SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Stent, Iliac Vein
Device Trade Name:	Zilver® Vena™ Venous Self-Expanding Stent
Device Procode:	QAN
Applicant's Name and Address:	Cook Ireland, Ltd. O'Halloran Road National Technology Park Limerick, Ireland
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P200023
Date of FDA Notice of Approval:	October 9, 2020

II. INDICATIONS FOR USE

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

III. CONTRAINDICATIONS

The Zilver Vena Venous Self-Expanding Stent System is contraindicated for use in:

- Patients who are judged to have a lesion that prevents complete inflation of a balloon dilatation catheter or proper placement of the stent or the stent delivery system.
- Patients who cannot receive intraprocedural anti-coagulation therapy.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Zilver Vena Venous Self-Expanding Stent labeling (Instructions for Use).

V. DEVICE DESCRIPTION

The Zilver Vena Venous Self-Expanding Stent (the Zilver Vena Venous Stent) is a self-expanding nitinol (nickel titanium alloy) stent preloaded onto a delivery system. To facilitate fluoroscopic visualization of the stent, four radiopaque gold markers are positioned on each end of the stent (Figure 1). Post-deployment, the stent is designed to impart an outward radial force upon the inner lumen of the vessel, thereby establishing patency of the stented region. The Zilver Vena Venous Stent is available in diameters of 10 mm, 12 mm, 14 mm, and 16 mm (based on inner diameter) and lengths of 40 mm, 60 mm, 100 mm, and 140 mm (Table 1).

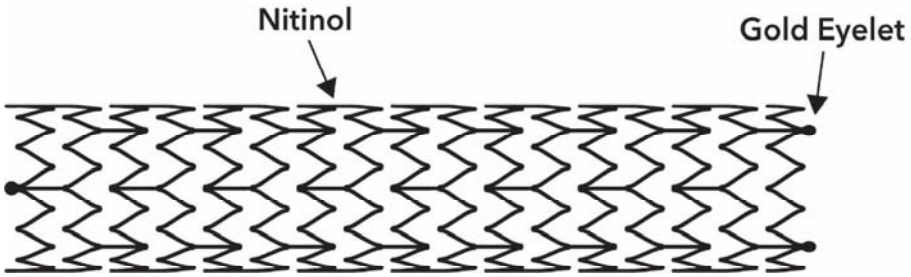
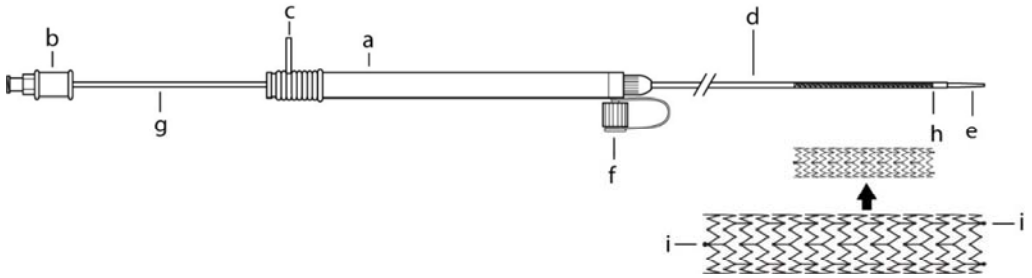


Figure 1. Schematic Drawing of the Zilver Vena Venous Stent

The Zilver Vena Venous Stent is preloaded within a 7 Fr (2.3 mm) delivery system (Figure 2). The delivery system is available in 80 cm and 120 cm lengths and is compatible with a 0.035" wire guide. The delivery system is used to deliver the stent to the appropriate anatomical location. When in position, the stent is deployed by retracting the handle while holding the metal cannula stationary (i.e., the "pin & pull" technique).



a. Handle
b. Hub
c. Safety Lock
d. Delivery System: Outer Sheath
e. Tip of Delivery System Inner Catheter
f. Side-arm Flushing Port
g. Metal Cannula
h. Radiopaque Marker on the Delivery System
i. Gold Radiopaque Markers

Figure 2. Schematic Drawing of the Zilver Vena Venous Stent and Delivery System

Table 1. Zilver Vena Venous Stent and Delivery System Size Matrix

2.3 mm (7 French) Delivery System									
Stent Length (mm)		40		60		100		140	
Delivery System (cm)		80	120	80	120	80	120	80	120
Stent Inner Diameter (mm)	10	X	X	X	X	X	X	X	X
	12	X	X	X	X	X	X	X	X
	14	NA	NA	X	X	X	X	X	X
	16	NA	NA	X	X	X	X	X	X

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives used in the treatment and management of patients with symptomatic iliofemoral venous outflow obstruction. The current standard of care includes:

- Noninvasive treatment (exercise, leg elevation, compression therapy, and/or drug therapy such as oral anticoagulation, including Vitamin K antagonists or direct oral anticoagulants);
- Minimally invasive treatment (thrombectomy and/or thrombolysis, balloon angioplasty, and/or stent placement); and
- Surgical treatment (endophlebectomy or bypass).

Each alternative has its own advantages and disadvantages. The physician should fully discuss these alternatives with the patient to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Zilver Vena Venous Stent has been commercially available outside the United States since October 2010. It was first marketed in the European Union and has been commercialized in the Middle East/Africa, Asia, and South America (Table 2).

The device has never been withdrawn from any market for any reason related to safety or effectiveness.

Table 2. Commercial Availability of the Zilver Vena Venous Stent

Region	Countries		
Europe, Middle East, and Africa	• Belarus • Bulgaria • Croatia • Egypt • France • Iran • Israel • Italy	• Jordan • Kuwait • Latvia • Lebanon • Palestine • Poland • Russia • Saudi Arabia	• Serbia • Slovakia • Spain • Turkey • Ukraine • United Arab Emirates
Asia	• China • Hong Kong	• India • Malaysia	• Singapore • Thailand
South America	• Argentina • Brazil • Chile	• Colombia • Costa Rica • Ecuador	• Mexico • Peru • Uruguay
Other	• Australia	• Canada	• New Zealand

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) that may be associated with the use of the device:

- Abdominal or back pain
- Abrupt stent closure
- Allergic reaction to anticoagulant and/or antithrombotic therapy or contrast medium
- Allergic reaction to nitinol (nickel-titanium)
- Amputation
- Aneurysm
- Arrhythmia
- Arteriovenous fistula
- Bleeding associated with anticoagulation
- Death
- Embolism
- Fever
- Hematoma/hemorrhage at access site
- Hypersensitivity reactions
- Hypertension
- Hypotension, nausea, or symptoms of a vasovagal response
- Infection/abscess formation at access site
- Intimal injury/dissection
- Myocardial infarction (MI)
- Pseudoaneurysm formation
- Pulmonary embolism

- Renal failure
- Restenosis, occlusion, or thrombosis of the stented vein
- Septicemia/bacteremia
- Stent malapposition
- Stent migration or embolization
- Stent strut fracture
- Stroke
- Tissue necrosis
- Vasospasm
- Vessel perforation/rupture
- Worsened pain

For the specific adverse events that occurred in the clinical study, please see Section X, *D. Safety and Effectiveness Results* below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Biocompatibility Testing

A thorough panel of biocompatibility testing was performed on the Zilver Vena Venous Stent and delivery system in accordance with ISO 10993-1, *Biological evaluation of medical devices – Part 1: Evaluation and testing*, the FDA Guidance for Industry and Food and Drug Administration Staff, *Use of International Standard ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process* (June 16, 2016), and 21 CFR 58 Good Laboratory Practice (GLP) requirements. Specifically, the Zilver Vena Venous Stent was assessed by tests considered appropriate for devices categorized as a permanent blood-contacting implant (i.e., > 30 days), and the Zilver Vena Venous Stent delivery system was assessed by tests considered appropriate for devices categorized as an externally communicating device in contact with circulating blood for a limited period (i.e., ≤ 24 hours).

Tables 3 and 4 summarize the test results for the Zilver Vena Venous Stent and delivery system, respectively.

