November 21, 2022
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Venous stent
Brand Name	Zilver Vena Venous Stent
Applicant	Cook Medical Japan G.K.
Date of Application	March 31, 2022 (Application for marketing approval)

Results of Deliberation

In its meeting held on November 21, 2022, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is designated as a medical device subject to a use-results survey. The product is not classified as a biological product or a specified biological product.

The use-results survey period should be 7.5 years. The product should be approved with the following conditions.

Approval Conditions

1. The product must be used for patients eligible for the treatment, who should be selected by physicians with adequate knowledge and experience in the treatment of lower limb venous disease. Before using the product, the physicians must have acquired skills to handle the product and various knowledge including procedure-associated complications, and medical institutions must have a system prepared for the use of the product. To fulfill these requirements, the applicant is required to take necessary measures, such as disseminating the guidelines for proper use jointly prepared with relevant academic societies and offering seminars.
2. The applicant is required to conduct a use-results survey, which is to be continued over a period of time covering all patients treated with the product to obtain post-marketing data from a certain number of patients, report the survey result to the Pharmaceuticals and Medical Devices Agency, and take other measures as appropriate.

Review Report

November 2, 2022
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Classification	Instrument & Apparatus 07, Organ Function Replacement Device
Term Name	Venous stent
Brand Name	Zilver Vena Venous Stent
Applicant	Cook Medical Japan G.K.
Date of Application	March 31, 2022
Reviewing Office	Office of Medical Devices II

Review Results

November 2, 2022

Classification	Instrument & Apparatus 07, Organ Function Replacement Device
Term Name	Venous stent
Brand Name	Zilver Vena Venous Stent
Applicant	Cook Medical Japan G.K.
Date of Application	March 31, 2022

Results of Review

The "Zilver Vena Venous Stent" (hereinafter referred to as the "Zilver Vena Stent") is a venous stent intended for use to improve the luminal diameter of the iliofemoral veins for the treatment of symptomatic iliofemoral venous outflow obstruction that is difficult to treat with conventional therapies. The Zilver Vena Stent is comprised of a self-expanding stent, a delivery system that deploys the stent to the lesion site, and other accessories.

The applicant submitted nonclinical data supporting the physicochemical properties, biological safety, mechanical safety, stability and durability, performance, and directions for use of the Zilver Vena Stent. There was no particular problem in the data submitted.

To support the clinical evaluation of the Zilver Vena Stent, the applicant submitted the results of a prospective, multi-center, single-arm clinical study conducted in the US and Taiwan to evaluate the efficacy and safety of the Zilver Vena Stent in the treatment of symptomatic iliofemoral venous outflow obstruction (the VIVO study).

The primary efficacy endpoint of this clinical study was the "12-month primary quantitative patency rate." The primary quantitative patency was defined as a treated venous segment continuously retaining a minimum lumen diameter (MLD) that is >50% of the immediately post-stenting MLD since the index procedure (uninterrupted or intervention-free) as demonstrated by core lab-assessed venography. The 12-month primary quantitative patency rate was 89.9% (95% confidence interval [CI], 85.1%, 93.4%). The lower limit of the 95% confidence interval was 85.1%, which exceeds the protocol-defined performance goal of 76% ($P < 0.0001$). The secondary endpoint of the "change in Venous Clinical Severity Score (VCSS) from baseline to 1 and 12 months post-procedure" showed a significant decrease from baseline, supporting the clinical efficacy of the treatment with the Zilver Vena Stent. The Zilver Vena Stent also improved the primary quantitative patency rate and clinical symptoms in subjects who met the expected eligibility criteria in Japan, demonstrating the efficacy of the Zilver Vena Stent.

The primary safety endpoint of the "30-day freedom from major adverse event rate" was 96.7%, which exceeds the protocol-defined performance goal of 87%. The data showed the clinically acceptable safety

of the Zilver Vena Stent. No adverse event specific to the Zilver Vena Stent was reported. No adverse event had a higher incidence than that reported in literature reports describing stent therapy for the treatment of the target disease in and outside Japan. The incidence of stent migration, which is a potential risk of venous stents, was 0.82% (2 of 243 subjects) in the VIVO study and 0.017% ([redacted] events as of the end of December 2021) in the post-marketing setting (reported as malfunctions). The incidence of stent migration in the VIVO study tended to be higher than that reported in the latest literature. However, in light of the limited sample size of the study and stent migration attributable to inappropriate size selection, its risk can be mitigated through training, offering advice in the instructions for use, and other measures. It is difficult, on the basis of the current limited evidence, to recommend a specific protocol for post-stenting anticoagulant therapy or antiplatelet therapy that will accommodate patients of various characteristics. Therefore, a decision on anticoagulant or antiplatelet therapy should be made by physicians acquainted with these therapies for the disease and be individualized according to patient characteristics at present.

