CLINICAL INVESTIGATION PLAN

Evaluation of the Zilver® Vena™ Venous Stent in the Treatment of Symptomatic Iliofemoral Venous Outflow Obstruction (VIVO Clinical Study)

Global Clinical Number 11-010

Sponsor: Cook Research Incorporated
1 Geddes Way
West Lafayette, IN 47906
USA

Manufacturer: Cook Ireland Ltd.
O'Halloran Road
National Technology Park
Limerick
Ireland

Summary of Revisions

Version #	Description	Date
11-010-01	Original version	06 Nov 2012
11-010-02	Clarified exclusion criteria; revised analysis plan	24 Jan 2013
11-010-03	Added exclusion criterion; modified additional measures; revised analysis plan for primary safety hypothesis	05 Apr 2013
11-010-04	Added exclusion criterion; clarified exclusion criteria; clarified medication requirements, study procedure, and follow-up schedule	23 Oct 2014
11-010-05	Refined study design; modified exclusion criterion; administrative changes	24 Jun 2015
11-010-06	Omitted interim analysis	23 Jan 2017
11-010-07	Updated Sponsor information; administrative changes	22 Mar 2018

Clinical Investigation Plan Signature Page

This clinical investigation will be conducted in accordance with the Clinical Investigation Plan, ICH GCP, ISO 14155, 21 CFR 812, and other applicable requirements as appropriate. The Clinical Investigation Plan will be revised, as appropriate, based on new information.

Sponsor:

Jennifer L. Kerr

Signature

28 Mar 2018

dd/mmm/yyyy

Jennifer L. Kerr — President, Cook Research Incorporated

Printed Name — Title

Clinical Investigation Plan Signature Page, Continued

Co-Global Principal Investigator

I hereby confirm that I approve of this Clinical Investigation Plan and agree to comply with its terms as laid out in this document.

Signature	08/MAY/2018 dd/mmm/yyyy
Printed Name ANTHONY J. COMEROTA	Title CO-P.I.

Clinical Investigation Plan Signature Page, Continued

Co-Global Principal Investigator

I hereby confirm that I approve of this Clinical Investigation Plan and agree to comply with its terms as laid out in this document.

Signature	08/May/2018 dd/mmm/yyyy
LV Hofmann, MD Printed Name	Co-Global PI Title

Clinical Investigation Plan Signature Page, Continued

Principal Clinical Investigator

I hereby confirm that I approve of this Clinical Investigation Plan and agree to comply with its terms as laid out in this document.

Signature	dd/mmm/yyyy
Printed Name	Title

CONFIDENTIALITY STATEMENT

This document will be treated as a confidential document for the sole information and use of the clinical investigation team and the IRB/EC.

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APPENDICES

1.0 General Information

1.1 Global Sponsor, Monitor, and Data Coordinating Center

Cook Research Incorporated
1 Geddes Way
West Lafayette, IN 47906
USA

1.2 Manufacturer

Cook Ireland Ltd.
O'Halloran Road
National Technology Park
Limerick
Ireland

1.3 Investigation Administration

This investigation will be conducted in accordance with global regulations including ICH GCP, ISO 14155, and 21 CFR 812.

1.4 Investigator

Contact information and qualifications of the co-global principal investigators, principal clinical investigators, clinical investigators, and core laboratories will be maintained by the data coordinating center.

1.5 Monitoring Arrangements

The conduct of the clinical study will be supervised through a process of centralized and on-site monitoring. The data coordinating center will remotely monitor the study for data completeness and for adverse events. On-site monitoring will be implemented as necessary throughout the course of the study. The investigator/institution will provide direct access to source data/documents for study-related monitoring, audits, IRB/EC review and regulatory inspection. Written procedures for monitoring the study are maintained by the data coordinating center and are summarized in Appendix A.

2.0 Approval and Agreement of the Clinical Investigation Plan

The sponsor, co-global principal investigators, and principal clinical investigators for each investigative site will agree to this document and any modifications. Justification for any modifications will be documented. Approval and agreement will be indicated by signing and dating the signature page included in this document.

3.0 Clinical Investigation Plan Overview

The following is a Clinical Investigation Plan to evaluate the safety and effectiveness of the Zilver® Vena™ Venous Stent in the treatment of symptomatic iliofemoral venous outflow obstruction. Patients with symptomatic venous outflow obstruction in one iliofemoral venous segment will be eligible to receive the Zilver® Vena™ Venous Stent. The treated venous segment (i.e., study lesion) will not extend into the inferior vena cava or below the level of the lesser trochanter.

Primary study endpoints will include freedom from major adverse events at 30 days and primary quantitative patency at 12 months. The secondary endpoint will be the change from baseline in the Venous Clinical Severity Score (VCSS) at 1 and at 12 months. [Information redacted due to confidential content.]

This study is designed as a prospective, non-randomized, multi-center study involving up to 40 investigative sites globally. The results of this study will be compared to performance goals derived from the literature. The clinical study intends to enroll 243 patients, and will involve follow-up through 3 years post stent placement. The study flow diagram is presented in Figure 3.1.

