonable out-of-pocket costs to treated subjects associated with travel, parking, or other expenses associated strictly with completing the protocol requirements of this study that would not normally be covered under routine medical coverage for the subject's underlying medical condition. This will be provided on a case-by-case basis and will require Sponsor (and/or designee) approval.

21.14. Clinical Trial Reports

All information and data generated in association with the study will be held in strict confidence and remains the sole property of the Sponsor. The PI agrees to use this information for the sole purpose of completing the study and for no other purpose without prior approval of the Sponsor.

All progress reports will be generated and submitted to FDA by the Sponsor in compliance with periodic reporting requirements. If requested, all participating PIs and clinical sites should provide assistance to the Sponsor regarding the data and any other pertinent information to be included in the study reports.

All progress reports submitted to FDA will be summarized by the Sponsor and distributed to each site for IRB/EC review, which shall include all relevant feedback and/or approval provided by FDA.

Upon receipt of the final study data and the final reports from each center, the Sponsor will complete a final study report. Copies of the final report will be provided to each PI.

21.15. Publication Policies

At the conclusion of the study, a multi-center manuscript led by the national study PI will be prepared with the assistance of Vesper Medical for publication in a reputable scientific journal. The publication of the principal results from any single center experience within the trial is not allowed until the preparation and publication of the multi-center results as indicated in the Clinical Trial Agreement. Exceptions to this rule require the prior approval of National PI and Vesper Medical. For the purposes of timely abstract presentation and publication, secondary publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all multi-center data and/or single-center experience reports will require review from Vesper Medical.

This study is registered with clinicaltrials.gov (NCT Number Pending).

21.16. Medicare Study Criteria

The study's results information on all pre-specified outcomes, including negative outcomes, will be submitted to ClinicalTrials.gov not later than one year after the study completion date, where the completion date is defined as the date that the final subject was examined or received an intervention for purposes of data collection for the primary outcome measure. Results submission could be delayed if an extension is granted to the results submission deadline; however, the release of all results on pre-specified outcomes will be hastened if the study is terminated early.

It is not anticipated that the device under investigation will affect the Medicare population any differently than subjects in the PIs' general population for this same condition, including populations eligible for Medicare due to age (e.g., 65 years or older), disability, or other eligibility status. The incidence of chronic venous disease (CVD) increases with age. Advanced manifestations CEAP class 3-6 disease tend to be poorly tolerated in the geriatric set, particularly after the age of 80 years.[34] The geriatric population aged 80 years and older with severe manifestations of chronic venous disease face diminishing therapeutic options. Self-applied compression is often not possible because of frailty or arthritis. Significant limb swelling diminishes mobility, affects independent living, and precipitates institutionalization. Iliac vein stenting may have a role as it appears to be safe and effective in this advanced stage of life.[34] Because the incidence of CVD increases with age the results of this study are expected to be generalizable to the Medicare eligible population primarily due to age but not necessarily due to disability or other eligibility status.

22. ECONOMIC ANALYSIS

Vesper Medical, Inc. may collect procedural and reimbursement data (if applicable) from multiple sources including but not limited to hospital billing forms and Medicare claims data. Any data collected will be used to perform an economic analysis for the Vesper DUO Venous Stent System.

23. STUDY DEFINITIONS

Term	Definition
Adverse Device Effect (ADE)	An adverse device effect is defined as any untoward adverse event related to the use of an investigational or unintended response to a medical device.
	Note 1: This definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device
	Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Adverse Event (AE)	An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects whether or not related to the investigational device/procedure.
Allergic Reaction	An allergic reaction characterized by rash, nausea, vomiting, upper respiratory congestion, urticaria, shortness-of-breath, vasovagal reaction, or general collapse (anaphylaxis).
Clinically driven Target Lesion Reintervention (CD-TLR)	Endovascular or surgical procedure for new, recurrent, or worsening symptoms and core lab adjudicated >50% stenosis or occlusion within the stented segment confirmed by diagnostic IVUS
Clinically driven Target Vessel Reintervention (CD-TVR)	Endovascular or surgical procedure performed on the target vessel for new, recurrent, or worsening symptoms
Device Deficiency	Inadequacy of a medical device related to its identity, quality, durability, reliability, safety, or performance, such as malfunction, misuse or not observing the IFU, and inadequate labeling.
Device Malfunction	Failure of a device to meet its performance specifications or otherwise perform as intended.
Device Success	Device Success is defined as:

Term	Definition
	• Successful deployment of the DUO Stent(s) at the intended target site, AND • Successful withdrawal of the delivery catheter(s) from the introducer sheath, AND • The DUO Stent remaining at the intended deployment location through completion of the index procedure as determined by the PI
Duplex Ultrasound (DUS)	A form of medical ultrasonography that includes the following elements on the same screen ("duplex") to facilitate interpretation 1) B-mode, pulsed Doppler display to visualize the structure within a vessel and 2) Color-Doppler display to visualize the blood flow and hemodynamics within a vessel.
Index Procedure	The interventional procedure during which the study device is advanced through the introducer sheath and the subject is enrolled.
Intent-to-treat (ITT) subjects	A subject is defined as an ITT and officially enrolled in the study once the DUO Venous Stent System is advanced through the introducer sheath.
Lesion Success	Lesion success defined as target lesion patency of ≤50% residual diameter or area stenosis of the stented segment at the completion of the procedure, as assessed by the core laboratory.
Major Amputation	Any above the ankle amputation to the target limb.
Myocardial Infarction (MI)	Q wave MI (QWMI): requires one of the following criteria:
	• Chest pain or other acute symptoms consistent with myocardial ischemia and new pathological Q waves in two or more contiguous ECG leads
	• New pathologic Q waves in two or more contiguous ECG leads and elevation of cardiac enzymes above normal.

Term	Definition
	Non-Q Wave MI (NQWMI): defined as either: elevated CK = 2X the laboratory upper limit of normal with the presence of an elevated CK-MB (any amount above the laboratory upper limit of normal) in the absence of new pathological Q waves or elevated CK-MB = 3X the laboratory upper limit of normal in the absence of new pathological Q waves.
Per-protocol (PP) subjects	The PP population will be defined as ITT subjects with evaluable data that have met the definition for device success, excluding subjects with major deviations, such as those who meet criteria for a protocol violation(s), as determined by the Sponsor.
Primary Assisted Patency	Primary assisted patency at 12 months defined as freedom from DUS core laboratory adjudicated occlusion or stenosis >50% within the stented segment following a reintervention due to a >50% but <100% stenosis. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS is required.
Primary Efficacy Endpoint	Primary patency of stented segment at 12 months defined as freedom from: ▪ Duplex Ultrasound (DUS) core laboratory adjudicated occlusion or stenosis >50% within the stented segment. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS is required ▪ CEC adjudicated clinically driven target lesion reintervention (CD-TLR) defined as endovascular or surgical procedure for new, recurrent, or worsening symptoms and >50% stenosis or occlusion within the stented segment confirmed by diagnostic IVUS
Primary Safety Endpoint	Freedom from major adverse events (MAEs) at 30 days post index procedure, as adjudicated by the Clinical Events Committee (CEC) or Core Laboratory, including: ▪ Device or procedure-related death ▪ Device or procedure-related bleed at the target vessel and/or target lesion or at the access site requiring surgical or endovascular intervention or blood transfusion ≥2 units