Table 3. Summary of Biocompatibility Testing for the Zilver Vena Venous Stent

Test Name	Purpose of Testing	Test Results
Cytotoxicity (ISO MEM elution method)	Determine the potential for the test article to cause cytotoxicity	Pass; the test article showed no evidence of causing cell lysis or toxicity

Test Name	Purpose of Testing	Test Results
Sensitization (ISO guinea pig maximization sensitization study)	Investigate the potential for delayed dermal contact sensitization	Pass; the test article extract showed no evidence of causing delayed dermal contact sensitization in the guinea pig and is not considered a sensitizer
Irritation or intracutaneous reactivity (ISO intracutaneous study)	Determine if the test article causes local dermal irritation following intracutaneous injection in rabbits	Pass; no evidence of significant irritation over the 72-hour test period from the test article extracts injected intracutaneously into rabbits compared to the control extracts
Acute systemic toxicity (ISO systemic toxicity study)	Determine if the test article causes local dermal irritation following injection in mice	Pass; no mortality or evidence of systemic toxicity over the 72-hour test period from the test article extracts injected into mice
Material-mediated pyrogenicity (USP material-mediated pyrogenicity study)	Determine if the test article induces a pyrogenic response following intravenous injection in rabbits	Pass; the test article extract was considered nonpyrogenic. The rise in temperature during the 3-hour observation period after extract injection in rabbits was within acceptable USP limits
Subacute/subchronic toxicity (subchronic intravenous toxicity study)	Determine if the test article causes systemic toxicity	Pass; no evidence of systemic toxicity from the test article extracts injected intravenously into rats
Implantation (ISO muscle implantation study – 2 weeks)	Determine if the test article causes a local tissue response after 2 weeks implantation into muscle tissue of rabbits	Pass; microscopically, the test article was classified as a nonirritant compared to the negative control article
Implantation (muscle implantation with systemic toxicity study – 4 weeks)	Determine if the test article causes a local tissue response after 4 weeks implantation into muscle tissue of rabbits	Pass; microscopically, the test article was classified as a nonirritant compared to the negative control article
Implantation (muscle implantation with systemic toxicity study – 13 weeks)	Determine if the test article causes a local tissue response after 13 weeks implantation into muscle tissue of rabbits	Pass; microscopically, the test article was classified as a nonirritant compared to the negative control article
Hemocompatibility (hemolysis study)	Determine if the test article causes hemolysis	Pass; both the test article in direct contact with blood and the test article extract were nonhemolytic
Hemocompatibility (*in vivo* thromboresistance study)	Determine if the placement of the test article would cause thrombosis during simulated clinical use	Thrombogenicity evaluated as part of the *in vivo* animal studies (Section B) showed no evidences of thromboses in vessels implanted with Zilver Vena Venous Stents
Hemocompatibility (plasma recalcification time study)	Determine if the test article causes a change in degree of inhibition or promotion of clotting time	Pass; the test article extract had no significant effect on recalcification time compared to the negative control
Hemocompatibility (C3a complement activation assay)	Evaluate the test article's potential to activate the C3a complement system	Pass; the test article extract was considered a nonactivator of the complement system

Test Name	Purpose of Testing	Test Results
Hemocompatibility (SC5b-9 complement activation assay study)	Evaluate the test article's potential to activate the SC5b-9 complement system	Pass; the test article extract was considered a nonactivator of the complement system

Table 4. Summary of Biocompatibility Testing for the Zilver Vena Venous Stent Delivery System

Test Name	Purpose of Testing	Test Results
Cytotoxicity (ISO elution method)	Determine the potential for the test article to cause cytotoxicity	Pass; the test article showed no evidence of causing cell lysis or toxicity
Sensitization (ISO guinea pig maximization sensitization study)	Investigate the potential for delayed dermal contact sensitization	Pass; the test article extract showed no evidence of causing delayed dermal contact sensitization in the guinea pig and is not considered a sensitizer
Irritation or intracutaneous reactivity (ISO intracutaneous study)	Determine if the test article causes local dermal irritation following intracutaneous injection in rabbits	Pass; no evidence of significant irritation over the 72-hour test period from the test article extracts injected intracutaneously into rabbits compared to the control extracts
Acute systemic toxicity (ISO acute systemic toxicity study)	Determine if the test article causes local dermal irritation following injection in mice	Pass; no mortality or evidence of systemic toxicity over the 72-hour test period from the test article extracts injected into mice
Material-mediated pyrogenicity (USP material-mediated pyrogenicity study)	Determine if the test article induces a pyrogenic response following intravenous injection in rabbits	Pass; the test article extract was considered nonpyrogenic. The rise in temperature during the 3-hour observation period after extract injection in rabbits was within acceptable USP limits
Hemocompatibility (Hemolysis)	Determine if the test article causes hemolysis	Pass; both the test article in direct contact with blood and the test article extract were nonhemolytic
Hemocompatibility (SC5b-9 complement activation assay study)	Evaluate the test article's potential to activate the SC5b-9 complement system	Pass; the test article extract was considered a nonactivator of the complement system

Chemical characterization of the Zilver Vena Venous Stent was used to address the endpoints of carcinogenicity and genotoxicity. Chemical characterization was conducted in accordance with the FDA Guidance for Industry and Food and Drug Administration Staff, *Use of International Standard ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process* (June 16, 2016), ISO 10993-18 (2005), *Biological evaluation of medical devices – Part 18: Chemical characterization of materials*, and ISO 10993-17 (2002), *Biological evaluation of medical devices – Part 17: Establishment of allowable limits for leachable substances.*

Chemical characterization testing included:

- Exhaustive extraction: water/hexane/ethanol

- Inductively coupled plasma (ICP)/mass spectroscopy (MS): water
- Ion chromatography (IC): water
- Gas chromatography (GC)/mass spectroscopy (MS): water/hexane/ethanol
- Fourier transform infrared spectroscopy (FTIR): water/hexane/ethanol
- Ultra performance liquid chromatography-mass spectrometry (UPLC-MS): water/hexane/ethanol

The results for all tests were acceptable.

The biocompatibility test results demonstrate that both the stent and delivery system are biocompatible and nonpyrogenic, indicating that the Zilver Vena Venous Stent is safe and acceptable for clinical use.

B. Animal Studies

The safety and biological response specific to the Zilver Vena Venous Stent was assessed in sheep. Specifically, four animal studies (26 stents assessed in 20 animals) were completed in accordance with 21 CFR 58 (Good Laboratory Practice) as summarized in Table 5.

Table 5. Summary of Animal Testing for the Zilver Vena Venous Stent

Study Objective	Device Size (mm) and Samples (N)	Implant Duration; Number of Animals	Results
Evaluate acute performance characteristics of the stent and delivery system (deliverability and deployability)	14 x 140 (N=4)	Procedural; 4 animals	All stents and delivery systems were tracked, the stents were deployed, and the delivery systems were withdrawn without difficulty or incident, with no evidence of vessel injury or damage and no evidence of stent fracture. All devices achieved a rating of adequate (i.e., acceptable for clinical use) or better for each performance characteristic.
Evaluate acute performance characteristics and the 1-month safety of and biological response to the stent	14 x 140 (N=8)	1 month; 5 animals	• All stents were deployed and the delivery systems withdrawn without difficulty or incident, with no evidence of vessel injury or damage and no evidence of stent fracture. • At 1-month follow-up, angiography and histomorphometry indicated that the stents were patent. Histopathology revealed complete endothelialization, with minimal injury and minimal to mild inflammation.
Evaluate acute performance characteristics and the 3-month safety of and biological response to the stent	14 x 140 (N=8)	3 months; 7 animals	• All stents were deployed and the delivery systems withdrawn without difficulty or incident, with no evidence of vessel injury or damage and no evidence of stent fracture. All achieved a rating of adequate or better for each performance characteristic. • At 3-month follow-up, angiography showed the stented vessels to be patent with no evidence of vessel damage or injury (i.e., no evidence of thrombus deposition, dissection, aneurysm, contrast extravasation, spasm, or filling defects). Histomorphometry confirmed stent patency at follow-up. High-resolution radiography revealed no strut fractures at follow-up. Histopathology revealed that all vessels were healed with minimal injury and inflammation and 100% endothelialization.
Evaluate acute performance characteristics and the 1-month safety of and biological response to the stent	10 x 140 (N=6)	1 month; 4 animals	• All stents were deployed and the delivery systems withdrawn without difficulty or incident, with no evidence of vessel injury or damage and no evidence of stent fracture. • At 1-month follow-up, angiography and histomorphometry indicated that stents remained patent. Histopathology revealed nearly complete endothelialization, with minimal injury and minimal to mild inflammation.

The animal studies demonstrate that the delivery systems were tracked, the stents deployed, and the delivery systems withdrawn without difficulty or incident and that the stents did not cause any abnormal localized tissue responses. Moreover, the results showed no safety problems associated with the stents. Therefore, the animal testing

results for the Zilver Vena Venous Stent support a reasonable assurance of device safety and effectiveness.

C. Non-clinical Bench Testing

Comprehensive non-clinical bench testing was conducted as part of the design verification and validation to support the safety and effectiveness of the Zilver Vena Venous Stent and delivery system. The test plan was developed in accordance with appropriate guidance documents and international standards, including FDA's Guidance for Industry and Staff, *Non-clinical tests and recommended labeling for intravascular stents and associated delivery systems* (2005, 2010, supplemented in 2015), and ISO 25539-2 (2012), *Cardiovascular implants – Endovascular devices – Part 2: Vascular Stents*. The test results are presented in Table 6. The test results verified that the Zilver Vena Venous Stent and delivery system met their product performance and design specifications and would perform as intended under anticipated clinical conditions. Table 6 indicates which tests were performed on both nonaged and aged (1-year and 3-year timepoints) devices in order to support the product shelf life.