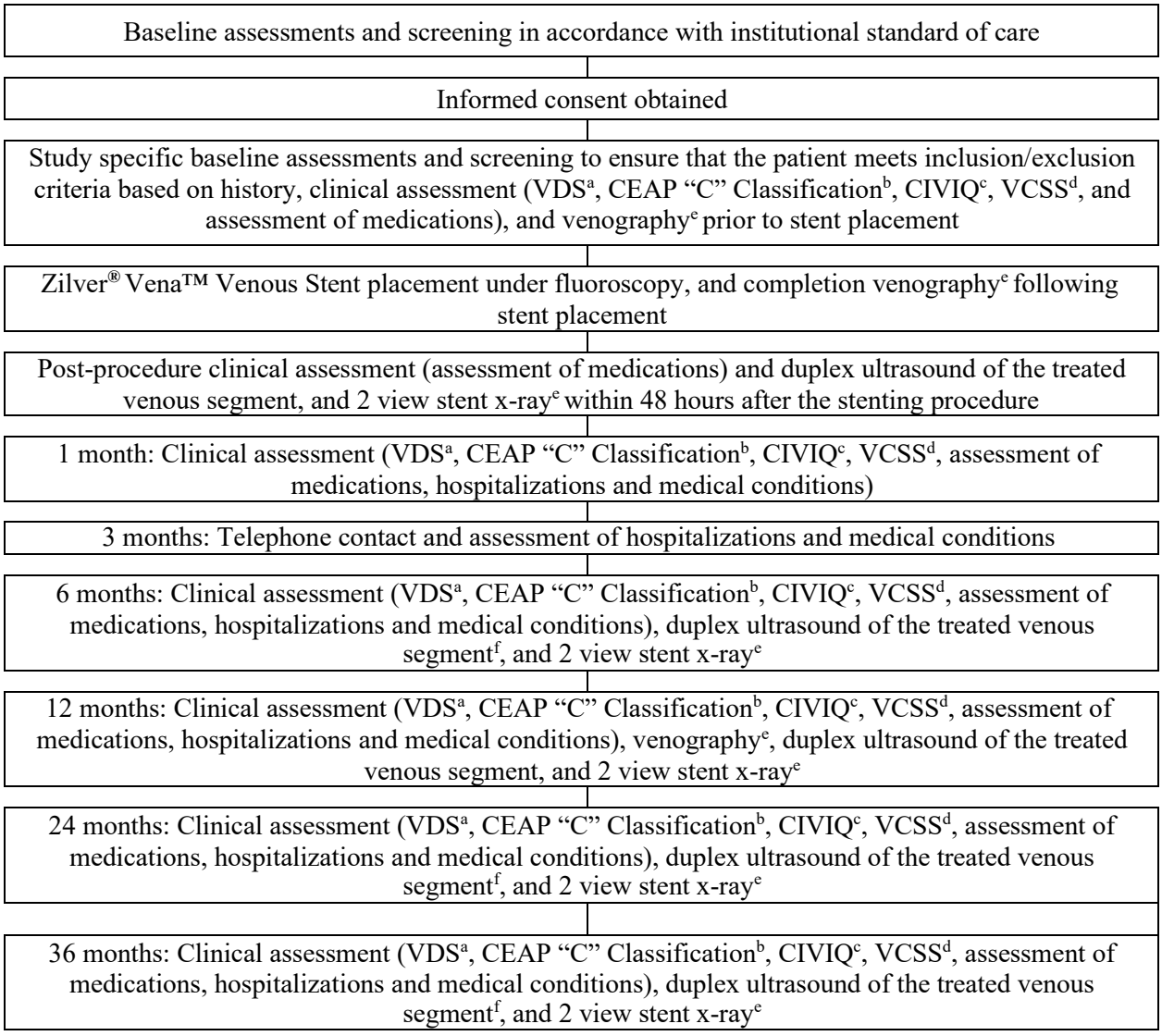


Figure 3.1. Study flow diagram

[a]VDS: Venous Disability Score, [b]CEAP: score of Clinical, Etiological, Anatomic, and Pathophysiologic features, [c]CIVIQ: Chronic Venous Insufficiency Quality of Life Questionnaire, [d]VCSS: Venous Clinical Severity Score
[e]Both obliques of the pelvis recommended.
[f]If patient is symptomatic and ultrasound is inadequate to assess clinical patency, venography will be performed.

4.0 Objectives of the Clinical Investigation

4.1 Objectives

The objectives of this investigation are to evaluate the safety and effectiveness of the Zilver® Vena™ Venous Stent in the treatment of symptomatic iliofemoral venous outflow obstruction.

4.1.1 Primary Safety Endpoint

The primary safety endpoint will be 30-day freedom from major adverse events (MAE), where MAE is defined as procedural bleeding requiring transfusion, procedure- or device-related death, clinically driven target lesion reintervention, clinical migration, new symptomatic pulmonary embolism, or procedure-related perforation requiring open surgical repair or flow-limiting dissection of the target vessel.

4.1.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint will be primary quantitative patency (see Definitions) of the Zilver® Vena™ Venous Stent as assessed by venography at 12-month follow-up.

4.1.3 Secondary Endpoints

The secondary endpoint will be the change from baseline in the VCSS at 1 and at 12 months.

4.1.4 Additional Measures

[Information redacted due to confidential content.]

4.2 Specific Hypotheses to be Accepted or Rejected by Statistical Data

4.2.1 Primary Safety Hypothesis

The primary safety endpoint is 30-day freedom from major adverse events (MAE), and will be analyzed based on the intent-to-treat population. The analysis requires that the performance goal (π_{PGS}) of 87% be met for 30-day freedom from MAE, where π_{PGS} is a weighted average of 85% (computed based on safety data for patients with acute disease, defined as initial symptom onset within 30 days of the procedure) and 88% (computed based on safety data for patients with chronic disease, defined as initial symptom onset greater than 30 days before the procedure), with the weight being prespecified as 30% acute patients and 70% chronic patients. Both 85% and 88% were computed based on 30-day safety data available in the published literature describing patients treated with commercially available stents for acute and chronic iliofemoral venous outflow obstruction, respectively.[1-39] The safety of the Zilver® Vena™ Venous Stent will be established provided the null hypothesis is rejected in favor of the alternative hypothesis with the Binomial test for one proportion at the Type I error level of 0.025.

Let π_S (where S stands for safety) be the probability that a randomly selected patient is free from a MAE at 30 days, then the hypothesis is formulated as follows:

> *Null Hypothesis*: The 30-day freedom from MAE for patients treated with the Zilver® Vena™ Venous Stent does not meet the performance goal (87%).
>
> $H_0: \pi_S \leq \pi_{PGS}$; or $H_0: \pi_S \leq 87\%$
>
> *Alternate Hypothesis*: The 30-day freedom from MAE for patients treated with the Zilver® Vena™ Venous Stent meets the performance goal (87%).
>
> $H_a: \pi_S > \pi_{PGS}$; or $H_a: \pi_S > 87\%$

4.2.2 Primary Effectiveness Hypothesis

The primary effectiveness endpoint is 12-month primary quantitative patency, and will be analyzed based on the intent-to-treat population. The analysis requires that the performance goal

(π_{PGE}) of 76% be met for primary quantitative patency at 12 months. The performance goal was derived based on 12-month patency data available in published literature describing patients treated with commercially available stents for acute and chronic iliofemoral venous outflow obstruction.[1-39] Patency outcomes were similar among patients with acute and chronic disease. The effectiveness of the Zilver® Vena™ Venous Stent will be established provided the null hypothesis is rejected in favor of the alternative hypothesis with the Binomial test for one proportion at the Type I error level of 0.025.

Let π_E (where E stands for effectiveness) be the probability that a randomly selected patient's treated segment is primary patent (quantitative) at 12 months, then the hypothesis is formulated as follows:

Null Hypothesis: The 12-month primary quantitative patency for patients treated with the Zilver® Vena™ Venous Stent does not meet the performance goal (76%).

H_0: $\pi_E \leq \pi_{PGE}$; or H_0: $\pi_E \leq 76\%$

Alternate Hypothesis: The 12-month primary quantitative patency for patients treated with the Zilver® Vena™ Venous Stent meets the performance goal (76%).

H_a: $\pi_E > \pi_{PGE}$; or H_a: $\pi_E > 76\%$

Study success requires that both primary hypotheses (i.e., safety and effectiveness) be met.

4.2.3 Secondary Endpoint Hypothesis

The secondary endpoint is the change from baseline in the VCSS at 1 month and at 12 months. The change from baseline in VCSS at 1 month and at 12 months will be tested against 0 for statistical significance at the Type I error level of 0.05.

Let S_{diff} be the change from baseline on VCSS at a specific time point, then the hypothesis is formulated as follows:

Null Hypothesis: The change from baseline on VCSS at a time point for patients treated with the Zilver® Vena™ Venous Stent is not significantly different from 0.

$H_0: S_{diff} = 0$

Alternate Hypothesis: The change from baseline on VCSS at a time point for patients treated with the Zilver® Vena™ Venous Stent is significantly different from 0.

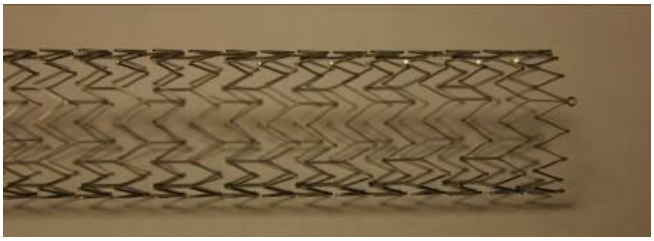
$H_a: S_{diff} \neq 0$

Paired t-test will be used to evaluate the secondary hypotheses. In the analyses of VCSS, multiplicity will be adjusted using the Holm procedure due to the presence of multiple time points.

5.0 Device Description and Intended Use

5.1 General Device Description

The Zilver® Vena™ Venous Stent (Figure 5.1) is a self-expanding, slotted tube nitinol stent. It is designed to provide support while maintaining flexibility in the vessel upon deployment. Post-deployment, the stent is designed to impart an outward radial force upon the inner lumen of the vessel, establishing patency in the stented region. The device is intended for insertion into the iliofemoral venous system using percutaneous access. The stent is pre-loaded in a 7.0 French over-the-wire delivery catheter. The delivery catheter is available in 80 cm and 120 cm lengths.

Figure 5.1. Zilver®  Vena™ Venous Stent

Please reference the manufacturer's Instructions for Use for the device sizes available for the clinical investigation.