Term	Definition
	▪ Device or procedure-related venous injury occurring in the target vessel and/or target lesion location or at the access site requiring surgical or endovascular intervention ▪ Major amputation of the target limb ▪ Clinically significant pulmonary embolism, confirmed by CT angiography ▪ Stent embolization outside of the target vessel ▪ Presence of new thrombus within the stented segment
Procedural Success	Lesion success without the occurrence of major adverse events (MAEs) from the time of treatment through to discharge
Restenosis	Reoccurrence of narrowing or blockage of the stented segment.
Secondary Efficacy Endpoints:	▪ Subject symptom relief via VCSS pain score at 12 months ▪ Primary assisted patency at 12 months o Defined as freedom from DUS core laboratory adjudicated occlusion or stenosis >50% within the stented segment following a reintervention due to a >50% but <100% stenosis. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS is required. ▪ Secondary patency at 12 months o Defined as freedom from DUS core laboratory adjudicated occlusion or stenosis >50% within the stented segment following a reintervention due to 100% occlusion. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS is required.
Secondary Target Lesion Patency	Secondary patency at 12 months defined as freedom from DUS core laboratory adjudicated occlusion or stenosis >50% within the stented segment following a reintervention due to 100%

Term	Definition
	occlusion. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS is required.
Serious Adverse Device Event (SADE)	A serious adverse device effect (SADE) is defined as an adverse device effect (ADE) that results in any of the consequences characteristics of a serious adverse event (SAE).
Serious Adverse Event (SAE)	A serious adverse event (SAE) is defined an adverse event that:
	• led to death
	• led to a serious deterioration in the health of the subject, that either resulted in:
	○ a life-threatening illness or injury, or
	○ resulted in a permanent impairment of a body structure or a body function, or
	○ required in-patient hospitalization or prolongation of existing hospitalization, or
	○ resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function, or
	○ led to fetal distress, fetal death or a congenital abnormality or birth defect.
	Note: Planned hospitalization for a pre-existing condition, or a procedure required by the investigational plan without serious deterioration in health, is not considered a serious adverse event.
Stented Segment	The area of vessel treated with the DUO Venous Stent System.
Study Device Procedure Start/End Time	Start: The time the first DUO Venous Stent System is advanced through the introducer sheath End: The time of withdrawal of last post-DUO Stent PTA balloon catheter
Target Lesion Patency	Primary patency of the stented segment at 12 months defined as freedom from:

Term	Definition
	▪ Duplex Ultrasound (DUS) core laboratory adjudicated occlusion or stenosis >50% within the stented segment. If DUS shows >50% stenosis or occlusion, confirmation by diagnostic IVUS is required. ▪ CEC adjudicated clinically driven target lesion reintervention (CD-TLR) defined as endovascular or surgical procedure for new, recurrent, or worsening symptoms and >50% stenosis or occlusion within the stented segment confirmed by diagnostic IVUS
Target Lesion Reintervention (TLR)	Any reintervention (endovascular or surgical) to the target lesion(s) occurring after the index procedure through the 36-month subject final visit.
Target Vessel	The vessel location(s) containing the obstructive lesion. Presence of unilateral, non-malignant venous obstruction of the common femoral vein (CFV), external iliac vein (EIV), common iliac vein (CIV), or any combination thereof, defined as a ≥50% reduction in target vessel lumen diameter and confirmed by venographic or IVUS imaging. The cranial point of the obstruction may extend to the iliac vein confluence of the inferior vena cava (IVC) and the caudal point may be 2mm above either the inflow of the deep femoral (or profunda) or the lesser trochanter, whichever is most cranial.
Target Vessel Reintervention (TVR)	Any reintervention (endovascular or surgical) to the target vessel(s) occurring after the index procedure through the 36-month subject final visit.
Unanticipated Adverse Device Event (UADE)	A UADE is defined as any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unplanned Procedure	A procedure that was not planned at the time of subject enrollment.