Table 6. Summary of Non-clinical Bench Testing for the Zilver Vena Venous Stent and Delivery System

Test	Purpose	Specification/ Acceptance Criterion	Results
Material Characterization			
Material composition	To verify the chemical composition of the stent implant	Material composition must comply with ASTM F2063, *Wrought Nickel-Titanium Shape Memory Alloy for Medical Devices and Surgical Implants*	The stent materials conform to material standards
Shape memory and superelasticity of intravascular stents	To verify the transition temperature of the nitinol implant	Stent comprises nitinol conforming to ASTM F2063; the austenite finish temperature of the electropolished stent is 25 ºC ± 5 ºC	The stent materials conform to applicable material standards
Stent corrosion resistance	To verify the stent's ability to resist corrosion (pitting)	The mean breakdown potential must be > 600 mV_{SCE} and the minimum breakdown potential must be > 300 mV_{SCE} Visual inspection completed for characterization purposes only	Pass
Fretting corrosion	To verify the stent's ability to resist fretting corrosion after fatigue analysis		Pass

Test	Purpose	Specification/ Acceptance Criterion	Results
Stent Dimensional and Functional Attributes			
Dimensional verification[a]	To evaluate the final stent dimension and ensure design specifications were met	The stent recovers to its specified, unconstrained diameter and expanded stent length	Pass
Percent surface area	To calculate the percent surface area of the expanded stent	N/A	Stented vessel covered surface areas were determined for 10 mm, 12 mm, 14 mm, and 16 mm devices using computer aided techniques
Foreshortening[a]	To determine the percent length change of the stent from its compressed to deployed state	N/A, report for characterization purposes	Assessed
Stent integrity[a]	To evaluate the integrity of the stent after deployment	No strut fractures allowed; no cracks visible on the stent surface greater than 10 µm when viewed at magnification 56X	Pass
Radial outward force[a]	To evaluate the outward radial force exerted by the stent	The radial force (normalized per unit length) shall be between 0.063 N/mm and 4.97 N/mm	Pass
Mechanical properties	Stent comprise nitinol conforming to ASTM F2063		
Stress/strain analysis (finite element analysis; FEA)	The stress and strain during loading and deployment, as well as in nonoverlapped distensible vein radial loading, axial loading, bending loading, May-Thurner loading and overlapped bending loading and May-Thurner loading, were characterized		
Fatigue analysis	To evaluate fatigue resistance under various loading conditions, including bending	Analyses must result in a fatigue safety factor > 1.0	Pass
Accelerated durability (fatigue testing)	To evaluate the durability of the stent under various loading conditions, including bending loading for 10 years of simulated use	The devices tested must withstand the loading conditions with no fracture	Pass

Test	Purpose	Specification/ Acceptance Criterion	Results
MRI safety and compatibility	To evaluate the MRI safety and compatibility of the stent	The displacement force deflection angle shall be ≤ 45°; the magnetically induced torque shall be ≤ the worst-case torque due to the earth's gravity; the RF heating of the stent during an MRI procedure 15 minutes in duration must have a CEM43 value of < 10 minutes Image artifact was for characterization only	Pass; results met the established acceptance criteria Assessed
Radiopacity	To evaluate the ability of the implant to be viewed under fluoroscopy	The stent gold rivets shall be visible using fluoroscopy	Pass
Crush resistance	To establish the crush resistance of the stent by examining the geometry following local compressive loading and compressive loading between parallel plates	The stent shall recover to its specified unconstrained diameter when released from a compressed state and will vary minimally over its length	Pass
Kink resistance	To evaluate the overall flexibility and kink resistance of the stent after deployment	No kink at radius of ≥ 19 mm	Pass
Delivery System Dimensional and Functional Attributes			
Dimensional verification[a]	To verify the delivery system meets dimensional criteria pre- and post-deployment	The maximum sheath outer diameter, delivery system length, and distance from the marker band distal edge to the Flexor distal edge will all be within design specifications	Pass
Delivery, deployment, and retraction[a]	To confirm the delivery system meets it prespecified acceptance criteria with respect to its delivery, deployment, and retraction under simulated use conditions	100% of delivery systems are able to be flushed, access the intended delivery location, and are able to be withdrawn 100% of deployments are successful in the mock vessel	Pass
Deployment force[a]	Determine the force to deploy the stent is within the user's ability to deliver the device accurately	The force to deploy the stent must be within the user's capability (i.e., ≤ 32N)	Pass
Deployment accuracy[a]	To assess the accuracy of deploying the stent at the target location.	The stent shall be deployed ± 4.0 mm from the intended deployment location.	Pass

Test	Purpose	Specification/ Acceptance Criterion	Results
Catheter bond strength and tip pull test[a]	To establish the bond strength of delivery system joints and verify that the strength of the bond joints is adequate for the intended use	The tensile and compressive strength of delivery system bonds will meet design requirements	Pass
Flexibility and kink test[a]	To evaluate the overall flexibility and kink resistance of the delivery system	Pre- and post-deployment, the delivery system does not kink at a radius of ≥ 19 mm	Pass

[a] Testing was performed on devices that had undergone aging conditions to support shelf life.

The testing detailed in Table 6 verified that the Zilver Vena Venous Stent and delivery system met the product performance and design specifications and would perform as intended under anticipated clinical conditions.

D. Sterilization, Packaging, and Shelf Life Testing

The Zilver Vena Venous Stent is sterilized by a validated ethylene oxide (EO) sterilization process to achieve a minimum sterility assurance level (SAL) of 10^{-6}. The methods used to validate the sterilization cycle are in accordance with ISO 11135 (2014), *Sterilization of healthcare products – Ethylene oxide: Requirements for development, validation and routine control of a sterilization process for medical devices*.

Product and package stability testing of the Zilver Vena Venous Stent was performed and validated to support the device's shelf life. Packaging testing included visual assessment, bubble leak testing, and seal strength testing at baseline and aged conditions. Non-clinical functional testing of the device after aging was performed as indicated in Table 6. Together, the data support a 3-year shelf life for the Zilver Vena Venous Stent.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish reasonable assurance of safety and effectiveness of the Zilver Vena Venous Stent for the treatment of patients with symptomatic iliofemoral venous outflow obstruction in the United States and Taiwan under an Investigational Device Exemption (IDE #G110228). Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The Evaluation of the Zilver Vena Venous Stent in the Treatment of Symptomatic Iliofemoral Venous Outflow Obstruction (VIVO) Clinical Study was a prospective, global, multicenter, nonrandomized, single-arm clinical study intended to assess the safety and effectiveness of the Zilver Vena Venous Stent for the treatment of patients with symptomatic iliofemoral venous outflow obstruction. Patients with symptomatic venous outflow obstruction in one iliofemoral venous segment were eligible for enrollment. A total of 243 patients were treated with Zilver Vena Venous Stents between 13 December 2013 and 31 October 2016. The database for this PMA reflects data locked on 10 April 2020 and the data include 243 patients. Study patients were enrolled at 30 investigational sites, including 29 sites in the United States and 1 site in Taiwan.

The study protocol prespecified enrollment by disease status, i.e., acute (initial onset of symptoms within 30 days of the procedure) or chronic (initial onset of symptoms greater than 30 days prior to the procedure). The study population was prespecified to include 30% patients (73 patients) with acute disease and 70% patients (170 patients) with chronic disease.

The study was overseen by an independent Data Safety Monitoring Board (DSMB) in accordance with an established DSMB charter. An independent Clinical Events Committee (CEC) adjudicated predefined clinical events reported during the study in accordance with the CEC charter. An independent core laboratory provided uniformly defined imaging analysis.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the VIVO clinical study was limited to patients who met the following 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; and
2) planned stenting of the study lesion with only the Zilver Vena Venous Stent.

Patients were not permitted to enroll in the VIVO Clinical Study if they met any of the following exclusion criteria:

General Exclusion Criteria:

1) < 18 years of age;
2) unwilling to provide informed consent;
3) unwilling or unable to comply with all study related follow-up procedures;
4) pregnant or planning to become pregnant in the next 12 months;

5) simultaneous participation in another investigational drug or device study (the patient must have completed the follow-up phase for the primary endpoint of any previous study at least 30 days prior to enrollment in this study);
6) history of bleeding diathesis, uncorrectable hypercoagulopathy (i.e., hypercoagulopathy that cannot be adequately managed/controlled with medication), or refusal of blood transfusions;
7) history of intracranial hemorrhage;
8) a medical condition or disorder (e.g., cancer) that may limit life expectancy to less than 12 months or that may cause non-compliance with the Clinical Investigation Plan;
9) known hypersensitivity or contraindication to antiplatelet and/or anticoagulant therapy, nitinol, or contrast medium which cannot be adequately pre-medicated;
10) 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, or planned surgical or interventional procedures of the target limb any time after the study procedure;
11) surgical or interventional procedures for other medical conditions (i.e., not associated with the target limb) within 30 days prior to the study procedure, or planned surgical or interventional procedures within 30 days after the study procedure;
12) complications of an arterial or venous access site in the legs within 30 days prior to the study procedure;
13) untreated systemic or local infection, or infection treated for less than 10 days prior to the study procedure;
14) lesions with intended treatment lengths extending into the inferior vena cava or below the level of the lesser trochanter;
15) significant obstruction (i.e., > 20%) or occlusion of the inflow or outflow tract (i.e., ipsilateral tibial, popliteal, and femoral veins and inferior vena cava); if thrombus is treated prior to stenting the study lesion, treatment (thrombolysis or thrombectomy) must result in < 20% residual stenosis/obstruction;
16) lesion with malignant obstruction;
17) presence of symptomatic pulmonary embolism within 30 days prior to the study procedure;
18) previous stenting of the target vessel;
19) lesion located within or beyond a bypass graft; and
20) total venous occlusion that cannot be dilated to allow passage of the introducer system or wire guide.

Venographic Exclusion Criterion:

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

2. Follow-up Schedule

All patients underwent evaluation (clinical assessment and imaging evaluation) prior to the study procedure. Patient follow-up was scheduled at pre-discharge through 36 months. Follow-up included venography at 12 months, and ultrasound and X-ray at 6, 12, 24, and 36 months. In addition, clinical assessments occurred at 1, 6, 12, 24, and 36 months. Telephone contact was scheduled at 3 months. Table 7 provides the data collection schedule through the 36-month visit.