Devices under investigation will be tracked by the investigative site throughout the course of the study through the use of a product log, which includes information such as lot numbers, quantity and device disposition. Additionally, information such as the quantity, size(s) and lot number(s)

of devices used in patients will be recorded on Case Report Forms (CRFs).

5.2 Indication for Use

The Zilver® Vena™ Venous Stent is indicated for improving luminal diameter in the iliofemoral veins for the treatment of symptomatic venous outflow obstruction.

5.3 Instructions for Use

Please reference the manufacturer's Instructions for Use for the following:

- Complete instructions including storage and handling requirements, preparation for use, precautions to be taken.
- Summary of the necessary training and experience required for use of these devices.
- Complete description of the procedures involved in the use of these devices.

6.0 Preliminary Investigations and Justification

6.1 Literature Review

Please reference the Investigator's Brochure for a complete literature review and evaluation.

6.2 Non-Clinical Testing

Non-clinical tests were conducted in accordance with Good Laboratory Practice requirements, or performed in compliance with verified methods and Standard Operating Procedures to maintain the integrity of the results. *In vitro* and *in vivo* testing has established the safety of the device for its intended purpose. Please reference the Investigator's Brochure for a summary of non-clinical testing.

6.3 Previous Clinical Experience

Please reference the Investigator's Brochure for a complete description of the previous clinical experiences with the device or other similar devices.

7.0 Risk Analysis and Risk Assessment

Please reference the Investigator's Brochure for a complete risk analysis.

7.1 Risks and Foreseeable Adverse Device Effects

Please reference the Investigator's Brochure for a list of adverse events that may be considered as potential risks associated with the use of the Zilver® Vena™ Venous Stent

7.2 Methods to Minimize Risks

The device design, non-clinical testing, clinical study design, and the manufacturer's Instructions for Use are intended to minimize the risks associated with the use of this device.

This device will be used only by trained healthcare professionals who are experienced in the study procedure. Patients will be selected according to the labeled indication and in accordance with inclusion/exclusion criteria outlined in this document.

The risks of the study have been minimized and the potential benefits outweigh the risks in light of the importance of the knowledge to be gained about the safety and effectiveness of the Zilver® Vena™ Venous Stent.

8.0 Design of the Clinical Investigation

8.1 Type of Investigation

This is a prospective, non-randomized, multi-center study that is intended to enroll 243 patients at up to 40 investigative sites globally. At least half of the study patients will be enrolled at US sites. The results of this single-arm study will be compared to performance goals derived from the literature.

8.2 Rationale

The purpose of this study is to evaluate the safety and effectiveness of the Zilver® Vena™ Venous Stent in patients with symptomatic iliofemoral venous outflow obstruction.

The endpoints were chosen as applicable measures of device effectiveness and safety because of their similarity to those of interest in the literature.

8.3 Measures to be Taken to Avoid or Minimize Bias

Patients with symptomatic iliofemoral venous outflow obstruction will be screened consecutively to mitigate selection bias. Investigational sites should maintain a screening log of patients. For patients who are excluded from the study, the log indicates the primary inclusion/exclusion criterion that is violated.

The study will utilize uniform definitions for study endpoints, event adjudication by an independent clinical events committee, and imaging data analysis by a centralized core laboratory. Study results will be analyzed in accordance with a prospectively defined analysis plan.

8.4 Variables to be Measured to Demonstrate Achievement of Endpoints

Imaging analysis will be performed by independent core laboratories.

The clinical data and imaging measurements will be collected on standardized CRFs, which may serve as source documents. The schedule for assessments is summarized in Table 8.1.

Table 8.1. Data Collection Schedule

	Pre-Procedure	Procedure	Post-Procedure[a]	1 month	3 months	6 months	12 months	24 months	36 months	Prior to reintervention	Post reintervention
Clinical assessment including CEAP "C" classification, CIVIQ, VCSS, VDS	X			X		X	X	X	X	X	
Venography[b]		X[e]					X			X	X
2 view Stent X-ray[c]			X			X	X	X	X	X	X
Duplex Ultrasound[d]			X			X[f]	X	X[f]	X[f]	X	X
Telephone contact					X						

[a]Performed prior to hospital discharge or within 48 hours.

[b]Venography must be in approximately two orthogonal views.

[c]Both obliques of the pelvis recommended.

[d]Duplex ultrasound must include the treated venous segment, including cranial and caudal vessel segments.

[e]Venography, ultrasound, IVUS, or CTV performed within 1 month prior to the study procedure are acceptable for the purposes of documenting in-flow tract patency. Venography, IVUS, or CTV performed within 1 month prior to the study procedure are acceptable for the purposes of documenting out-flow tract patency. Venography is required pre and post stent placement for all procedural assessments to the study vessel and treated venous segment.

[f]If patient is symptomatic and ultrasound is inadequate to assess clinical patency, venography will be performed.

8.5 Inclusion and Exclusion Criteria

Patient eligibility for enrollment will be based on known information at the time of the procedure. Information obtained at a later date may contradict these criteria, but this will not be considered a violation of the Clinical Investigation Plan. [Information has been redacted due to confidential content.]

Inclusion Criteria:

1) symptomatic venous outflow obstruction in one iliofemoral venous segment (i.e., one limb) per patient, demonstrated by:
    - CEAP "C" ≥ 3, **or**
    - VCSS pain score ≥ 2

General Exclusion Criteria:

1) < 18 years of age;
2) pregnant or planning to become pregnant in the next 12 months;
3) 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 patients at high risk for pulmonary embolism) within 30 days prior to the study procedure;
4) surgical or interventional procedures for other medical conditions (i.e., not associated with the target limb) within 30 days prior to the study procedure;
5) lesions with intended treatment lengths extending into the inferior vena cava or below the level of the lesser trochanter;
6) lesion with malignant obstruction;

7) previous stenting of the target vessel; and

Venographic Exclusion Criterion:

1) iliofemoral venous segment unsuitable for treatment with available sizes of study devices.

8.6 Point of Enrollment

Patients may be enrolled in the study if all inclusion and no exclusion criteria are met.

Patients who meet the inclusion/exclusion criteria (i.e., meet the inclusion criteria and none of the exclusion criteria) will be invited to participate in this investigation. All patients eligible for entry into the study will have the Clinical Investigation Plan explained to them, as well as potential risks and benefits of their participation in the study. Each patient who agrees to participate will be required to sign an informed consent document prior to the procedure or any study-specific testing. If new information is obtained after a patient receives treatment with the device, patients who have not exited the study will be informed about the new information, and will be re-consented at the discretion of the investigator and/or the site's IRB/EC.

Point of enrollment (and inclusion in the intent-to-treat population) occurs when the Zilver® Vena™ Venous Stent delivery system is introduced into the patient's body.

8.7 Methods

8.7.1 Duration of the Study

Enrollment is expected to be completed within 60 months of enrolling the first patient. Twelve-month post-procedure clinical and imaging data are expected to be available approximately 14 months after the last patient is enrolled in the study with follow-up to continue for 36 months following initial stent placement.

8.7.2 Medications

Patients should receive aspirin prior to stent implantation. Following stent implantation, patients will receive one anticoagulant for a minimum of 6 months and aspirin for the duration of the study. Multiple anticoagulants should only be used for bridging purposes. Clopidogrel may be substituted for aspirin at the discretion of the physician. Doses will be in accordance with physician discretion and institutional standard of care. Anticoagulant and antiplatelet medications will be recorded on the appropriate Case Report Form throughout the study.

8.7.3 Pre-Procedure

A pre-procedure clinical assessment will be completed including medical history and documentation of the symptom(s) indicative of venous outflow obstruction, using VDS, CEAP "C" Classification, CIVIQ, and VCSS scores, and assessment of medications.