The Zilver Vena Stent therapy is intended for patients with severe symptomatic venous disease who have currently no other effective therapeutic option but off label use of an arterial stent. The benefits of the treatment with the Zilver Vena Stent outweigh its risk. The submitted data demonstrate the clinical usefulness of the Zilver Vena Stent.

For effective and safe introduction of the Zilver Vena Stent to Japan, it is essential for physicians or medical teams with sufficient experience and achievements in the standard treatment of this disease to acquire knowledge and skills for the Zilver Vena Stent and relevant procedures through training etc. so as to appropriately select patients. The treatment with the Zilver Vena Stent should be performed at medical institutions with a system prepared for emergency including surgery to address stent migration, pulmonary embolism, and other complications.

The Zilver Vena Stent will be the first iliofemoral venous stent in Japan. It is important to gather information on patient characteristics, anticoagulant/antiplatelet therapy, adverse events, etc. from patients treated with the Zilver Vena Stent through a use-results survey, and to take additional risk mitigation measures as necessary.

As a result of its review, PMDA has concluded that the Zilver Vena Stent may be approved for the intended use shown below with the following approval conditions, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

The Zilver Vena Venous Stent is used to improve the luminal diameter of the iliofemoral veins for the treatment of symptomatic iliofemoral venous outflow obstruction that is difficult to treat with conventional therapies.

Approval Conditions

1. The product must be used for patients eligible for the treatment, who should be selected by physicians with adequate knowledge and experience in the treatment of lower limb venous disease. Before using the product, the physicians must have acquired skills to handle the product and various

knowledge including procedure-associated complications, and medical institutions must have a system prepared for the use of the product. To fulfill these requirements, The applicant is required to take necessary measures, such as disseminating the guidelines for proper use jointly prepared with relevant academic societies and offering seminars.

2. The applicant is required to conduct a use-results survey, which is to be continued over a period of time covering all patients treated with the product to obtain post-marketing data from a certain number of patients, report the survey report to the Pharmaceuticals and Medical Devices Agency, and take other measures as appropriate.

Review Report

November 2, 2022

Product for Review

Classification	Instrument & Apparatus 07, Organ Function Replacement Device
Term Name	Venous stent
Brand Name	Zilver Vena Venous Stent
Applicant	Cook Medical Japan G.K.
Date of Application	March 31, 2022
Proposed Intended Use	The Zilver Vena Venous Stent is used in the iliofemoral veins to improve the luminal diameter of the veins for the treatment of symptomatic iliofemoral venous outflow obstruction.

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List of Abbreviations

BMI	Body Mass Index
CDT	Catheter Directed Thrombolysis
CEAP	Clinical manifestation‐Etiologic‐Anatomic distribution-Pathophysiologic
CEC	Clinical Events Committee
CFV	Common Femoral Vein
CIVIQ	Chronic Venous Insufficiency Questionnaire
DVT	Deep Vein Thrombosis
FDA	Food and Drug Administration
FEA	Finite Element Analysis
ITT	Intent-To-Treat
IVC	Inferior Vena Cava
IVR	Interventional Radiology
MAE	Major Adverse Event
MLD	Minimum Lumen Diameter
MR	Magnetic Resonance
NIVL	Nonthrombotic Iliac Vein Lesions
PTS	Post-Thrombotic Syndrome
PTE	Pulmonary Thromboembolism
QOL	Quality of Life
Stent migration	Stent migration
VCSS	Venous Clinical Severity Score
VDS	Venous Disability Score

I. Product Overview

The “Zilver Vena Venous Stent” (hereinafter referred to as the “Zilver Vena Stent”) is a venous stent intended for use to improve the luminal diameter of the iliofemoral veins for the treatment of symptomatic iliofemoral venous outflow obstruction, which is difficult to treat with conventional therapies. The Zilver Vena Stent comprises of a self-expanding nitinol (nickel-titanium alloy) stent, a delivery system that deploys the stent to the lesion site, and a syringe, accessory (Figure 1).

The delivery system is available in 2 working lengths of 80 and 120 cm. Table 1 presents the available sizes of the stent.