Clinical assessments included medical history and documentation of the symptom(s) indicative of venous outflow obstruction, using Venous Clinical Severity Score (VCSS), Venous Disability Score (VDS), Clinical Etiological Anatomical Pathophysiological (CEAP) "C" Classification, and Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ), and assessment of adverse events and medications. Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

Table 7. Data Collection Schedule for the VIVO Clinical Study

Data Collection	Pre-Procedure	Procedure	Post-Procedure	1 Month	3 Months	6 Months	12 Months	24 Months	36 Months
Clinical assessment[a]	X			X		X	X	X	X
Venography		X					X		
X-ray			X			X	X	X	X
Duplex ultrasound			X			X	X	X	X
Telephone contact					X				

[a] Clinical assessment included, VCSS, VDS, CEAP "C" classification, and CIVIQ score.

3. Clinical Endpoints

Primary Safety Endpoint

The primary safety endpoint was 30-day freedom from major adverse events (MAEs). MAEs were 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. Clinically driven reinterventions were reinterventions performed in a patient with recurrent symptoms of venous outflow obstruction of the target lesion and with venography showing a treated venous segment minimum lumen diameter (MLD) ≤ 50% of the immediate post-procedure stented MLD. Clinical

migration was defined as proximal or distal movement of the stent requiring surgical or endovascular intervention. Bleeding events occurring prior to study enrollment, and related to procedures such as thrombolysis or thrombectomy, were not considered procedural bleeding events.

The analysis requires that a single performance goal of 87% be met. The performance goal was 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 prior to the procedure), with the weight prespecified as 30% acute patients and 70% chronic patients. The weighted averages were based on published clinical literature and included a 10% margin. The study device was considered to have met the safety endpoint if the one-sided *p*-value from hypothesis testing (H_0: $\pi_S \leq 87\%$; H_a: $\pi_S > 87\%$) using exact binomial test was less than 0.025.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was primary quantitative patency at 12 months. Primary quantitative patency was defined as a treated venous segment (including the region within ± 1 cm proximal and/or distal of the treated venous segment) that retained (uninterrupted; intervention-free) an MLD > 50% of the immediate post-procedure stented MLD as demonstrated by venography as determined by the core laboratory. The statistical analysis plan pre-specified that missing data be addressed using multiple imputation with best-available data, case deletion, or other analyses (i.e. tipping point). The analysis plan specified assessment of patients with reinterventions within the treated venous segment as follows in relation to the primary effectiveness endpoint: failures were patients presenting with an MLD ≤ 50% of the immediate post-procedure stented MLD at reintervention occurring ≤ 410 days post-procedure, successes were patients presenting with an MLD > 50% of the immediate post-procedure stented MLD at reintervention occurring ≥ 320 days, and missing were patients presenting with an MLD > 50% of the immediate post-procedure stented MLD at reintervention < 320 days.

The analysis required that a single performance goal of 76% be met; the performance goal was derived based on 12-month patency data available in published literature and included a 10% margin. The study device was considered to have met the effectiveness endpoint if the one-sided *p*-value from hypothesis testing (H_0: $\pi_E \leq 76\%$ H_a: $\pi_E > 76\%$) using exact binomial test was less than 0.025.

Secondary Endpoint

The secondary endpoint was the change in VCSS from baseline to 1 month and 12 months. The study device was considered to have met the secondary endpoint if *p*-values from hypothesis testing (H_0: $S_{diff} = 0$ H_a: $S_{diff} \neq 0$) using paired t-test

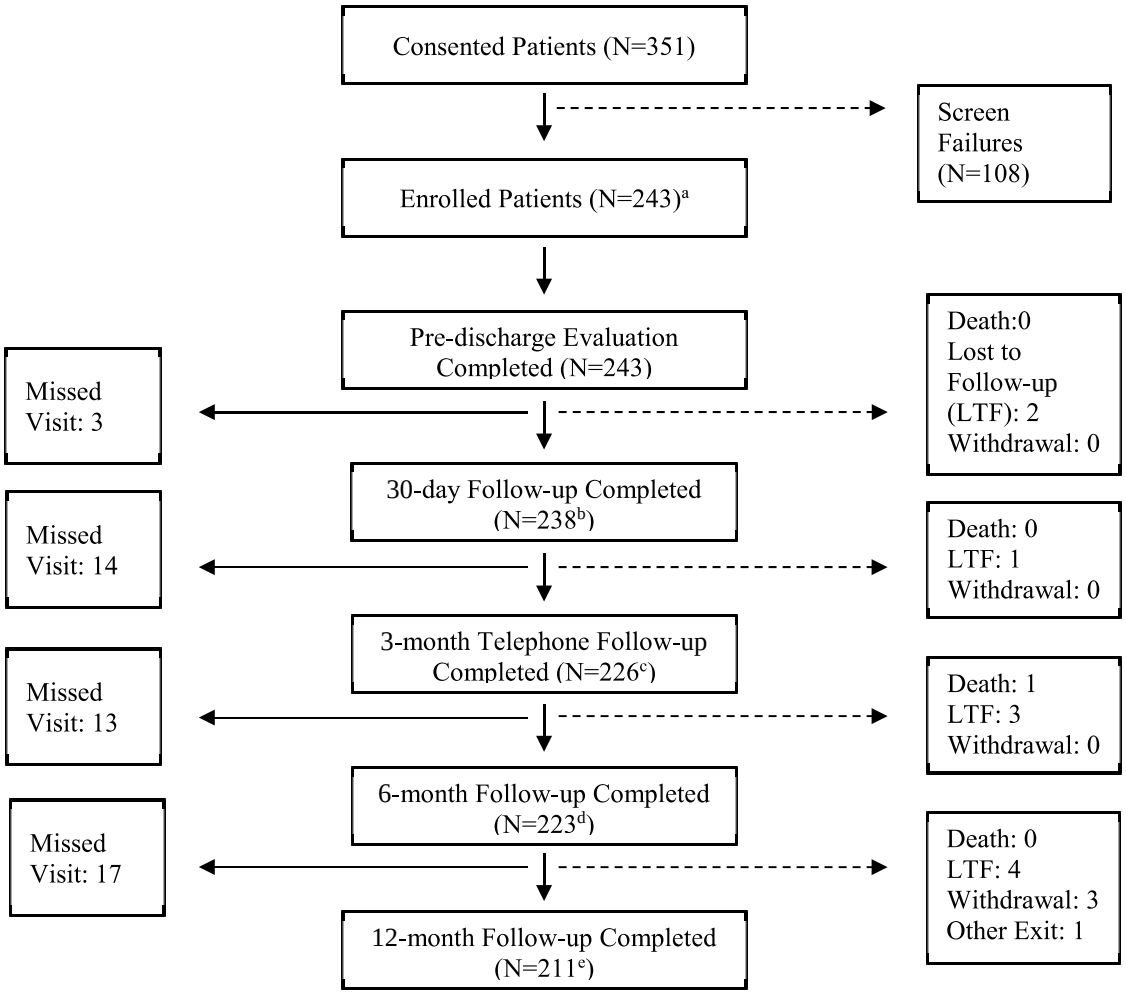
are less than 0.05. The p-values at 1 month and 12 months were adjusted for multiplicity using the Holm procedure at a family-wise type I error rate of 0.05.

Additional measures without prespecified hypothesis testing were collected through 3 years and included the following:

- Technical success, defined as successful delivery and deployment of the Zilver Vena Venous Stent in the intended location
- Procedural success, defined as improved flow through the target vessel demonstrated by diminished flow through collateral veins and/or reduced filling defect in the target vessel and no MAEs before discharge
- Adverse events
- Type, rate, and interval of clinically driven reintervention within the treated venous segment following treatment
- Type, rate, and interval of reintervention within the treated venous segment following treatment
- Rates of primary quantitative patency, assisted primary quantitative patency, and secondary quantitative patency
- Rate of patency by ultrasound
- Rate of clinical patency, defined as lack of occlusion of the treated venous segment determined by evidence of blood flow proximal and distal to the study lesion assessed via ultrasound and/or venography and no worsening of pain or edema from baseline (according to VCSS) as related to the target lesion
- Rate of modified clinical patency, defined as lack of occlusion of the treated venous segment determined by evidence of blood flow proximal and distal to the study lesion as assessed via ultrasound and/or venography and no worsening of pain or edema from baseline (according to VCSS) as related to the target lesion in two or more consecutive visits
- Device integrity (X-ray assessment for stent fracture)
- Device migration (X-ray assessment for migration)
- Change in VCSS from baseline
- Change in VDS from baseline
- Change in CEAP clinical classification (i.e., "C" classification) from baseline
- Change in CIVIQ score from baseline

B. Patient Accountability in the VIVO Clinical Study

Overall, 243 patients were enrolled in the VIVO Clinical Study. The number of patients available for analysis at each time point is shown in Figure 3.