24. REFERENCES

[1] Mahnken AH, Thomson K, de Haan M, O'Sullivan GJ. CIRSE standards of practice guidelines on iliocaval stenting. Cardiovasc Intervent Radiol 2014; 37(4):889-97.
[2] Milinis K, Thapar A, Shalhoub J, Davies AH. Antithrombotic therapy following venous stenting: international Delphi consensus. Eur J Vasc Endovasc Surg 2018; 55(4):537-44.
[3] Raju S, Neglén P, Carr-White PA, Fredericks R, Devidas M. Ambulatory venous hypertension: component analysis in 373 limbs. Vasc Surg 1999; 33:257-67.
[4] Neglén P, Thrasher TL, Raju S. Venous outflow obstruction: an underestimated contributor to chronic venous disease. J Vasc Surg 2003; 38(5):879-85.
[5] Chung JW, Yoon CJ, Jung SI, Kim HC, Lee W, Kim YI, et al. Acute iliofemoral deep vein thrombosis: evaluation of underlying anatomic abnormalities by spiral CT venography. J Vasc Interv Radiol 2004; 15(3):249-56.
[6] Mahnken AH, Thomson K, de Haan M, O'Sullivan GJ. CIRSE standards of practice guidelines on iliocaval stenting. Cardiovasc Intervent Radiol 2014; 37(4):889-97.
[7] Milinis K, Thapar A, Shalhoub J, Davies AH. Antithrombotic therapy following venous stenting: International Delphi consensus. Eur J Vasc Endovasc Surg 2018; 55(4):537-44.
[8] Razavi MK, Jaff MR, Miller LE. Safety and effectiveness of stent placement for iliofemoral outflow obstruction: Systematic review and meta-analysis. Circ Cardiovasc Interv 2015; 8:e002772.
[9] Neglén P, Hollis KC, Raju S. Combined saphenous ablation and iliac stent placement for complex severe chronic venous disease. J Vasc Surg 2006; 44(4):828-33.
[10] Milinis K, Thapar A, Shalhoub J, Davies AH. Antithrombotic therapy following venous stenting: international Delphi consensus. Eur J Vasc Endovasc Surg 2018; 55(4):537-44.
[11] Razavi MK, Jaff MR, Miller LE. Safety and effectiveness of stent placement for iliofemoral outflow obstruction: Systematic review and meta-analysis. Circ Cardiovasc Interv 2015; 8:e002772.
[12] Zollikofer CL, Largiader I, Bruhlmann WF, Uhlschmid GK, Marty AH. Endovascular stenting of veins and grafts: preliminary clinical experience. Radiology 1988; 167:707-12; Antonucci F, Salomonowitz E, Stuckmann G, Stiefel M, Largiader J, Zollikofer CL. Placement of venous stents: clinical experience with a self-expanding prosthesis. Radiology 1992; 183(2):493-97
[13] Neglén P, Hollis KC, Raju S. Combined saphenous ablation and iliac stent placement for complex severe chronic venous disease. J Vasc Surg 2006; 44(4):828-33.
[14] Neglén P, Thrasher TL, Raju S. Venous outflow obstruction: An underestimated contributor to chronic venous disease. J Vasc Surg 2003; 38(5):879-85
[15] Mahnken AH, Thomson K, de Haan M, O'Sullivan GJ. CIRSE standards of practice guidelines on iliocaval stenting. Cardiovasc Intervent Radiol 2014; 37(4):889-97.
[16] American College of Phlebology. Management of Obstruction of the Femoroiliocaval Venous System. http://www.phlebology.org/wp-content/uploads/2015/10/Management-of-Obstruction-of-the-Femoroiliocaval-Venous-System-Guidelines.pdf.
[17] Razavi MK, Jaff MR, Miller LE. Safety and effectiveness of stent placement for iliofemoral outflow obstruction: Systematic review and meta-analysis. Circ Cardiovasc Interv 2015; 8:e002772.
[18] Oguzkurt L, Tercan F, Pourbagher MA, Kizilkilic O, Turkoz R, Boyvat F. Computed tomography findings in 10 cases of iliac vein compression (May-Thurner) syndrome. Eur J Radiol 2005; 55(3):421-5; Wahlgren CM, Wahlberg E, Olofsson P. Endovascular treatment in postthrombotic syndrome. Vasc Endovascular Surg 2010; 44(5):356-60.
[19] Alhadad A, Lolbel T, Herbst A, Holst J, Alhadad H, Gottsater A. Iliocaval vein stenting: Long term survey of postthrombotic symptoms and working capacity. J Thromb Thrombolysis 2011; 31(2):211-16.
[20] Neglén P, Hollis KC, Olivier J, Raju S. Stenting of the venous outflow in chronic venous disease: long-term stent related outcome, clinical, and hemodynamic result. J Vasc Surg 2007; 46(5):979-90.