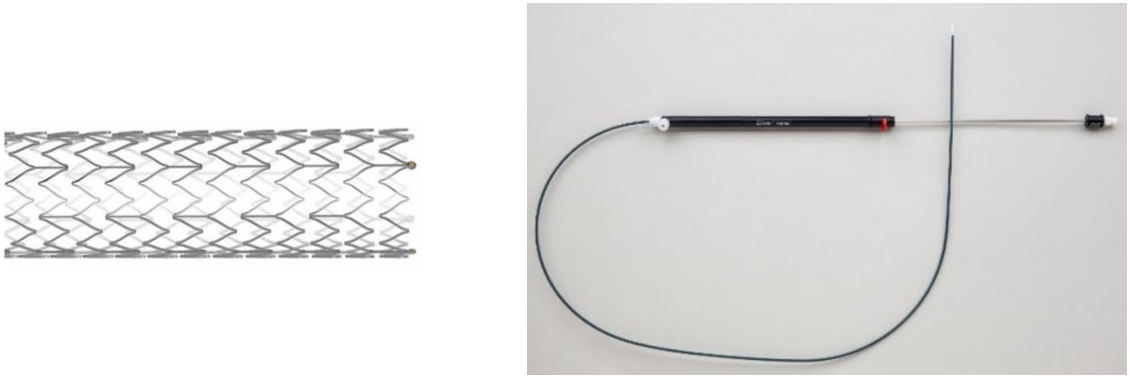


Figure 1. Appearance of the Zilver Vena Stent (left, stent; right, delivery system)

Table 1. Dimensions of the delivery system and the stent (nominal values)

Delivery system	Working length (cm)		80	120	80	120	80	120	80	120
	Outer diameter		7 Fr (2.3 mm)							
Stent	Length (mm)		40		60		100		140	
	Inner diameter (mm)	10	○	○	○	○	○	○	○	○
		12	○	○	○	○	○	○	○	○
		14			○	○	○	○	○	○
		16			○	○	○	○	○	○

II. Summary of the Data Submitted and Outline of the Review Conducted by the Pharmaceuticals and Medical Devices Agency

The following summarizes data submitted with the application by the applicant and their responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA).

The expert advisors present during the Expert Discussion on the Zilver Vena Stent declared that they did not fall under the Item 5 of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. History of Discovery, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

Iliofemoral outflow obstruction is a venous blood circulation disorder caused by the obstruction or stenosis of the iliofemoral vein (deep vein in the lower limb), which is a main venous outflow tract of the lower limb. The typical causes of iliofemoral outflow obstruction are acute deep vein thrombosis

(DVT), chronic DVT, and external compression on the vein (e.g., iliac vein compression syndrome such as May-Thurner syndrome presenting with the compression of the left common iliac vein by the right common iliac artery). Obstructed outflow from the lower limb leads to venous hypertension and secondary muscle pump dysfunction. Consequent valvular incompetence in the vein may cause blood retention in lower limb veins, resulting in chronic venous insufficiency and post-thrombotic syndrome (PTS). Symptomatic acute DVT is mainly manifested as pain and swelling, while symptomatic PTS is mainly manifested as edema, swelling, varicose vein, lipodermatosclerosis, pigmentation, and ulceration, etc.

Guidelines for Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis (Revised Version, 2017))[1] states that the goals of DVT treatment are "(1) the prevention of progression and recurrence of thrombi, (2) the prevention of thromboembolism, and (3) the mitigation of early and late sequelae. The treatment should ideally prevent complications of pulmonary thromboembolism, promptly remove and dissolve venous thrombi, and prevent the recurrence of thromboembolism so as to improve the venous patency and preserve the venous valvular function." The guidelines further mention that even deep veins which are completely obstructed by thrombi can be recanalized by thrombolysis over time (Figure 2).

Considering this treatment goal, conservative therapies (e.g., anticoagulant therapy and compression therapy) are still the standard of care for acute DVT, while severe acute iliofemoral venous thrombosis accompanied by serious arterial ischemia such as phlegmasia cerulea dolens requires immediate restoration of the blood flow by catheter directed thrombolysis (CDT) or surgical removal of the thrombus. For chronic DVT and PTS, conservative therapies, etc. are also the first-line therapy. DVT poorly responding to conservative therapies may also be treated with a catheter, but balloon angioplasty alone rarely succeeds because of recoil that is likely to occur in the veins, low-pressure organs. In May-Thurner syndrome with compressed and narrowed left iliac vein, balloon angioplasty alone can hardly maintain a venous lumen for a long term. Normally, these pathological conditions require metal stent placement. In Japan, however, no metal stent is approved for use in the iliofemoral vein, and arterial stents are used off-label out of necessity in clinical practice. Some research demonstrated a higher incidence of complications with arterial stents than that with iliofemoral venous stents, which are designed based on the anatomical characteristics and physiological behavior of the iliofemoral vein.[2]

The development of the Zilver Vena Stent began aiming for stenting in the iliofemoral vein of patients with symptomatic venous outflow obstruction. The product expands the venous lumen and improve the vascular patency, allowing improved blood flow and thereby alleviating clinical symptoms associated with the disease. The VIVO study was conducted in 2013 to evaluate the efficacy and safety of the Zilver Vena Stent in the treatment of symptomatic iliofemoral venous outflow obstruction. After the completion of patient enrollment to the VIVO study, the manually performed stent compression and loading in the delivery system were automated to improve the level of control in the manufacturing process. The applicant confirmed no impact of this change on the performance of the Zilver Vena Stent.