[a] 351 consented patients – 108 screen failures = 243 enrolled patients
[b] 243 enrolled patients – 2 discontinued patients – 3 missed visits = 238 patients with completed 30-day follow-up
[c] 243 enrolled patients – 3 discontinued patients – 14 missed visits = 226 patients with completed 3-month telephone follow-up
[d] 243 enrolled patients – 7 discontinued patients – 13 missed visits = 223 patients with completed 6-month follow-up
[e] 243 enrolled patients – 15 discontinued patients – 17 missed visits = 211 patients with completed 12-month follow-up

Figure 3. Subject Accountability for the VIVO Clinical Study

C. Study Population Demographics and Baseline Parameters

The demographics of the VIVO Clinical Study population are typical for an iliofemoral venous stent study performed in the United States. The mean age of enrolled patients was 53.0 ± 15.3 years (range: 18-89 years). The majority of patients were female (70.0%; 170/243) and white (81.5%; 198/243). More than half of the study patients had past or current DVT (67.5%; 164/243).

Table 8 provides a summary of the demographics and baseline characteristics for patients in the VIVO Clinical Study. Table 9 provides a summary of the VIVO patients' medical history and comorbid conditions at baseline.

Table 8. Demographics and Baseline Patient Characteristics for the VIVO Clinical Study

Demographic	Percent Patients (number/total number) or Mean ± SD (N, range)
Gender	
Male	30.0% (73/243)
Female	70.0% (170/243)
Age (years)	
All patients	53.0 ± 15.3 (243, 18-89)
Male	57.1 ± 13.2 (73, 23-82)
Female	51.2 ± 15.8 (170, 18-89)
Ethnicity	
White	81.5% (198/243)
Black or African American	11.9% (29/243)
Asian	3.3% (8/243)
Hispanic or Latino	2.9% (7/243)
First Nations/White	0.4% (1/243)
Height (in)	66.4 ± 4.2 (243, 54-79)
Weight (lbs)	197.0 ± 57.5 (243, 99.0-415.8)
Body mass index (BMI)	31.3 ± 8.5 (243, 17.5-64.8)

Table 9. Medical History and Comorbid Conditions for the VIVO Clinical Study

Condition	Percent Patients (number/total number)
Recent trauma (within 30 days)	1.2% (3/243)
Recent immobilization (within 30 days)	2.1% (5/243)
Cardiovascular	
Coronary artery disease	7.4% (18/243)
Previous myocardial infarction (MI)	4.1% (10/243)
Congestive heart failure	3.7% (9/243)
Vascular	
Bleeding diathesis/coagulopathy	7.0% (17/243)
Clotting disorder (family history)	7.9% (19/242)
Hypertension	43.2% (105/243)
Peripheral arterial disease	3.3% (8/243)
Presence of reflux (venous)	18.1% (44/243)
Existing tissue loss related to venous disease:	4.5% (11/243)
Gangrene	0% (0/11)
Stasis ulcers	100% (11/11)
Amputation	0% (0/11)
Past or current deep vein thrombosis (DVT):	67.5% (164/243)
Past DVT	27.4% (45/164)
Current and past DVT	15.9% (26/164)
Current DVT	56.7% (93/164)
Current DVT status:	
Acute (within 30 days)	49.6% (59/119)
Acute DVT on Chronic DVT/post-thrombotic syndrome	14.3% (17/119)
Chronic DVT/post-thrombotic syndrome	36.1% (43/119)
DVT (family history)	9.9% (24/242)
Pulmonary	
Chronic obstructive pulmonary disease (COPD)	5.8% (14/243)
Pulmonary embolism (PE):	14.8% (36/243)
Past PE	91.7% (33/36)
Current PE (within 30 days)	8.3% (3/36)
Renal	
Chronic renal failure	2.5% (6/243)
Endocrine	
Diabetes:	13.6% (33/243)
Type I	9.1% (3/33)
Type II	90.9% (30/33)
Hypercholesterolemia	31.7% (77/243)
Hypothyroidism	11.1% (27/243)
Gastrointestinal	
Gastrointestinal bleeding	1.2% (3/243)

Condition	Percent Patients (number/total number)
Neoplasms	
History of cancer:	16.9% (41/243)
Current cancer	7.3% (3/41)
Chemotherapy in the last 12 months	2.4% (1/41)
Undergone radiation treatment to the pelvis	14.6% (6/41)
Neurologic	
Stroke	2.5% (6/243)
Transient ischemic attack (TIA)	2.5% (6/243)
History of intracranial hemorrhage	0% (0/243)
Smoking status	
Never	62.1% (151/243)
Past	24.7% (60/243)
Current	13.2% (32/243)
Hormone-based contraceptives (females only)	11.8% (20/170)
Hormone replacement therapy	8.2% (20/243)
IVC filter present prior to study procedure	13.6% (33/243)

Baseline venous clinical assessments, lesion characteristics, and venographic measurements (Tables 10 and 11) were also as expected for this patient population. Most patients had a VCSS of 2 or greater (75.7%; 184/243); similarly, most patients had a CEAP "C" classification of 3 or greater (95.5%; 232/243). Study lesions were predominately located in the left leg (86.0%; 209/243) and most commonly affected the common iliac vein (CIV; 88.1%; 214/243) and the external iliac vein (EIV; 51.9%; 126/243). By core laboratory assessment, prior to stent placement, the mean lesion length was 98.6 mm ± 69.8 mm and the mean MLD was 6.0 mm ± 5.3 mm. Among lesions, 23.3% (52/233) were characterized as total occlusions pre-procedure.

Table 10. Baseline Venous Clinical Assessments for the VIVO Clinical Study

Assessment	Mean ± SD (N, range) or Percent Patients (number/total number)
VCSS	8.0 ± 4.2 (243, 1-24)
VDS	
0	5.3% (13/243)
1	28.0% (68/243)
2	41.6% (101/243)
3	25.1% (61/243)
CEAP "C" classification	
C0	0.4% (1/243)
C1	0.8% (2/243)
C2	3.3% (8/243)
C3	66.7% (162/243)
C4a	16.9% (41/243)
C4b	3.7% (9/243)
C5	2.9% (7/243)
C6	5.3% (13/243)
CIVIQ score	44.6 ± 23.5 (236, 1.3-98.8)

Table 11. Core Laboratory-Reported Baseline Lesion Characteristics and Venographic Measurements for the VIVO Clinical Study

Characteristic	Percent Patients (number/total number) or Mean ± SD (N, range)
Study lesion side	
Left	86.0% (209/243)
Right	14.0% (34/243)
Study lesion location[a]	
Common iliac vein (CIV)	88.1% (214/243)
External iliac vein (EIV)	51.9% (126/243)
Common femoral vein (CFV)	22.6% (55/243)
Femoral vein (FV)	2.1% (5/243)
Presence of collateral vessels	59.1% (143/242)
Presence of filling defect	50.4% (122/242)
Presence of thrombus	40.0% (96/240)
Lesion extending into the inferior vena cava	2.9% (7/243)
Lesion extending below the level of the lesser trochanter	4.6% (11/238)
Lesion length (mm)	98.6 ± 69.8 (232, 3.5-319)
MLD (mm)	6.0 ± 5.3 (233, 0-22.9)
Total occlusion (i.e., MLD of 0 mm)	22.3% (52/233)

[a] Lesions may involve more than one location; therefore, the total number of lesion locations is more than the total number of patients enrolled.

Details associated with the Zilver Vena Venous Stent implant procedure are summarized in Table 12. Stent placement occurred primarily via an ipsilateral popliteal vein (64.8%;

151/233) or ipsilateral femoral vein (30.0%; 70/233) approach. Procedures infrequently occurred via contralateral access (7.4%; 18/243); when used, contralateral access was often in combination with ipsilateral access (44.4%; 8/18). Pre-stent dilatation (64.6%; 157/243) and post-stent dilatation (96.7%; 235/243) was performed in most implant procedures. In total, 365 Zilver Vena Venous Stents were placed in 243 patients; most patients were implanted with one stent (57.2%; 139/243) or two stents (35.4%; 86/243).

Table 12. Procedure Characteristics for the VIVO Clinical Study

Characteristic	Percent Patients (number/total number)
Access Site[a]	
Ipsilateral Access sites	95.9% (233/243)
Popliteal vein	64.8% (151/233)
Femoral vein	30.0% (70/233)
Tibial vein	2.1% (5/233)
Jugular vein	0.4% (1/233)
"Other" vein	5.6% (13/233)
Contralateral Access site	7.4% (18/243)
Femoral vein	50.0% (9/18)
Jugular vein	44.4% (8/18)
Popliteal vein	5.6% (1/18)
Pre-stent dilatation	64.6% (157/243)
Post-stent dilatation	96.7% (235/243)
Number of Zilver Vena Venous Stents placed per patient	
1	57.2% (139/243)
2	35.4% (86/243)
3	7.4% (18/243)

[a] Access site(s) may involve more than one location; therefore, the total number of access site(s) may be more than the number of patients enrolled. "Other" access vein sites included great saphenous vein, collateral vein off the femoral vein, small saphenous vein, and lesser saphenous vein.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of the primary safety endpoint was based on a composite endpoint of 30-day freedom from MAEs (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).

Safety data through 30 days post-procedure were available for 240 of the 243 VIVO Clinical Study patients. The 3 patients with missing data included 2 patients who exited the study before 30 days without experiencing a MAE and

1 patient who was excluded from the analysis due to a technical failure (specifically, the stent was placed in an unintended vein).

The 30-day freedom from MAE rate for the analyzable population was 96.7% (232/240; Table 13), and the lower limit of the two-sided 95% confidence interval (CI) was 93.5%, which is greater than the performance goal of 87% ($p < 0.0001$). In summary, the null hypothesis for the 30-day primary safety hypothesis was rejected, supporting the safety of the Zilver Vena Venous Stent.