8.7.4 Procedure

- INR will be assessed within 24 hours prior to stent placement and will not be > 3 before proceeding with stent placement.
- I.V. heparin bolus should be administered per institutional standard of care based upon clinical indication and underlying disease process.
- Thrombolysis and/or thrombectomy are permitted prior to stent implantation in patients with thrombus present in the intended treatment segment (including the inflow and outflow segments). Vena cava filter placement is permitted prior to stent implantation in patients at high risk for pulmonary embolism (e.g., patients undergoing pre-procedure thrombolysis, those in whom tracking through the diseased vessel may cause material to dislodge from the vessel wall, and those at continued risk for pulmonary embolism for some other reason).
- Venography in approximately two orthogonal views will be performed prior to study enrollment to determine the status of the inflow tract (from the level of the popliteal vein to just caudal to the study lesion), outflow tract (from the vein just cranial to the study lesion up to the level of L1 in the inferior vena cava), and study lesion, as well as the vein size at the intended stent location. Ultrasound, IVUS, or CTV performed within 1 month prior to the study procedure are acceptable alternatives for the purposes of documenting in-flow tract patency. IVUS and CTV performed within 1 month prior to the study procedure are acceptable alternatives for the purposes of documenting out-flow tract patency. Any thrombus that requires treatment (thrombolysis and/or thrombectomy) must be treated prior to enrollment and treatment of the study lesion; there will be no residual obstruction/stenosis

>20% in the inferior vena cava or below the level of the lesser trochanter (e.g., in the femoral and/or popliteal veins).

- A calibration source (e.g., LeMaitre Ruler) will be in the field of view, but not overlapping the vessel. Vessel diameters immediately proximal and distal to the study lesion will be measured. The chosen stent diameter should be oversized 2-4 mm with respect to the estimated vessel diameter as determined by the best-available assessment (in preferential order):
    1. Diameter of the most normal looking segment of the common iliac, external iliac, or common femoral vein;
    2. Expanded balloon diameter used for predilatation; or
    3. Standard diameter of the vein to be stented.
- The study lesion length will be measured to determine the length of the stent required. To cover the entire study lesion, the cranial and caudal aspects of the stent should extend into the healthy tissue by 5-10 mm.
- Pre-dilation is recommended.
- The Zilver® Vena™ Venous Stent will be deployed in the intended location under fluoroscopy according to the manufacturer's Instructions for Use.
- Placement of additional stents to cover the full extent of the study lesion (including geographical miss or vascular injury) is allowed. Zilver® Vena™ Venous Stent(s) should be used. If more than one stent is placed, stents will be deployed and overlapped as recommended in the manufacturer's Instructions for Use. In addition, the diameters of additional stents may be increased or decreased depending on the extent of taper along the intended treatment length. Proximally, stents may protrude into the IVC, but will not appose the walls of the IVC (i.e., a stent protruding into the IVC is intended to protect the iliac ostium and prevent the development of stenosis at the IVC-common iliac vein confluence, not to treat lesions in the IVC). Distally, stents will not extend beyond the level of the lesser trochanter.
- If incomplete expansion exists within the stent at any point along the lesion, post-deployment balloon dilatation with a PTA balloon can be performed at the discretion of the physician. An appropriate size balloon catheter should be selected and the inflation diameter of the balloon used for post dilatation should approximate the diameter of the target vein.
- Final completion venography in approximately two orthogonal views will be performed of the treated segment and at least 1 cm cranial and caudal to the treated segment to assess stent position and patency.

8.7.5 Post-procedure/Pre-discharge

Post-procedure, patients will undergo observation and discharge according to institutional standard of care. Within 48 hours of the stenting procedure, patients must undergo a duplex ultrasound of the treated venous segment, including the cranial and caudal vessel segments, and a 2 view stent x-ray (both obliques of the pelvis recommended). Patients should resume normal activities with ambulation as soon as is feasible. Use of compression therapy is recommended in accordance with institutional standard of care.

8.7.6 Follow-up Schedule

Follow-up windows are intended as guidelines only. They are not absolute and are not intended to limit data collection due to scheduling conflicts.

- *1-month clinic visit (30 days ± 5 days)*: An office visit will be completed including documentation of VDS, CEAP "C" Classification, CIVIQ, and VCSS scores, and assessment of medications, hospitalizations and medical conditions.

- *3-month telephone contact (90 days ± 10 days)*: Patients will be contacted by telephone by the investigative site for clinical evaluation and assessment of hospitalizations and medical conditions. Up to three attempts should be made to contact the patient.

- *6-month clinic visit (180 days ± 30 days)*: An office visit will be completed including documentation of VDS, CEAP "C" Classification, CIVIQ, and VCSS scores, and assessment of medications, hospitalizations and medical conditions. Duplex ultrasound of the treated venous segment (including the cranial and caudal vessel segments) to assess clinical patency and 2 view stent x-ray (both obliques of the pelvis recommended) to assess device integrity will be performed. Confirmatory venography in approximately two orthogonal views will be performed if the patient is symptomatic and the ultrasound is inadequate to assess clinical patency.

- *12-month clinic visit (365 days ± 45 days)*: An office visit will be completed including documentation of VDS, CEAP "C" Classification, CIVIQ, and VCSS scores, and assessment of medications, hospitalizations and medical conditions. Venography in approximately two orthogonal views will be performed of the treated segment and at least 1 cm cranial and caudal to the treated segment to assess quantitative patency. A calibration source (e.g., LeMaitre Ruler) will be in the field of view, but not overlapping the vessel. Duplex ultrasound of the treated venous segment (including the cranial and

caudal vessel segments) to assess clinical patency, and 2 view stent x-ray (both obliques of the pelvis recommended) to assess device integrity will be performed.

- *24-month clinic visit (730 ± 60 days)*: An office visit will be completed including documentation of VDS, CEAP "C" Classification, CIVIQ, and VCSS scores, and assessment of medications, hospitalizations and medical conditions. Duplex ultrasound of the treated venous segment (including the cranial and caudal vessel segments) to assess clinical patency and 2 view stent x-ray (both obliques of the pelvis recommended) to assess device integrity will be performed. Confirmatory venography in approximately two orthogonal views will be performed if the patient is symptomatic and the ultrasound is inadequate to assess clinical patency.

- *36-month clinic visit (1095 ± 75 days)*: An office visit will be completed including documentation of VDS, CEAP "C" Classification, CIVIQ, and VCSS scores, and assessment of medications, hospitalizations and medical conditions. Duplex ultrasound of the treated venous segment (including the cranial and caudal vessel segments) to assess clinical patency and stent 2 view x-ray (both obliques of the pelvis recommended) to assess device integrity will be performed. Confirmatory venography in approximately two orthogonal views will be performed if the patient is symptomatic and the ultrasound is inadequate to assess clinical patency.

8.7.7 Imaging

An Imaging Manual (including venography, duplex ultrasound, and 2 view stent x-ray) will be provided by Cook for the investigator's and site's reference. Guidelines provided by the core lab and Cook should be followed for the imaging exams.

8.7.8 Reintervention within Treated Iliofemoral Venous Segment

If a patient requires reintervention within the treated venous segment (i.e., bypass, thrombectomy, PTA, etc.), the patient should be treated with the standard of care for the institution. The following must be performed prior to a reintervention:

- Clinical assessment (medications and adverse events),
- Documentation of VDS, CEAP "C" Classification, CIVIQ, and VCSS scores, and the symptom(s) indicative of the need for revascularization,
- Duplex ultrasound of the treated venous segment and the cranial and caudal vessel segments,

- 2 view stent x-ray (both obliques of the pelvis recommended),
- INR assessed within 24 hours of the reintervention, and
- The treated segment and at least 1 cm cranial and caudal to the treated segment will be assessed by venography in approximately two orthogonal views at the time of reintervention (i.e., prior to and immediately after the intervention); a calibration source (e.g., LeMaitre Ruler) will be in the field of view, but not overlapping the vessel. The venogram will be submitted to the data coordinating center along with a procedural report.