A request for early introduction of iliofemoral venous stents including the Zilver Vena Stent was submitted by the Japanese Society of Interventional Radiology (JSIR). The Zilver Vena Stent was

designated as a medical device that should be introduced early by the Study Group on the Early Introduction of Medical Devices, etc. with High Medical Need in its 32nd meeting on November 1, 2021.[3] As stated in the guidelines,[1] the choice of anticoagulant, catheter, or other therapies must be individualized based on the characteristics and risks of each patient from the viewpoint of the risk-benefit balance. Guidelines for proper use of iliofemoral venous stents are planned to be developed jointly by 5 academic societies concerned including the JSIR.

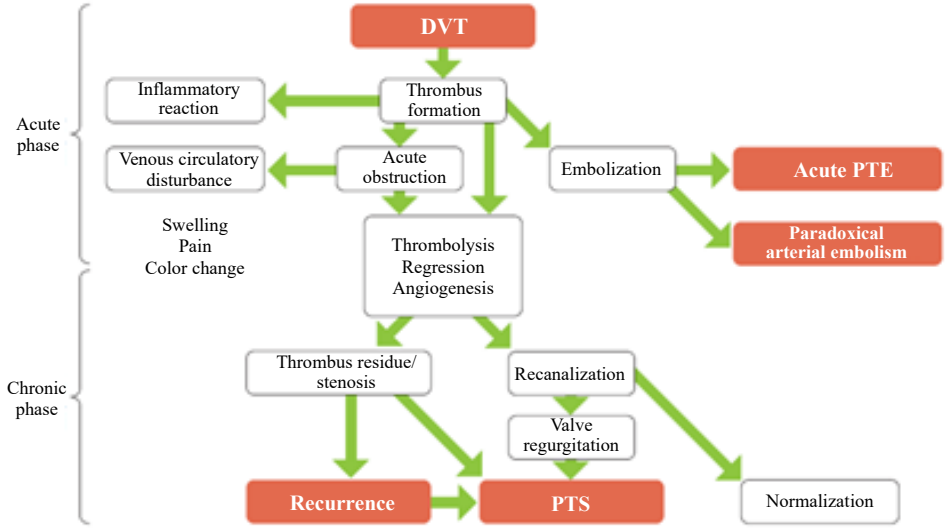


Figure 2. Change in the pathology of DVT[1]

1.A.(2) Use in foreign countries

Table 2 presents the information regarding the approvals and sales performance of the Zilver Vena Stent in foreign countries.

Table 2. Approvals and the number sold in foreign countries (as of the end of December 2021)

Country	Intended use	Date of approval	Number sold
Europe	The Zilver Vena Stent is used to improve the luminal diameter in the iliofemoral veins.	October 2010	[redacted]
US	The Zilver Vena Venous Self-Expanding Stent is intended for use in the iliofemoral veins to improve the luminal diameter of the veins for the treatment of symptomatic iliofemoral venous outflow obstruction.	October 2020	[redacted]
Others	The Zilver Vena Stent is used to improve the luminal diameter in the iliofemoral veins.	May 2011*	[redacted]

* Information from Australia, the first non-European or US country that approved the Zilver Vena Stent.

1.A.(3) Malfunctions and adverse events in foreign countries

Table 3 presents malfunctions reported for the Zilver Vena Stent in foreign countries as of December 2021.

Table 3. Malfunctions reported in foreign countries

Malfunctions	Number of events	Incidence* (%)
Restenosis	[redacted]	0.020
Breakage		0.020
Thrombosis		0.017
Compression		0.017
Migration		0.017
Deployment-related malfunction		0.015
Shortening		0.006
Stent elongation		0.006
Difficulty in deployment		0.006
Stent deployed before deployment procedure		0.006
Stent occlusion		0.003
Adverse biological reaction (allergic reaction)		0.003
Failure to function as intended		0.003
Failure to deploy		0.003
Difficulty in removal		0.003
Damage during shipping		0.003

* Incidence = (Number of events/[redacted] stents [Number of shipments]) × 100

1.B Outline of the review conducted by PMDA

The applicant's explanation about the cause analysis of the malfunctions reported in foreign countries:
The causes of breakage ([redacted] events) were improper use in [redacted] events, anatomical structure in [redacted] events, and nonuniform stent expansion and the use of excessively oversized stent in [redacted] events each. Thrombosis ([redacted] events) was associated with patient characteristics. Compression ([redacted] events) was suggestive of anatomical retraction. Deployment-related malfunctions ([redacted] events) occurred because of user errors in [redacted] events and anatomical structure in [redacted] events. Of the stent elongation ([redacted]events), [redacted] events that resulted in health injuries were due to anatomical structure.