Table 13. VIVO Clinical Study Primary Safety Endpoint (Analyzable Population)

30-day Freedom from MAE Rate (%; number/total number)	95% Exact CI	Performance Goal	*P*-value
96.7% (232/240)	93.5%-98.6%	87%	<0.0001

In total, 8 patients experienced a MAE through 30 days; MAEs reported through 30 days included clinically-driven target lesion reintervention (n=7) and new symptomatic pulmonary embolism (n=1). Table 14 summarizes these events, as well as all MAEs reported through 3 years. In total, 26 MAEs have been reported through 3 years. Clinically driven target lesion reinterventions accounted for the majority (n=16) of MAEs. The clinical migration reported was a stent migration to a patient's heart that required surgical removal; the CEC adjudicated this as technique-related (the stent was undersized). Although the stent migration was not identified until the 6-month imaging (x-ray and ultrasound), the migration was considered to have occurred on the day of the procedure. After an unsuccessful endovascular attempt to remove the migrated stent, the stent was removed from the pulmonary artery through sternotomy. The patient was reported to have developed atrial flutter 23 days after undergoing open surgery to remove the migrated stent.

Table 14. MAEs Reported Through 3 Years in the VIVO Clinical Study

Major Adverse Event (MAE)	Number of MAEs				Total
	0-30 Days	31-365 Days	366-730 Days	>730 Days	
Clinically driven target lesion reintervention	7	3	5	1	16
New symptomatic pulmonary embolism	1	1	1	6	9
Clinical migration	0	1	0	0	1
Procedure- or device-related death	0	0	0	0	0
Procedural bleeding requiring transfusion	0	0	0	0	0
Procedure-related perforation requiring open surgical repair	0	0	0	0	0
Flow-limiting dissection of the target vessel	0	0	0	0	0
Total	**8**	**5**	**6**	**7**	**26**

Note: bleeding events occurring prior to study enrollment, and related to procedures such as thrombolysis or thrombectomy, are not considered procedural bleeding events.

Adverse events that occurred in the VIVO Clinical Study

All adverse events reported in the VIVO Clinical Study through 3 years are summarized in Table 15. There were no unanticipated adverse device effects observed during the study. There were 5 patient deaths through 3 years; 3 of these deaths were related to cancer, 1 death was due to sepsis, and 1 death was due to suicide. The CEC adjudicated all mortalities as not related to the study device or procedure.

Table 15. All Adverse Events Reported Through 3 Years in the VIVO Clinical Study

Event Type	Percent Patients (number /total number)				Total Number of Events
	0-30 Days	31-365 Days	366-730 Days	>730 Days	
Access site/incision events	**0.8% (2/243)**	**0.4% (1/241)**	**0% (0/220)**	**0% (0/207)**	**3**
Infection requiring intervention	0.4% (1/243)	0% (0/241)	0% (0/220)	0% (0/207)	1
Hematoma requiring intervention	0.4% (1/243)	0.4% (1/241)	0% (0/220)	0% (0/207)	2
Abscess formation requiring intervention	0% (0/243)	0% (0/241)	0% (0/220)	0% (0/207)	0
Bleeding requiring transfusion	0% (0/243)	0% (0/241)	0% (0/220)	0% (0/207)	0
Cardiovascular	**1.2% (3/243)**	**2.9% (7/241)**	**1.8% (4/220)**	**1.9% (4/207)**	**19**
Cardiac arrhythmia requiring intervention	0.4% (1/243)	0.4% (1/241)	0.5% (1/220)	0.5% (1/207)	4
Chest pain	0.8% (2/243)	2.1% (5/241)	1.4% (3/220)	1.4% (3/207)	13
Myocardial infarction (MI)	0% (0/243)	0.8% (2/241)	0% (0/220)	0% (0/207)	2
Cerebrovascular/neurologic	**0% (0/243)**	**0.4% (1/241)**	**0% (0/220)**	**0.5% (1/207)**	**2**
Stroke	0% (0/243)	0.4% (1/241)	0% (0/220)	0.5% (1/207)	2
Pulmonary	**1.6% (4/243)**	**2.1% (5/241)**	**2.3% (5/220)**	**4.3% (9/207)**	**24**
Pulmonary embolism (PE)	0.4% (1/243)	0.4% (1/241)	0.5% (1/220)	2.9% (6/207)	9
Shortness of breath	1.6% (4/243)	1.7% (4/241)	1.8% (4/220)	1.4% (3/207)	15
Renal	**0% (0/243)**	**0.4% (1/241)**	**0.5% (1/220)**	**0% (0/207)**	**2**
Renal failure requiring intervention	0% (0/243)	0.4% (1/241)	0.5% (1/220)	0% (0/207)	2
Vascular	**5.3% (13/243)**	**8.3% (20/241)**	**8.6% (19/220)**	**2.9% (6/207)**	**72**
Arteriovenous fistula	0% (0/243)	0% (0/241)	0% (0/220)	0% (0/207)	0
Embolism	0% (0/243)	0% (0/241)	0.5% (1/220)	0% (0/207)	3
Hypertension requiring intervention	0% (0/243)	0.4% (1/241)	0.5% (1/220)	0% (0/207)	3
Hypotension requiring intervention	0% (0/243)	0% (0/241)	0% (0/220)	0.5% (1/207)	1
Occlusion	4.9% (12/243)	4.1% (10/241)	3.6% (8/220)	1.0% (2/207)	34
Pseudoaneurysm	0% (0/243)	0.4% (1/241)	0.5% (1/220)	0% (0/207)	2
Restenosis	0% (0/243)	2.9% (7/241)	2.7% (6/220)	1.0% (2/207)	17
Stasis ulcer of the study leg	0% (0/243)	2.1% (5/241)	0.5% (1/220)	1.0% (2/207)	9
Tissue necrosis of the study leg	0% (0/243)	0% (0/241)	0% (0/220)	0% (0/207)	0
Vascular injury	0.4% (1/243)	0% (0/241)	0.9% (2/220)	0% (0/207)	3

Event Type	Percent Patients (number /total number)				Total Number of Events
	0-30 Days	31-365 Days	366-730 Days	>730 Days	
Miscellaneous	**31.7% (77/243)**	**49.8% (120/241)**	**40.9% (90/220)**	**39.1% (81/207)**	**674**
Bleeding associated with anticoagulant/antiplatelet therapy	8.2% (20/243)	5.4% (13/241)	2.7% (6/220)	1.9% (4/207)	47
Fever requiring treatment	0.4% (1/243)	0% (0/241)	0.5% (1/220)	0.5% (1/207)	3
Hypersensitivity/allergic reaction	3.7% (9/243)	0% (0/241)	0% (0/220)	0% (0/207)	9
Nausea requiring treatment	0.8% (2/243)	0% (0/241)	0% (0/220)	0.5% (1/207)	3
Septicemia/bacteremia	0% (0/243)	0.8% (2/241)	1.8% (4/220)	0.5% (1/207)	9
Worsened pain of study leg	1.6% (4/243)	3.3% (8/241)	2.7% (6/220)	1.9% (4/207)	23
Abdominal pain	0.4% (1/243)	2.1% (5/241)	0.9% (2/220)	1.9% (4/207)	13
Back pain	2.5% (6/243)	2.5% (6/241)	0.5% (1/220)	1.0% (2/207)	15
Other	18.9% (46/243)	43.6% (105/241)	39.1% (86/220)	35.7% (74/207)	552

Note: Values in bold indicate total numbers of patients and events under each event type.

2. Effectiveness Results

The primary effectiveness endpoint was primary quantitative patency at 12 months. Primary quantitative patency was defined as a treated venous segment (including the region within ± 1 cm proximal and/or distal of the treated venous segment) that retained (uninterrupted; intervention-free) an MLD > 50% of the immediate post-procedure stented MLD as demonstrated by venography as determined by the core laboratory.

Among the 243 enrolled patients, 189 patients had venographic primary patency outcome data available and therefore make-up the analyzable population. The venographic results consisted of core laboratory assessed venogram results for 181 patients and site assessed venogram results for 8 patients, as per the analysis plan. Among the 189 analyzable patients, 19 patients had a loss of primary quantitative patency. Importantly, no patient experienced a surgical bypass of the treated segment or amputation of the extremity determined to result from venous outflow occlusion. For the 54 patients with a missing primary effectiveness outcome, the outcome was imputed by random sampling from the Bernoulli distribution based on outcomes for the 189 analyzable patients without covariate adjustment. The imputation was performed 20 times.

Table 16 presents the results of the intent-to-treat (ITT) analysis with multiple imputations for 12-month primary quantitative patency. The analysis was based on 189 patients with observed outcomes and 54 patients with imputed outcomes. The 12-month primary quantitative patency rate was 89.9%, and the lower limit of the two-sided 95% CI was 85.1%, which is greater than the performance goal of 76% ($p < 0.0001$).

Table 16. VIVO Clinical Study Primary Effectiveness Endpoint (ITT Population)

12-Month Quantitative Patency (%)	95% CI	Performance Goal	*P*-value
89.9%	85.1%-93.4%	76%	<0.0001

Similar results were obtained for patients with venographic primary patency outcome data, or the analyzable population (N=189 patients; 181 patients with core lab assessed venogram results and 8 with site assessed venogram results). As presented in Table 17, the 12-month primary quantitative patency rate for the analyzable population was 89.9% (170/189), and the lower limit of the two-sided 95% CI was 84.7%, which is greater than the performance goal of 76% ($p < 0.0001$).