The following must be performed following a reintervention:

- Duplex ultrasound of the study lesion and the cranial and caudal vessel segments, and
- 2 view stent x-ray (both obliques of the pelvis recommended).

All subsequent follow-up visits will remain time-indexed to the original study procedure. Patients with amputation or surgical bypass of the study lesion will be followed for thirty days after their reintervention. Patients with other reinterventions will return for office visits and will undergo all imaging follow-up and be monitored for adverse events and complications out to 36 months following the original study procedure. However, clinical assessments (i.e., VDS, CEAP "C" Classification, CIVIQ, and VCSS scores) will not be collected for the remainder of follow-up.

8.8 Criteria and Procedures for Withdrawal/Lost to Follow-Up

A patient may decide to withdraw from the study at any time either before or after undergoing the procedure without prejudice or loss of care. The patient should notify the investigator of his/her desire to withdraw. The investigator will notify the sponsor. The investigator may also decide to withdraw the patient from the study at any time based on medical judgment. In all instances of withdrawal, the appropriate study visit and study termination data will be submitted to the data coordinating center, and will include the reason why the patient has been withdrawn from the study. Any data collected on the patient up to the point of withdrawal may be used in the study.

In the event a patient is lost to follow-up or cannot be contacted for post-treatment assessments, at least three attempts may be made to locate the patient, and these efforts will be documented. If the patient cannot be located, a lost to follow-up entry will be submitted.

8.9 Participation Endpoints of the Study

A patient's participation in the study will end after any of the following:

- Completion of all scheduled clinical and imaging evaluations to 36 months;
- Patient withdrawal or lost to follow-up;
- Failure to gain target vessel access or deploy device, plus 30 days;
- Surgical bypass of the study lesion, plus 30 days;
- Amputation of the study limb, plus 30 days;
- Closure of the study; or
- Patient death.

8.10 Sample Size

Sample size calculations are presented in section 9.1. Based on this analysis, it is estimated that a minimum of 218 patients is required to fulfill enrollment. Cook intends to enroll 243 patients at up to 40 investigative sites to account for those who withdraw or are lost to follow-up. Consistent with the derivation of the primary safety hypothesis, approximately 30% of the enrolled patient population will have acute disease (defined as initial symptom onset within 30 days of the procedure) and approximately 70% of the enrolled patient population will have chronic disease (defined as initial symptom onset greater than 30 days of the procedure). At least half of the study patients will be enrolled at US sites. It is estimated that enrollment of 243 patients will take approximately 60 months.

8.11 Period of Use for the Device or its Control

The follow-up period extends to 36 months after implantation and utilizes both clinical and telephone assessments in order to permit a realistic evaluation of the performance of the device and to identify associated adverse device effects over that period.

8.12 Limitations of the Investigation

To achieve valid data upon which to base evaluation of the safety and effectiveness of the Zilver® Vena™ Venous Stent, all patients will be required to meet clinical investigation plan-specified inclusion/exclusion criteria. While controlling the homogeneity of the patient population allows inferences to be made about the effect of treatment, it may limit the overall range of patients to which the inferences may be applied.

Based on the indications for use of this device learned from non-clinical experience and the guidance of clinicians currently treating venous outflow obstruction, certain anatomical considerations for device size selection will result in restricting the sample of patients selected for the study to a subset of the population of patients experiencing symptomatic iliofemoral venous outflow obstruction. Additionally, this study is not designed to provide data beyond 3 years of follow-up.

8.13 Safety Monitoring

A Data Safety Monitoring Board (DSMB) consisting of independent physicians and at least one independent statistician, who are not investigators in the study, nor have a conflict of interest with the conduct and administration of the study, will be convened on a regular basis to evaluate study progress and review adverse events.

An independent Clinical Events Committee (CEC) consisting of physicians, who are not investigators in the investigation, nor have a perceived conflict of interest with the conduct and administration of the investigation, will be established to adjudicate applicable clinical events reported during the investigation. This adjudication will be performed to assess whether the events were due to a pre-existing or unrelated condition, procedure-related, technique-related, and/or device-related.

A central core laboratory will be used for image analysis to provide uniformly defined morphological and morphometric analysis of images.

Regularly scheduled review/monitoring of all patient data will be conducted at the data coordinating center, in part, for identification of adverse events and assurance that they are correctly reported to the DSMB and CEC.

9.0 Statistical Considerations

9.1 Endpoint Analyses

For the primary effectiveness and safety endpoints, the hypotheses will be tested at the significance level of 0.025. If both the safety and effectiveness hypotheses are met, the study will be considered successful.

The test statistic for hypotheses testing of the secondary endpoint is the absolute change from baseline in the VCSS at 1 month and at 12 months. Paired t-test will be used to evaluate the secondary hypotheses. In the analyses of VCSS, multiplicity will be adjusted using the Holm procedure due to the presence of multiple time points.

Full statistical details (including endpoint analyses) are in the Statistical Analysis Plan for the study.

9.2 Sample Size Calculations

Evaluation of the primary safety hypothesis of 30-day freedom from MAE and the primary effectiveness hypothesis of 12-month primary quantitative patency requires 218 patients to determine if the performance goals have been met. Allowing for an additional 10% of patients who withdraw or are lost to follow-up, Cook intends to enroll 243 patients.

A Bayesian adaptive study was simulated to determine the sample size required to test the study hypotheses with sufficient statistical power (in the frequentist context). For the power calculations, the true quantitative patency rate following treatment with the Zilver® Vena™ Venous Stent was assumed to be 86% and the true rate of freedom from MAE at 30 days was assumed to be 97%. The results of the simulations indicate that a sample size of 218 will provide a minimum power of 0.90 with a Type I error of 0.025 for each endpoint.

It has been prespecified that patients enrolled in this study will include approximately 30% acute patients and 70% chronic patients. This patient population was defined based on the published literature describing patients treated for iliofemoral venous obstruction[1-39] and the pattern of enrollment for the first 109 patients enrolled. Specific definitions for acute and chronic iliofemoral venous outflow obstruction are provided in Appendix B.

Full statistical details on sample size calculation are in the Statistical Analysis Plan for the study.

9.3 Site-level Poolability

Poolability of data from multiple sites will be verified by examining the primary safety and effectiveness measures among sites. Site-level poolability will be considered appropriate provided that these measures are similar among sites. It is expected that important patient baseline characteristics, such as age, sex/gender, BMI, lesion length, known thrombophilia, anticoagulation/antiplatelet medication usage, stent extension below the inguinal ligament, stent extension into the common femoral vein, stent expansion into the IVC, presence of occlusive obstruction, presence of reflux, adjunctive procedures performed in addition to stent placement (thrombolysis, thrombectomy, IVC filter), and previous DVT may differ among sites. The influence of these patient characteristics on site poolability will also be examined.

It is expected that some sites will have too few patients to provide reasonable site-level estimates of primary and secondary measures. Each investigative site will be allowed to enroll no more than 49 patients (20% of the total enrollment) to ensure the overall result is not biased by the results from a single site. Pooling of this information will be explored based on hospital size (large versus small), site enrollment (large versus small), type of hospital (community versus teaching), and other group-wise strategies.

US versus OUS poolability analysis will be accomplished by incorporating a covariate indicating whether a patient belongs to US or OUS.

9.4 Planned Subgroups, Interactions, and Covariates

In addition to the site level poolability, the primary and secondary endpoints will be analyzed against relevant demographic and comorbidity variables in the context of sub-group analyses or included in the analysis models as covariates.