PMDA's view:
The risk of malfunctions due to improper use and user errors can be mitigated by the provision of detailed instructions on proper use as one of post-marketing safety measures as described later in Section 7. The malfunctions associated with patient characteristics or anatomical structure were not specific to the Zilver Vena Stent, and their incidences were within the acceptable range. Information about patient characteristics and malfunctions, etc. should be collected continuously in the post-marketing setting and additional risk mitigation measures should be taken as necessary. Stent migration is reviewed in Section 6.

2. Specifications

2.(1) Performance and safety specifications

2.(1).A Summary of the data submitted

The proposed performance and safety specifications for the stent of the Zilver Vena Stent were corrosion resistance, corrosion resistance after bending fatigue loading, corrosion resistance after compression fatigue loading, radial force, compressive resistance, stent deployment uniformity, stent integrity, kink resistance, magnetic resonance (MR) compatibility, visibility, bending fatigue, and compression fatigue. The proposed performance and safety specifications of the delivery system were tensile strength/strength at junction, force required for deployment, positioning accuracy, flexibility and kink resistance, and radiopacity. Appearance, biological safety, ethylene oxide sterilization residuals, and

bacterial endotoxins were proposed as performance and safety specifications common to the stent and delivery system.

2.(1).B Outline of the review conducted by PMDA

PMDA asked the applicant to explain the justification of the specification limits of the radial force and kink resistance because the Zilver Vena Stent is a stent intended for use in veins.

The applicant's response:

The specification limits of the radial force of the Zilver Vena Stent were determined based on the physician's opinion that it should be at least the value (0.063 N/mm) of [redacted]. Taking into consideration [redacted], it is reasonable to refer to the physician's opinion in determining the lower specification limit of the radial force of the Zilver Vena Stent. The upper specification limit of 4.97 N/mm was determined based on [redacted]. The kink resistance of the Zilver Vena Stent was determined as <19 mm based on the curvature radius at the confluence of the inferior vena cava and the iliofemoral vein, which is assumed to be the largest bend in clinical use.

PMDA's view:

The applicant's explanation about the specification limits is reasonable because the results of clinical study and foreign use experience of the Zilver Vena Stent have revealed no malfunction due to excessive or insufficient radial force. The applicant's explanation about the specification limit of kink resistance is also acceptable. PMDA reviewed the justifications of the proposed performance and safety specifications (tests, methods, and limits), and concluded that there was no particular problem in the submitted data.

2.(2) Physicochemical properties

2.(2).A Summary of the data submitted

To support the physicochemical properties of the Zilver Vena Stent, corrosion resistance, corrosion resistance after bending fatigue loading, and corrosion resistance after compression fatigue loading were tested. The applicant submitted all test results meeting their respective predefined acceptance criteria.

2.(2).B Outline of the review conducted by PMDA

PMDA reviewed the data on the physicochemical properties of the Zilver Vena Stent and concluded that there was no particular problem in the submitted data.

2.(3) Biological safety

2.(3).A Summary of the data submitted

To support the biological safety of the Zilver Vena Stent, the applicant submitted the results of biological safety studies conducted in accordance with the "Basic principles of biological safety evaluation required for marketing application for medical devices (in Japanese)" (PFSB/ELD/OMDE Notification No. 0301-20, dated March 1, 2012) and ISO 10993-1.

The applicant also submitted the data on the delivery system of the Zilver Vena Stent for cytotoxicity, sensitization potential, intradermal reaction, acute systemic toxicity, pyrogenicity, blood compatibility (hemolysis), and blood compatibility (blood clotting). There was no problematic finding in any of the test results submitted.

The applicant omitted biological safety data of the stent of the Zilver Vena Stent because of its known raw materials that have previously been used for Zilver PTX Drug-Eluting Peripheral Stent (Approval number 22400BZX00013000).

2.(3).B Outline of the review conducted by PMDA

PMDA reviewed the data on the biological safety of the Zilver Vena Stent and concluded that there was no particular problem in the submitted data.