Table 17. VIVO Clinical Study Primary Effectiveness Endpoint (Analyzable Population)

12-month Quantitative Patency (%; number/total number)	95% Exact CI	Performance Goal	*P*-value
89.9% (170/189)	84.7% - 93.8%	76%	<0.0001

In summary, the null hypothesis for the 12-month primary effectiveness endpoint was rejected, supporting the effectiveness of the Zilver Vena Venous Stent.

3. Secondary Endpoint

The secondary hypothesis was the change in VCSS from baseline to 1 month and 12 months. The secondary endpoint hypotheses for 1 month and 12 months were tested by a paired t-test with *p*-values adjusted for multiple comparisons using the Holm's procedure to control for a family-wise Type I error rate of 0.05, with 95% CIs also reported.

The results for the change in VCSS from baseline to 1 month, 12 months, 2 years, and 3 years are provided in Table 18. Compared to baseline, the mean change (note: negative change is improvement) in VCSS was -3.0 (95% CI: -3.5 to -2.6) at 1 month ($p < 0.0001$) and -4.2 (95% CI: -4.7 to -3.7) at 12 months ($p < 0.0001$). Therefore, the null hypothesis is rejected at both 1 month and 12 months.

Table 18. VIVO Clinical Study Secondary Endpoint (Change in VCSS from Baseline)

VCSS Assessment Time Point	VCSS Mean ± SD (N, range)	VCSS Change from Baseline Mean (N, 95% CI)	*P*-value[a]	Accept/Reject Null Hypothesis
Baseline	8.0 ± 4.2 (243, 1-24)	NA	NA	NA
1 month	5.0 ± 4.0 (233, 0-23)	-3.0 (233, -3.5 to -2.6)	<0.0001	Reject
12 months	3.8 ± 4.0 (202, 0-27)	-4.2 (202, -4.7 to -3.7)	<0.0001	Reject
2 years	3.7 ± 3.5 (190, 0-20)	-4.2 (190, -4.8 to -3.7)	NA	NA
3 years	3.7 ± 3.6 (173, 0-21)	-4.1 (173, -4.6 to -3.5)	NA	NA

[a] *p*-values for 1 month and 12 months were adjusted for multiplicity using Holm's procedure.

These data demonstrate significantly improved VCSS score at 1 month, with continued or maintained improvement through 12 months following stent placement. The improvement in VCSS was sustained through 2 years and 3 years post-treatment, supporting device effectiveness and demonstrating clinical benefit for patients receiving the Zilver Vena Venous Stent.

4. Additional Measures

This section presents the additional measures that were assessed for the VIVO Clinical Study. The additional measures included many device-related effectiveness measures and clinical benefit measures, including technical success, procedural success, device integrity, device migration, rate of freedom from clinically driven reintervention, rate of freedom from reintervention, rate of primary quantitative patency, rate of patency by ultrasound, rate of assisted primary quantitative patency, rate of secondary quantitative patency, rate of clinical patency, rate of modified clinical patency, and change in VCSS, VDS, CEAP "C" classification, and CIVIQ score from baseline. Additional measures were not hypothesis driven; descriptive statistics are presented.

Procedural success measures included technical success (ability to deliver and deploy the study stent in the intended location) and procedural success (improved flow through the target vessel demonstrated by diminished flow through collateral vein and/or reduced filling defect in the target vessel and no MAE before discharge). Technical success was assessed for all study stents and was reported based on site assessment. The rate of technical success was 97.3% (355/365 stents). Procedural success was assessed for all patients with evidence of collateral veins or filling defect in the target vessel at the time of the procedure, and any patient with a MAE before discharge was considered a failure. Procedure success included core laboratory assessment of procedure imaging. The rate of procedural success was 96.7% (175/181 patients).

Table 19 summarizes the Kaplan Meier estimates for freedom from stent fracture and stent migration through 3 years. The core laboratory reported no stent fractures through 3 years and 1 stent migration through 3 years. The stent

migration was the clinical migration of the study stent to the patient's heart, as described above in the Safety Results.

Table 19. VIVO Clinical Study Device Measures (Kaplan-Meier estimate ± SD) through 3 years

X-Ray Assessment Time Point	Freedom from Stent Fracture Kaplan Meier Estimate ± SD	Freedom from Stent Migration Kaplan Meier Estimate ± SD
0 days	100%	100%
12 months	100%	99.7% ± 0.3%
2 years	100%	99.7% ± 0.3%
3 years	100%	99.7% ± 0.3%

Table 20 reports the results for 12-month quantitative patency outcome measures. These results demonstrate the effectiveness of the Zilver Vena Venous Stent in establishing and maintaining patency through 12 months. Table 21 reports the results for reintervention and patency outcome measures through 3 years.

Table 20. VIVO Clinical Study Quantitative Patency Measures (binary rates and Kaplan-Meier estimate ± SD) through 410 days

Measure	Binary Rate Outcomes	Kaplan-Meier Estimate Outcomes (n=243)
12-month rates of primary quantitative patency		
Overall study population	89.9% (170/189)	89.8% ± 3.5%
Population classified as acute	86.3% (44/51)	88.7% ± 5.2%
Population classified as chronic	91.3% (126/138)	90.4% ± 4.0%
Population with past or current DVT at enrollment	85.3% (110/129)	85.0% ± 5.3%
Population with no past or current DVT at enrollment	100% (60/60)	100%
12-month assisted primary quantitative patency	91.4% (170/186)	90.0% ± 3.5%
12-month secondary quantitative patency	98.9% (185/187)	98.9% ± 0.7%

Table 21. VIVO Clinical Study Reintervention and Patency Measures (binary rates and Kaplan-Meier estimate ± SD) through 3 years

Measure	Binary Rate Outcomes	Kaplan-Meier Estimate Outcomes (n=243)
12-month Outcomes (through 410 days)		
12-month rate of freedom from clinically driven reintervention[a]	94.8% (201/212)	95.3% ± 1.5%
12-month rate of freedom from reintervention[b]	85.8% (188/219)	86.7% ± 2.3%
12-month patency by ultrasound	91.2% (187/205)	92.0% ± 2.0%
12-month clinical patency	79.4% (166/209)	80.7% ± 2.8%
12-month modified clinical patency	87.5% (182/208)	88.3% ± 2.3%
2-year Outcomes (through 730 days)		
2-year rate of freedom from clinically driven reintervention[a]	92.0% (173/188)	93.2% ± 1.8%
2-year rate of freedom from reintervention[b]	81.9% (172/210)	83.4% ± 2.5%
2-year patency by ultrasound	88.5% (161/182)	90.3% ± 2.2%
2-year clinical patency	72.7% (133/183)	76.8% ± 3.0%
2-year modified clinical patency	82.4% (145/176)	85.6% ± 2.6%
3-year Outcomes (through 1,095 days)		
3-year rate of freedom from clinically driven reintervention[a]	90.2% (147/163)	92.6% ± 2.0%
3-year rate of freedom from reintervention[b]	78.9% (146/185)	82.9% ± 2.6%
3-year patency by ultrasound	85.9% (128/149)	90.3% ± 2.2%
3-year clinical patency	66.7% (108/162)	74.4% ± 3.3%
3-year modified clinical patency	75.8% (116/153)	81.5% ± 3.6%

[a]Clinically driven reinterventions were reinterventions performed in patients 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 (MLD) ≤ 50% of the immediate post-procedure stented MLD. Most commonly, the clinical symptom in these patients was edema or pain.

[b]Reinterventions were any endovascular or surgical intervention performed in a treated venous segment (including the region within ± 1 cm proximal and/or distal to the treated venous segment). Reinterventions were those treatments in the treated venous segment when the MLD was >50% of the immediate post-procedure stented MLD or treatments reported outside the treated venous segment, in the presence or absence of clinical symptoms.

Table 22 presents the change in the clinical scores of VDS, CEAP "C", and CIVIQ through 3 years. The data demonstrate that stent placement resulted in clinical improvement, as demonstrated by improved clinical scores following stent placement, which were maintained through 3 years. Specifically, the number of patients with a VDS of 2 or 3 or a CEAP "C3" classification decreased dramatically from pre-procedure to 1 month, with continued or maintained improvement through 3 years. Likewise, an improvement in the CIVIQ score was observed at 1 month, with continued or maintained improvement through 3 years following stent placement.