[21] Hurst DR, Forauer AR, Bloom JR, Greenfield LJ, Wakefield TW, Williams DM. Diagnosis and endovascular treatment of iliocaval compression syndrome. J Vasc Surg. 2001; 34(1):106-13.
[22] Nazarian GK, Austin WR, Wegryn SA, Bjarnason H, Stackhouse DJ, Castanesa-Zuniga WR, et al. Venous recanalization by metallic stents after failure of balloon angioplasty or surgery: four-year experience. Cardiovasc Intervent Radiol. 1996; 19(4):227-33.
[23] O'Sullivan GJ, Semba CP, Bittner CA, Kee ST, Razavi MK, Sze DY, et al. Endovascular management of iliac vein compression (May-Thurner) syndrome. J Vasc Interv Radiol. 2000; 11(7):823-36.
[24] Binkert CA, Schoch E, Stuckmann G, Largiader J, Wigger P, Schoepke W, et al. Treatment of pelvic venous spur (May-Thurner syndrome) with self-expanding metallic endoprostheses. Cardiovasc Intervent Radiol. 1998; 21(1):22-26.
[25] Nazarian GK, Bjarnason H, Dietz CA Jr, Bernadas CA, Hunter DW. Iliofemoral venous stenosis: effectiveness of treatment with metallic endovascular stents. Radiology. 1996; 200(1):193-99.
[26] Lamont JP, Pearl GJ, Patetsios P, Warner MT, Gable DR, Garrett W, et al. Prospective evaluation of endoluminal venous stents in the treatment of the May-Thurner syndrome. Ann Vasc Surg. 2002; 16(1):61-64.
[27] Razavi M, Marston W, Black S, Bentley D, Neglén P. The initial report on 1-year outcomes of the feasibility study of the VENITI VICI VENOUS STENT in symptomatic iliofemoral venous obstruction. J Vasc Surg Venous Lymphat Disord. 2018; 6(2):192-200.
[28] O'Sullivan G, Sheehan J, Lohan D, McCann-Brown JA. Iliofemoral venous stenting extending into the femoral regions: initial clinical experience with the purpose-designed Zilver Vena stent. J Cardiovasc Surg. 2013 April; 54(2):255-61.
[29] Neglén P, Hollis KC, Olivier J, Raju S. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clinical, and hemodynamic result. J Vasc Surg. 2007; 45(6):979-90.
[30] Neglén P, Raju S. Balloon dilation and stenting of chronic iliac vein obstruction: technical aspects and early clinical outcome. J Endovasc Ther 2000; 7(2):79-91.
[31] Mahnken AH, Thomson K, de Haan M, O'Sullivan GJ. CIRSE standards of practice guidelines on iliocaval stenting. Cardiovasc Intervent Radiol 2014; 37(4):889-97.
[32] Mahnken AH, Thomson K, de Haan M, O'Sullivan GJ. CIRSE standards of practice guidelines on iliocaval stenting. Cardiovasc Intervent Radiol 2014; 37(4):889-97.
[33] Lichtenberg M, de Graaf R, Erbel C. Standards for recanalization of chronic venous outflow obstructions. Vasa. 2018; 47(4):259-66.
[34] Raju S, Ward M. Utility of iliac vein stenting in elderly population older than 80 years. J Vasc Surg Venous Lymphat Disord. 2015; 3(1):58-63.