2.(4) Mechanical safety

2.(4).A Summary of the data submitted

To support the mechanical safety of the Zilver Vena Stent, the applicant submitted data from tests on radial force, compressive resistance, force required for deployment, stent integrity and stent deployment uniformity, kink resistance (single stent and overlapping stents), stent shortening (with or without restraint), tensile strength/strength at junction, and MR compatibility. Radial force, stent integrity and development uniformity were tested using samples before the change in the loading method. The applicant submitted the results of these tests as reference data. MR compatibility was tested using samples that did not undergo the loading process.

All tests met their respective predefined acceptance criteria. The tests also showed no substantial impact of the change in the loading method on the test results. These findings demonstrated the mechanical safety of the Zilver Vena Stent.

2.(4).B Outline of the review conducted by PMDA

PMDA reviewed the data on the mechanical safety of the Zilver Vena Stent and concluded that there was no particular problem in the submitted data.

2.(5) Stability and durability

2.(5).A Summary of the data submitted

The applicant omitted test results supporting the stability of the Zilver Vena Stent and submitted a self-declaration, which states that its shelf-life of 3 years was determined based on the results of necessary stability study in accordance with the “Handling of stability studies for determining shelf life in the application for marketing approval (certifications) of medical devices (in Japanese)” (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012).

To support the durability of the Zilver Vena Stent, the applicant submitted test data on bending fatigue by finite element analysis (FEA) (single stent and overlapping stents), compression fatigue by FEA (simulated May-Thurner syndrome) (single stent and overlapping stents), bending fatigue, and

compression fatigue. The FEA tests were conducted using samples before the change in the loading method.

2.(5).B Outline of the review conducted by PMDA

PMDA asked the applicant to explain the reasons for selecting bending fatigue and compression fatigue as fatigue loads on the stent placed in the iliofemoral vein, justifications for omitting other fatigue load tests and for the conditions of the bending and compression fatigue tests.

The applicant's explanation:

To assess the fatigue behaviors of the Zilver Vena Stent, the following biologically related fatigue loads were selected based on clinical literature data, inputs from physicians, and tests using samples: Outward radial force load for venous stent (similar to pulsating fatigue load assessed for arterial stents), axial load, bending load, and compression load simulating May-Thurner syndrome. Those loads were assessed by FEA. The fatigue analysis showed that bending fatigue, compression load simulating May-Thurner syndrome, and [redacted] resulted in the lowest fatigue safety factor. On the basis of this outcome, the loading modes and samples were selected for the tests.

The bending radius for the bending fatigue test was determined based on the [redacted] according to the results of research on the axial and bending movements of vein samples during walking. The compression load test simulating May-Thurner syndrome was conducted with reference to the publication by Jeon et al,[5] which shows that the stent was stenosed at the site where the right iliac artery overlaps the left iliac vein. On the basis of this information, physiologically appropriate loads were generated by locally compressing the vein where the stent was placed through the iliac artery ([redacted]) that crosses the iliac vein at right angles and [redacted]. In addition, pulsations ([redacted]) of the iliac artery were applied on the stent.

PMDA accepted the applicant's explanations, reviewed the data on the stability and durability of the Zilver Vena Stent, and concluded that there was no particular problem in the submitted data.

2.(6) Performance

2.(6).A Summary of the data submitted

To support the performance of the Zilver Vena Stent, the applicant submitted data from an animal study assessing delivery and deployment performance and animal studies testing 1-month and 3-month placement, respectively, all of which used samples before the change in the loading method.

The animal study to assess delivery and deployment performance involved 4 sheep, each having 1 stent (14 × 140 mm) placed in the left iliofemoral vein using the delivery system of the Zilver Vena Stent. The animals underwent angiography before and after stenting and the assessment of vascular injury in the access route and stented segment. A series of procedures using the Zilver Vena Stent (insertion of the delivery system, stenting, preparation of devices, insertion, pushability, trackability, flexibility,

radiopacity, easiness of deployment, interactions with assistance devices, removal, and post-procedural inspection) were also assessed by the intervention physician on [redacted].

All of the stented blood vessels were widely patent, with normal blood flow maintained. Gross histology of the blood vessels removed revealed a mild sign of vascular injury in the stented segment, but no significant injuries such as rupture and dissection. No damage such as fractures was observed on the stents placed. All procedures were assessed [redacted], and the results were acceptable.

The animal study (1-month placement) involved 9 sheep, each having 1 stent (14 × 140 mm or 10 × 140 mm) placed in the external jugular vein. The animals underwent fluoroscopy for stent damage, quantitative angiography for venous assessment, and histopathology of the stented segment at 1 month after the procedure.