Table 22. VIVO Clinical Study Clinical Outcome Measures

Clinical Measure	Time Point				
	Pre-procedure	1 Month	12 Months	2 Years	3 Years
VDS (percent patients [number/total number])					
0	5.3% (13/243)	40.8% (95/233)	55.0% (111/202)	53.2% (101/190)	57.2% (99/173)
1	28.0% (68/243)	34.3% (80/233)	27.7% (56/202)	31.6% (60/190)	28.3% (49/173)
2	41.6% (101/243)	21.5% (50/233)	14.4% (29/202)	13.7% (26/190)	11.6% (20/173)
3	25.1% (61/243)	3.4% (8/233)	3.0% (6/202)	1.6% (3/190)	2.9% (5/173)
CEAP "C" Classification (percent patients [number/total number])					
C0	0.4% (1/243)	25.3% (59/233)	36.1% (73/202)	30.0% (57/190)	27.7% (48/173)
C1	0.8% (2/243)	9.0% (21/233)	14.9% (30/202)	11.6% (22/190)	12.7% (22/173)
C2	3.3% (8/243)	7.3% (17/233)	9.9% (20/202)	11.6% (22/190)	12.1% (21/173)
C3	66.7% (162/243)	34.3% (80/233)	20.8% (42/202)	29.5% (56/190)	30.6% (53/173)
C4a	16.9% (41/243)	13.7% (32/233)	13.4% (27/202)	10.5% (20/190)	10.4% (18/173)
C4b	3.7% (9/243)	4.3% (10/233)	1.5% (3/202)	2.1% (4/190)	1.7% (3/173)
C5	2.9% (7/243)	3.4% (8/233)	1.5% (3/202)	2.6% (5/190)	2.3% (4/173)
C6	5.3% (13/243)	2.6% (6/233)	2.0% (4/202)	2.1% (4/190)	2.3% (4/173)
CIVIQ Score (mean [N; 95%CI])					
Mean change from baseline	NA	-20.5 (209; -23.6 to -17.3)	-22.6 (168; -26.2 to -19.0)	-22.1 (155; -26.0 to -18.2)	-20.8 (131; -24.8 to -16.8)

N/A = not applicable.

In summary, the Zilver Vena Venous Stent was associated with high technical and procedural success rates, a low rate of migration, and no fractures. Finally, the low reintervention rates, favorable patency rates, and improvements in venous clinical symptoms (as measured by VDS, CEAP "C" classification, and CIVIQ score) demonstrate the clinical benefit of the Zilver Vena Venous Stent.

5. Subgroup Analyses

Although the study was not powered for this purpose, patient characteristics were evaluated for their potential contribution to the treatment effect and overall event rates. Analyses to evaluate impacts on the primary and secondary endpoints of the evaluable patients were conducted for predefined characteristics such as age, sex, presence of thrombotic disease, presence of occlusive disease, presence of thrombophilia, venous disease status (acute or chronic), and DVT status. No significant impact on the endpoint was found for any of the aforementioned covariates; specifically, no differences were noted based on age or gender. As expected, patients with less severe disease tended to perform slightly better than patients with more severe venous disease (DVT, longer lesion length, etc.). However, given the robust study results of the overall study data, interpretation of most results was limited due to the small sample size of the subgroups.

6. Pediatric Extrapolation

In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 36 principal investigators, of whom none were full-time or part-time employees of the sponsor and 5 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c), and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 5
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. Summary of Supplemental Clinical Information

The VIVO-EU Clinical Study was a prospective, nonrandomized, multicenter study in Europe that enrolled patients with symptomatic obstruction in up to two iliofemoral venous segments. The study was designed to assess the performance of the Zilver Vena Venous Stent in the treatment of patients with symptomatic iliofemoral venous outflow obstruction.

A total of 35 patients were enrolled at five European sites. The study entry criteria were similar to the VIVO Clinical Study with the exception that there was no limitation associated with significant obstruction or occlusion of the inflow or outflow tract, and inclusion of bilateral limbs with obstruction and malignant obstruction was allowed. Patient follow-up included clinical assessments at 1, 6, and 12 months and noninvasive ultrasound at 6 and 12 months. Study assessments included: 1) procedural success; 2) MAEs; 3) qualitative patency at 6 and 12 months post-procedure; 4) clinical symptoms of venous insufficiency at 1, 3, 6, 9, and 12

months post-procedure; and 5) reintervention within the treated venous segment. An independent core laboratory was used for image analysis. Study follow-up is complete.

Patient demographics and medical history were comparable to the VIVO Clinical Study; specifically, the mean age was 45.1 ± 15.5 years, most patients were female (77.1%; 27/35) and white/Caucasian (68.6%; 24/35), and more than half of the study population had acute or chronic DVT (62.9%; 22/35). Lesions were predominantly left-sided (94.1%; 32/35) and most commonly affected the common iliac vein (94.1%; 32/35) and external iliac vein (38.2%; 13/35). The mean lesion length was 89.3 mm ± 58.6 mm based on core laboratory assessment. In total, 45 Zilver Vena Venous Stents were implanted to treat study patients' iliofemoral venous lesions.

MAEs were defined as procedural bleeding requiring transfusion, procedure- or device-related death, clinically driven target lesion reintervention for occlusion, stent migration requiring an intervention, procedure- or device-related symptomatic pulmonary embolism, or procedure-related uncorrectable perforation or flow-limiting dissection of the target vessel. In total, three MAEs were reported in the study, including two clinically driven reinterventions for occlusion and one procedure- or device-related symptomatic pulmonary embolism.

Freedom from occlusion (lack of occlusion of the treated venous segment by evidence of blood flow proximal, within, and distal to the study lesion) was determined by Kaplan-Meier estimate. The 6-month and 12-month rate of freedom from occlusion was 88.2%.

Qualitative patency (defined as a 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 VCSS]) was similarly determined by Kaplan-Meier estimate. The 6-month rate of qualitative patency was 88.2% and the 12-month rate of qualitative patency was 85.2%.

In total, seven reinterventions were reported in five patients; reinterventions occurred between 4 and 392 days after stent placement. Clinical measures included VCSS, VDS, CEAP "C" classification, and CIVIQ score. Stent placement resulted in clinical improvement, as demonstrated by improvement in each respective clinical score following stent placement, which was maintained through 12 months.

In conclusion, the results from the VIVO-EU Clinical Study provide supportive evidence confirming the safety and effectiveness of the Zilver Vena Venous Stent for the treatment of patients with symptomatic iliofemoral venous outflow obstruction.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The non-clinical engineering testing conducted on the stent and delivery system demonstrates that the performance characteristics of the device met the product specifications. The test results obtained from sterilization testing demonstrate that the product can be adequately sterilized and is acceptable for clinical use. The shelf life testing has established acceptable performance for a labeled shelf life up to 3 years.

The VIVO Clinical Study was a prospective, global, multi center, nonrandomized, single-arm clinical study intended to evaluate the Zilver Vena Venous Stent for the treatment of patients with symptomatic iliofemoral venous outflow obstruction. The primary effectiveness endpoint was primary quantitative patency at 12 months and was defined as a treated venous segment that retained (uninterrupted; intervention-free) an MLD > 50% of the immediate post-procedure stented MLD as demonstrated by venography as determined by the core laboratory.

The 12-month primary quantitative patency rate for the intent-to-treat population was 89.9% with a 95% CI of 85.1%-93.4% and met the performance goal of 76% (one-sided p-value < 0.0001). Likewise, the 12-month quantitative patency rate for the analyzable population (i.e., the 189 patients with venographic primary patency outcome data available) was 89.9% (170/189) with a 95% Exact CI of 84.7%-93.8% and met the performance goal of 76% (one-sided p-value < 0.0001). These results support the effectiveness of the Zilver Vena Venous Stent for the treatment of patients with symptomatic iliofemoral venous outflow obstruction.

The secondary endpoint was the change in VCSS from baseline to 1 month and 12 months; the VCSS score improved significantly ($p < 0.0001$) at both time points as compared to baseline. Additionally, patient clinical scores improved, as demonstrated by improvements in VDS, CEAP "C" classification, and CIVIQ scores following stent placement. Improvements in clinical scores were observed at 1 month and these improvements continued or were maintained through 3 years. Performance data through 3 years is adequate to support the sustained effect of the Zilver Vena Venous Stent. These data demonstrate the clinical benefit of the Zilver Vena Venous Stent for the treatment of patients with symptomatic iliofemoral venous outflow obstruction.

B. Safety Conclusions

The biocompatibility testing, chemical characterization testing, and animal testing demonstrate reasonable assurance of the safety of the device for the intended use.

In the VIVO Clinical Study, the primary safety endpoint was 30-day freedom from MAEs (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). The 30-day freedom from MAE rate was 96.7% (232/240) with a 95% Exact CI of 93.5%-98.6%, and met the performance goal of 87% ($p < 0.0001$). Safety data through 3 years is adequate to support the sustained safety profile of the Zilver Vena Venous Stent. These data support the safety of the Zilver Vena Venous Stent for the treatment of patients with symptomatic iliofemoral venous outflow obstruction.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefits of the Zilver Vena Venous Stent include improving or restoring blood flow in patients with symptomatic iliofemoral venous outflow obstruction to improve patient symptoms and quality of life.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Overall, the occurrence and adverse event types reported in the VIVO Clinical Study align with the adverse events from published clinical literature and are expected in the patient population evaluated.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for using the Zilver Vena Venous Stent to improve luminal diameter in patients with symptomatic iliofemoral venous outflow obstruction.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device.

D. Overall Conclusions

The non-clinical and clinical data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The results from the prospective, multicenter, nonrandomized, single-arm VIVO Clinical Study demonstrate that the Zilver Vena Venous Stent is safe and effective for improving luminal diameter in patients with symptomatic iliofemoral venous outflow obstruction when used in accordance with the associated device labeling including the Instructions for Use. Results from the VIVO-EU

Clinical Study provide additional evidence to support the safety and effectiveness of the Zilver Vena Venous Stent.

XIV. CDRH DECISION

CDRH issued an approval order on October 9, 2020.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.