The analysis may include the covariates of age, BMI, lesion length, known thrombophilia, anticoagulation/antiplatelet medication usage, sex/gender, stent extension below the inguinal ligament, stent extension into the common femoral vein, stent extension into the inferior vena cava, presence of occlusive obstruction, presence of reflux, adjunctive procedures performed in addition to stent placement (thrombolysis, thrombectomy, IVC filter), previous DVT, etc.

Planned subset analyses include: non-thrombotic versus post-thrombotic obstruction on chronic venous disease, occlusive versus non-occlusive obstruction, presence versus absence of

thrombophilia, stent extension into the IVC/common femoral vein, and presence versus absence of reflux.

9.5 Missing Data

Missing data will be addressed using two primary strategies: 1) multiple imputation with best available data, if appropriate, and 2) case deletion. The first strategy is multiple imputation with best available data, if appropriate. This method will be used to predict missing endpoint and imaging data. Previous clinical trial experience suggests that some portion of the imaging data may not meet the criteria for accurate review by the core laboratory; however, it is recognized that the investigator uses this information to provide the best possible care for the patient. Therefore, it is reasonable to substitute any missing core laboratory measurements with the corresponding measurements made by the investigator or institutional staff. In addition, the absence or presence of clinical sequelae may supplement the required missing core laboratory assessment of device performance. This strategy is a best approximation of the missing data value.

Statistical imputation strategies originating from Schafer[40] may also be used, supplemented with notes provided by Schafer.[41] The computations (with no covariates) will be performed using PROC MI and PROC MIANALYZE in SAS version 9.3 or later, or WinBUGS 1.4 or later. Unless evidence suggests otherwise, missing at random data will be assumed.

The second strategy is case deletion. If the amount of missing data does not result in a reduction of analyzable patients to a number that is below that which is required for sufficient statistical power of the primary endpoints, then case deletion will be the method of choice for that analysis.

Additional analyses may also be performed to address missing data, including tipping point analysis.

9.6 Future Use of Study Data

[Information redacted due to confidential content.]

10.0 Emergency Situations

Patients will not be treated with the Zilver® Vena™ Venous Stent in emergency situations where prior consent of the patient is not possible.

11.0 Deviations from Clinical Investigation Plan

Investigators are not allowed to deviate from this Clinical Investigation Plan without prior authorization by the sponsor except under emergency situations when necessary to preserve the rights, safety and well-being of study patients.

Deviations (failures to follow requirements of the Clinical Investigation Plan) and non-compliances (failures to follow applicable regulations) will be recorded together with an explanation. Deviations or non-compliances that impact the rights, welfare, or safety of patients will be reported to the sponsor and IRB/EC as required and as soon as possible.

If appropriate, corrective and preventive actions will be discussed by the sponsor, investigator, and/or the IRB/EC to determine a suitable course of action.

12.0 Procedure for Reporting Adverse Events

Events known to be related to pre-existing conditions or existing at admission are not considered adverse events. Additionally, common standard of care practices are not considered adverse events (e.g., centers located at high geographical altitudes that discharge all patients on home oxygen therapy regardless of procedure).

All adverse events are to be reported to the data coordinating center using the appropriate Case Report Form. In cases of adverse device effects (adverse event with relation to the study device) or major or serious adverse events, completed forms should be submitted to the data coordinating center immediately upon knowledge of the event. The data coordinating center will review the information submitted for possible reporting to the sponsor. In accordance with applicable requirements, the principal investigator will notify the local IRB/EC, while the sponsor will notify the regulatory authority. If indicated, all principal investigators and investigative sites in the study will be notified of applicable events by the sponsor. Refer to the Investigator's Brochure for a list of potential adverse events related to this study.

13.0 Early Termination or Suspension of the Investigation

Any decision to suspend enrollment or terminate the study, either completely or at one or more sites, will be made by the sponsor and, if appropriate, the local IRB/EC. If a decision is made to terminate the study, all patients already treated will be followed per institutional standard of care.

14.0 Ethical Considerations

This clinical investigation will be conducted according to the Declaration of Helsinki and in accordance with global regulations including but not limited to: ICH GCP, ISO 14155, and 21 CFR 812.

The investigator is responsible for obtaining approval of this clinical investigation by the relevant IRB/EC at their associated institution. The study will not begin until a favorable opinion of the IRB/EC has been obtained. The investigator is responsible for complying with requirements imposed by their IRB/EC and/or regulatory authority. Furthermore, the investigator will ensure that local regulations concerning data protection are followed.

15.0 Publication Policy

Publication policy, rights and obligations for this Investigation have been negotiated, detailed and defined in the Investigation Contractual Documents and Agreements with the investigation site and investigators.

16.0 Data Collection

Patient data will be collected and entered by trained personnel at the clinical site onto electronic Case Report Forms (eCRFs) through an Electronic Data Capturing (EDC) system. This is a secure, web-based system, allowing those with permission to access data from any location at any time. Source data is to be retained for data entered into the eCRF system. Data obtained and simultaneously entered into the EDC system may also serve as source documentation (e.g., telephone assessments, CIVIQ). Site personnel are required to undergo data entry training and will have unique login names and passwords in order to enter patient data. In accordance with 21 CFR Part 11, the eCRF system creates a secure, computer-generated, time stamped audit trail to record the date and time of operator entries and actions that create, modify, or delete electronic records..

17.0 Data Reporting

Progress reports and a final report at the conclusion of the clinical investigation will be submitted by the investigators and sponsor to the regulatory bodies and IRBs/ECs as required by local regulations.

18.0 Data Management and Quality Assurance

Each principal investigator or appropriately trained designee will enter the clinical data into the EDC system on standardized Case Report Forms. Investigators will provide all applicable clinical data and documentation to the sponsor. Patient data and documents pertaining to the study will be kept and archived by the sponsor. Data will be reviewed for missing data, data consistency, and reasonableness of responses. Discrepancies will be resolved through a formal query process involving direct contact with investigators or research coordinators. The data coordinating center is responsible for database management, data verification, data archiving and data retention.

As needed to assist the sponsor in its research (e.g., during evaluation of an adverse event), data will be accessible to the sponsor, the participating investigators, the manufacturer, and companies or individuals the sponsor authorizes.

19.0 Insurance

The devices are covered by the sponsor's product liability insurance. A clinical study insurance policy will be taken out according to local requirements.

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APPENDIX A

Written Procedures for Monitoring Investigations

A. Selection of the monitor.

Designated by the sponsor to oversee the investigation, the monitor may be an employee of Cook, an employee of a monitoring organization (CRO) or an independent contractor or consultant. The monitor will be qualified by training and experience to monitor the investigation in accordance with all applicable regulations and standards for conducting clinical investigations.

B. General duties of the monitor.

The monitor must ensure that the investigation is conducted in accordance with:

1. The signed investigator agreement.
2. The Clinical Investigation Plan (CIP).
3. Any conditions imposed by the IRB/EC or regulatory authority.
4. The requirements of the applicable regulations and standards.

C. Reports by the monitor to the sponsor.

1. Any non-compliance with the items listed above. In the event that the investigator is not complying with the requirements outlined above, it is the sponsor's responsibility to secure compliance.
2. Any adverse events/effects that are potentially reportable to a regulatory authority.

D. Initiating the investigation.

Prior to initiating any clinical use of the device, the monitor will participate in a pre-investigation or initiation visit with each investigative site.

At a minimum, the following items will be addressed during the site initiation visit:

- Provide training to investigator on his/her responsibilities per the investigator agreement, applicable laws, regulations and standards; and
- Provide training to investigator that the IRB/EC approval letter and informed consent/patient information is on file before initiation of the clinical investigation.