One of the 8 stents with a diameter of 14 mm (5 animals) had a small mural thrombus. All of the other stented blood vessels were widely patent, with normal blood flow maintained. No damage to the blood vessels or stents was observed. All of the sample stents (14 of 14 stents, 100%) were covered by mature neointima and were integrated into the venous wall. The assessed pathological sections of the stented segment showed calcification or necrosis on 6 of 43 cross-sections and the disruption of neointima by a mural thrombus on 1 of 43 cross-sections that was not in contact with the stent. However, vascular patency was maintained on all cross-sections.

The animal study (3-month placement) involved 7 sheep, each having 1 stent (14 × 140 mm) placed in the external jugular vein. The animals underwent the same assessments as those after 1-month placement.

All of the stented blood vessels were patent, with normal blood flow maintained. Minimal stenosis (1.2% ± 8.4% on average) was observed. No damage to the blood vessels or stents was observed. All of the sample stents (8 of 8 stents, 100%) were covered by mature neointima and were integrated into the venous wall. Calcification or necrosis was observed on 1 of 24 cross-sections. However, vascular patency was maintained on all cross-sections.

The calcification or necrosis observed 1- and 3-month post-stenting was minimal and clinically insignificant. The disruption of neointima caused by mural thrombi 1-month post-stenting was not considered to be causally related to the Zilver Vena Stent because it occurred a while after the procedure at a site that was not in contact with the stent.

2.(6).B Outline of the review conducted by PMDA

PMDA asked the applicant to explain the justification for the diameters of stented blood vessels and the stent diameters in the animal studies selected for proper assessment of the impact of the Zilver Vena Stent on the blood vessel.

The applicant's explanation:

In all animal studies of the Zilver Vena Stent, stent diameters were oversized by approximately 1 to 4 mm with respect to the vascular diameters of animals. The directions for use of the Zilver Vena Stent

recommend the use of a stent 1 to 4 mm larger than the estimated vascular diameter. The assessments in all animal studies were conducted under conditions that would be equivalent to or severer (with oversized stents) than in clinical use.

PMDA's view:
The vascular diameters and stent diameters in the animal studies of the Zilver Vena Stent were acceptable because those study conditions were selected taking into consideration the oversizing rate in clinical use. The applicant's discussions on the findings in the animal studies were also acceptable. In the clinical study of the Zilver Vena Stent, post-stenting perforation, rupture, and dissection were observed but resolved without additional treatment. These findings, therefore, were clinically acceptable.

Based on the above, PMDA reviewed the data on the performance of the Zilver Vena Stent and concluded that there was no particular problem in the submitted data.

2.(7) Directions for use

2.(7).A Summary of the data submitted

To support the directions for use of the Zilver Vena Stent, a simulation test was conducted with 10 × 140-mm stents, which require the maximum force for deployment, and 16 × 60-mm stents, which require the minimum force for deployment, in mock blood vessels. The applicant submitted the test results of the flexibility and kink resistance of the delivery system, stenting accuracy, integrity of the delivery system after stenting, and radiopacity, all of which met predefined acceptance criteria.

2.(7).B Outline of the review conducted by PMDA

PMDA reviewed the data on the directions for use of the Zilver Vena Stent and concluded that there was no particular problem in the submitted data.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that the Zilver Vena Stent meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Ministerial Announcement No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the Zilver Vena Stent to the Essential Principles as follows.

1) PMDA's view on the conformity to Article 1, which specifies preconditions for designing medical devices (particularly, conditions for users, such as technical knowledge, experience, education, and training for intended users):
   As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," critical elements to maintain the risk-benefit balance of the Zilver Vena Stent include the selection of patients, users, and qualified medical institutions; training

of healthcare professionals; and adherence to the guidelines for proper use. To this end, approval conditions should be attached so that necessary measures are taken.

2) PMDA's view on the conformity to Article 2, which specifies requirements for risk management throughout the product life cycle of medical devices:
As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," the safety and efficacy of the Zilver Vena Stent should be investigated in clinical practice in Japan because no clinical efficacy and safety results of the Zilver Vena Stent available from Japanese patients. PMDA instructed the applicant to conduct a use-results survey.

3) PMDA's view on the conformity to Article 3, which specifies requirements for the performance and functions of medical devices, and Article 6, which specifies the efficacy of medical devices:
As described earlier in Section "2.(6).B Outline of the review conducted by PMDA," the performance of the Zilver Vena Stent was confirmed. In addition, as described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," the clinical study yielded satisfactory results with the Zilver Vena Stent and demonstrated the efficacy and safety of the Zilver Vena Stent in patients selected as eligible. The Zilver Vena Stent conforms to Articles 3 and 6.