Additionally, training may be provided to the investigator on:

- The regulatory status of the device/product(s) and the requirements for the accountability of same;
- The nature of the CIP;
- The requirements for an adequate and well-controlled clinical investigation;
- His or her obligation to obtain informed consent in accordance with applicable regulations;
- His or her obligation to ensure continuing review of the clinical investigation by the IRB/EC in accordance with conditions of approval and applicable regulations and to keep the sponsor informed of such IRB/EC approval and subsequent IRB/EC actions concerning the investigation;
- The importance of access to an adequate number of suitable subjects to conduct the investigation;
- The importance of adequate facilities for conducting the clinical investigation; and
- The importance of sufficient time from other obligations to carry out the responsibilities to which the investigator is committed by applicable regulations.

E. During the course of the investigation, at the direction of the Project Manager, the monitor should visit the site frequently enough to ensure that:

- The facilities and research staff used by the investigator continue to be acceptable for purposes of the clinical investigation;
- The applicable version of the CIP and agreements are being followed;
- Changes to the CIP, informed consent/patient information have been approved by the IRB/EC and/or reported to the sponsor and the IRB/EC;
- Accurate, complete, and current records are being maintained;
- Accurate, complete, and timely reports are being made to the sponsor and IRB/EC; and
- The investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.

As appropriate, the following tasks could be performed during periodic visits:

- Adverse event review to ensure that events are appropriately reported within the time periods required by the sponsor, CIP, IRB/EC, and applicable regulatory requirements; and

- Source data verification per the monitoring plan to determine that:
  - Informed consent/patient information has been documented in accordance with applicable regulations and expectations of local IRB/EC;
  - The information recorded in the Case Report Forms (paper or electronic) is complete, accurate, and legible;
  - There are no omissions in the CRFs of specific data elements, such as the administration to any patient of concomitant test articles or the development of an intercurrent illness;
  - Missing visits or examinations are noted; and
  - Subjects failing to complete the clinical investigation and the reason for each failure are noted.

F. Records of the monitor.

The monitor will prepare and maintain records of each initiation visit and each periodic visit, general site contact, or discussion. These will include:

1. Date, name and address of the investigator, and names of other staff members present at each meeting.
2. A summary of the findings of the visit.
3. A statement of any action taken by the monitor or investigator to correct any deficiencies noted.
4. The monitor will immediately notify the sponsor of any conditions of non-compliance with the CIP, conditions of IRB/EC or regulatory authority approval, or the applicable regulations.

APPENDIX B

Definitions

Adverse Event, Early – Undesirable clinical event that occurs ≤ 30 days following initial stent placement.

Adverse Event, Late – Undesirable clinical event that occurs > 30 days following initial stent placement.

Adverse Event, Major (MAE) – Procedural bleeding requiring transfusion, procedure- or device-related death, clinically driven target lesion reintervention, clinical migration, new symptomatic pulmonary embolism, or procedure-related perforation requiring open surgical repair or flow-limiting dissection of the target vessel (note: bleeding events occurring prior to study enrollment, and related to procedures such as thrombolysis or thrombectomy, are not considered procedural bleeding events).

CEAP[a] – A system of scoring venous disease according to Clinical, Etiological, Anatomic, and Pathophysiologic features. For the purpose of this investigation, the clinical classification ('C') will be used. The scoring system for the clinical classification is as follows:

CEAP Clinical Classification

Class	Presenting feature
C0	No visible or palpable signs of venous disease
C1	Telangiectasias or reticular veins
C2	Varicose veins
C3	Edema
C4a	Pigmentation and/or eczema
C4b	Lipodermatosclerosis and/or atrophie blanche
C5	Healed venous ulcer
C6	Active venous ulcer

[a] Eklöf B, Rutherford RB, Bergan JJ, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004;40:1248-1252.

Clinically driven Reintervention – A reintervention performed in a patient with recurrent symptoms of venous outflow obstruction of the target lesion and with venography showing a treated venous segment (including the region within ± 1 cm proximal and/or distal to the treated venous segment) minimum lumen diameter ≤ 50% of the immediate post-procedure stented minimum lumen diameter.

CIVIQ[b] – The Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ) is a validated, independent measure of perceived quality of life specific for patients with chronic lower limb venous insufficiency. The questionnaire evaluates pain and the psychological, physical, and social effect of the disease on overall quality of life.

Hematoma/hemorrhage – A localized collection of blood, usually clotted, in an organ, intra- or extravascular space or tissue, due to a break in the wall of a blood vessel. Extravascular hemorrhage includes bleeding outside the body.

Iliofemoral Venous Outflow Obstruction, Acute – Initial onset of symptoms is ≤30 days prior to the study procedure.

Iliofemoral Venous Outflow Obstruction, Chronic – Initial onset of symptoms is >30 days prior to the study procedure.

INR – The International Normalized Ratio is a measure of coagulation expressed as the ratio of prothrombin time to a normal, control sample, raised to the power of the International Sensitivity Index (ISI) sample used as control.

Migration, Clinical – Proximal or distal movement of a stent requiring surgical or endovascular intervention.

Migration, Radiographic – Greater than 1 cm proximal or distal movement of a stent confirmed with imaging with no clinical sequelae.

[b] Launois R, Reboul-Marty J, Henry B. Construction and validation of a quality of life questionnaire in chronic lower limb venous insufficiency (CIVIQ). Qual Life Res 1996;5:539-554.

New York Heart Association Classification

Class I: Cardiac disease resulting in no limitation of ordinary physical activity. Ordinary physical activity (i.e., walking several blocks or climbing stairs) does not cause undue fatigue, palpitation, dyspnea, or anginal pain. Symptoms may occur with marked exertion.

Class II: Cardiac disease resulting in slight limitation of ordinary physical activity. Patient is comfortable at rest. Ordinary physical activity such as walking more than two blocks or climbing more than one flight of stairs results in fatigue, palpitation, dyspnea, anginal pain, or similar symptoms.

Class III: Cardiac disease resulting in marked limitation of physical activity. The patient is comfortable at rest, but activities such as walking one to two blocks or climbing one flight of stairs cause fatigue, palpitation, dyspnea, anginal pain or similar symptoms.

Class IV: Cardiac disease resulting in dyspnea at rest which increases with any physical activity and inability to perform any physical activity without discomfort. Symptoms of cardiac insufficiency or anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Occlusion, Early – No flow within the treated venous segment (including the region within ± 1 cm proximal and/or distal to the treated venous segment) occurring $\leq$ 24 hours of the procedure as demonstrated by duplex ultrasound or venography. An occlusion occurring within 24 hours of the procedure will be considered thrombotic in nature, regardless of whether it is successfully treated with thrombolysis/thrombectomy.

Occlusion, Intermediate – No flow within the treated venous segment (including the region within ± 1 cm proximal and/or distal to the treated venous segment) occurring > 24 hours after the procedure, but $\leq$ 30 days after the procedure as demonstrated by duplex ultrasound or venography. An occlusion occurring within 30 days of the procedure will be considered thrombotic in nature, regardless of whether it is successfully treated with thrombolysis/thrombectomy.

Occlusion, Late – No flow within the treated venous segment (including the region within ± 1 cm proximal and/or distal to the treated venous segment) occurring > 30 days after the procedure as demonstrated by duplex ultrasound or venography.

Outflow Obstruction – Documented iliofemoral venous obstruction (e.g., recanalization of the vein with multiple channels, documented collaterals as determined by imaging).

Patency, Clinical – Lack of occlusion of the treated venous segment determined by evidence of blood flow both proximal and distal to the study lesion assessed via ultrasound and/or venography and no worsening of pain or edema symptoms from baseline (according to Venous Clinical Severity Score; VCSS) as related to the target lesion.

Patency, Quantitative – A treated venous segment (including the region within ± 1 cm proximal and/or distal to the treated venous segment) minimum lumen diameter > 50% of the immediate post-procedure stented minimum lumen diameter as demonstrated by venography.

Patency, Primary Quantitative – A treated venous segment retains primary quantitative patency provided that uninterrupted (intervention-free) quantitative patency remains since the initial procedure as determined by the core laboratory. Failure of primary quantitative patency occurs at the time of one of the following: loss of quantitative patency, occlusion of the treated segment, surgical bypass of the treated segment, or amputation of the extremity determined to result from venous outflow occlusion.

Patency, Assisted Primary Quantitative – A treated venous segment retains assisted primary quantitative patency if, following successful treatment at the initial procedure, the segment subsequently requires an intervention to assist quantitative patency without an episode of occlusion. Failure of primary assisted quantitative patency occurs at the time of one of the following: total occlusion of the treated segment, surgical bypass of the treated segment, or amputation of the extremity determined to result from venous outflow occlusion.

Patency, Secondary Quantitative – A treated venous segment retains secondary quantitative patency if, following successful treatment at the initial procedure, the segment subsequently becomes totally occluded and then successfully reopened in a secondary procedure. Failure of secondary quantitative patency occurs at the time of surgical bypass of the treated segment or amputation of the extremity determined to result from venous outflow occlusion.

Pulmonary Embolism (PE) – Emboli to lungs via the pulmonary artery, which can arise from deep venous thrombosis in the lower extremities or pelvis. Pulmonary emboli should be objectively documented using pulmonary arteriography, cross-sectional imaging, or significant change in ventilation/perfusion lung scan indicative of PE, or at autopsy. PE will be categorized by type.[c]

Pulmonary Embolism (PE), Massive – Acute PE with sustained hypotension (systolic blood pressure < 90 mmHg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular [LV] dysfunction), pulselessness, or persistent profound bradycardia (heart rate < 40 bpm with signs or symptoms of shock).

Pulmonary Embolism (PE), Submassive – Acute PE without systemic hypotension (systolic blood pressure ≥ 90 mmHg) but with either right ventricular (RV) dysfunction or myocardial necrosis, where:

RV dysfunction is defined as the presence of at least 1 of the following:

- RV dilation (apical 4-chamber RV diameter divided by LV diameter > 0.9) or RV systolic dysfunction on echocardiography;
- RV dilation (4-chamber RV diameter divided by LV diameter > 0.9) on CT;
- Elevation of BNP (> 90 pg/mL);
- Elevation of N-terminal pro-BNP (> 500 pg/mL); or
- Electrocardiographic changes (new complete or incomplete right bundle-branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion).

Myocardial necrosis is defined as either of the following:

- Elevation of troponin I (> 0.4 ng/mL) or
- Elevation of troponin T (> 0.1 ng/mL).

Pulmonary Embolism (PE), Low-risk – Acute PE and the absence of the clinical markers of adverse prognosis that define massive or submassive PE.

[c] Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the American Heart Association. Circulation. 2011;123:1788-1830.

Pulmonary Embolism (PE), Symptomatic – Thrombotic embolism to the lungs via the pulmonary artery that causes symptoms (hypoxia and chest pain) and/or is associated with a clinical sign, biomarker elevation, or abnormal test (e.g., bradycardia or tachycardia, sustained hypotension, elevated troponins or natriuretic peptides, right ventricular dysfunction). Symptomatic PE will be objectively documented showing occlusive filling defects in the lobar or main pulmonary arteries on pulmonary arteriography or cross-sectional imaging. Similarly, changes in ventilation/perfusion lung scan or at autopsy may be indicative of lobar or main pulmonary artery PE.

Reintervention – Any endovascular or surgical intervention performed in a treated venous segment.

Renal Failure – Acute or progressive renal insufficiency leading to the need for dialysis.

Renal Insufficiency – A rise in creatinine of more than 30% above the pre-procedure level resulting in a creatinine level > 2.0 mg/dl that does not spontaneously resolve.

Restenosis (binary) – Recurrent narrowing of the treated venous segment (including the region within ± 1 cm proximal and/or distal to the treated venous segment) resulting in a minimum lumen diameter ≤ 50% of the immediate post-procedure stented minimum lumen diameter as demonstrated by venography.

Stent Strut Fracture[d,e]

Type I:	Single strut fracture only
Type II:	Multiple single strut fractures that can occur at different sites
Type III:	Multiple strut fractures resulting in complete transection of the stent, without displacement of the stent segments
Type IV:	Multiple stent fractures resulting in displacement of segments of the stent.
Type V:	Spiral fractures, without complete transection, which could result in stent displacement.

[d] Rocha-Singh KJ, Jaff MR, Crabtree TR, et al. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Catheter Cardiovasc Interv 2007;69:910-919.
[e] Jaff M, Dake M, Pompa J, et al. Standardized evaluation and reporting of stent fractures in clinical trials of noncoronary devices. Catheter Cardiovasc Interv 2007;70:460-462.

Success, Procedural – Improved flow through the target vessel demonstrated by diminished flow through collateral veins and/or reduced filling defect in the target vessel and no major adverse events before discharge.

Success, Technical – Successful delivery and deployment of the Zilver® Vena™ Venous Stent.

Thrombosis – Platelet or fibrin deposition within the treated venous segment successfully treated with thrombolysis or thrombectomy.

Venous Clinical Severity Score[f] – a method of classifying the disease severity in chronic venous insufficiency, validated for use post-intervention.

Attribute	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
Pain or other discomfort (i.e., aching, heaviness, fatigue, soreness, burning) -Presumes venous origin	None	Occasional pain or other discomfort (i.e., not restricting regular daily activities)	Daily pain or other discomfort (i.e., interfering with but not preventing regular daily activities)	Daily pain or discomfort (i.e., limits most regular daily activities)
Varicose Veins -"Varicose" veins must be ≥ 3 mm in diameter to qualify in the standing position.	None	Few: scattered (i.e., isolated branch varicosities or clusters) Also includes corona phlebectatica (ankle flare)	Confined to calf or thigh	Involves calf and thigh
Venous Edema -Presumes venous origin	None	Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee and above
Skin Pigmentation -Presumes venous origin -Does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases	None or focal	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Inflammation -More than just recent pigmentation (i.e., erythema, cellulitis, venous eczema, dermatitis)	None	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Induration -Presumes venous origin of secondary skin and subcutaneous changes (i.e., chronic edema with fibrosis, hypodermitis). Includes white atrophy and lipodermatosclerosis	None	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Active ulcer number	0	1	2	> 3
Active ulceration duration (longest active)	N/A	< 3 mo	> 3 mo but < 1 yr	Not healed > 1 yr
Active ulcer size (largest active)	N/A	Diameter < 2 cm	Diameter 2-6 cm	Diameter > 6 cm
Use of compression therapy	0 Not used	1 Intermittent use of stockings	2 Wears stockings most days	3 Full compliance: stockings

Venous Disability Scoring[g] **–** A method of classifying the extent of disability based on venous symptoms and the ability to perform normal activities with or without lower extremity compression:

Venous Disability Scoring

Score	Presenting feature
0	Asymptomatic
1	Symptomatic, usual activity*, without use of lower extremity compression
2	Usual activities only with compression and/or limb elevation
3	Unable to complete usual activity, even with compression and/or limb elevation
*usual activities are patients activities before onset of disability from venous disease	

[f] Vasquez M, Rabe E, McLafferty R, Shortell C, Marston W, Gillespie D, Meissner M, and Rutherford R. Revision of the venous clinical severity score: Venous outcomes consensus statement: Special communication of the American Venous Forum Ad Hoc Outcomes Working Group. J Vasc Surg 2010 Nov; 52(5):1387-1396.
[g] Rutherford RB, Padberg FT, Comerota AJ, Kistner RL, Meissner MH, and Moneta GL. Venous severity scoring: An adjunct to venous outcome assessment. J Vasc Surg 2000; 31:1307-1312.