4) PMDA's view on the conformity to Article 4, which specifies the shelf-life or durability of medical devices:
As described earlier in Section "2.(5).B Outline of the review conducted by PMDA," the applicant submitted a self-declaration stating that the shelf-life of the Zilver Vena Stent was determined based on the results of necessary stability studies in accordance with the "Handling of stability studies for determining the shelf life in the application for marketing approvals (certifications) for medical devices (in Japanese)" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012). The Zilver Vena Stent conforms to Article 4.

5) PMDA's view on the conformity to Article 7, which specifies requirements for the chemical properties, biological safety, etc. of medical devices:
As described earlier in Section "2.(3).B Outline of the review conducted by PMDA," the Justification of the biological safety etc. of the Zilver Vena Stent were confirmed. The Zilver Vena Stent conforms to Article 7.

6) PMDA's view on the conformity to Article 8, which specifies anti-microorganism contamination measures for medical devices:
As described later in Section "5.B Outline of the review conducted by PMDA," the anti-microorganism contamination measures for the Zilver Vena Stent were shown to be valid. The Zilver Vena Stent conforms to Article 8.

7) PMDA's view on the conformity to Article 17, which specifies requirements for publicizing information including precautionary advice or the communication of information to users via instructions for use, etc. (the Information on Precautions etc.):
As described later in Section "6.B Outline of the review conducted by PMDA" and Section "7.B Outline of the review conducted by PMDA," users must understand the risk of the Zilver Vena Stent, select eligible patients for the treatment, and adhere to the guidelines for proper use to balance the risk and benefit. To this end, the applicant needs to provide information through the Information on Precautions etc., the guidelines for proper use, training, etc. PMDA instructed the applicant to communicate to users the importance of adherence to the guidelines for proper use, which define requirements for patients, users, and medical institutions providing the treatment, training, etc., via the Information on Precautions etc.

PMDA comprehensively reviewed the conformity of the Zilver Vena Stent to the Essential Principles and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, risk management system and implementation for the Zilver Vena Stent in accordance with ISO 14971:2019 "Medical devices – Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management taking into account the discussion presented earlier in Section "3.B Outline of the review conducted by PMDA" and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the sterilization method for the Zilver Vena Stent (sterilization validation, ethylene oxide sterilization residuals, and bacterial endotoxins).

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process of the Zilver Vena Stent and concluded that there was no particular problem in the submitted data.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

6.A Summary of the data submitted

The applicant submitted the results of the VIVO study that was conducted to evaluate the efficacy and safety of the Zilver Vena Stent.

The VIVO study (Studied period, December 13, 2013 to November 20, 2019)

6.A.1) Methodology

As shown in Table 4, the VIVO study was a prospective, multi-center, single-arm clinical study conducted at 29 sites in the US and 1 study site in Taiwan to evaluate the efficacy and safety of the Zilver Vena Stent in the treatment of symptomatic iliofemoral venous outflow obstruction.

Table 4. Outline of the VIVO study

Item	Outline
Type of the study	Prospective, multi-center, single-arm clinical study
Study population	Patients with symptomatic iliofemoral venous outflow obstruction in 1 iliofemoral venous segment (Clinical manifestation–Etiologic–Anatomic distribution-Pathophysiologic [CEAP] C [clinical] classification ≥3, or VCSS pain score ≥2)

Key inclusion criteria	• Symptomatic venous outflow obstruction in 1 iliofemoral venous segment (i.e., 1 limb) per patient,
	  • CEAP C classification ≥3, or
	  • VCSS pain score ≥2
	• No stenting scheduled for the target lesion with other than the study device

Key exclusion criteria	General exclusion criteria • History of bleeding diathesis, uncorrectable hypercoagulopathy (hypercoagulopathy that cannot be adequately managed with medication), or refusal of blood transfusions • Known hypersensitivity or contraindication to antiplatelet and/or anticoagulant therapy, nitinol, or contrast medium and that cannot be adequately pre-medicated • Surgical or interventional procedures of the target limb (except for thrombolysis or thrombectomy in preparation for the investigational procedure, or inferior vena cava filter placement before stenting for patients at high risk of pulmonary embolism) ≤30 days before stenting or planned surgical or interventional procedures of the target limb at any time after stenting • Surgical or interventional procedures for other medical conditions (not associated with the target limb) ≤30 days before stenting or planned surgical or interventional procedures ≤30 days after stenting • Complications of arterial or venous access site in the legs ≤30 days before stenting • Lesions extending into the inferior vena cava or below level of lesser trochanter • Severe obstruction (>20%) or occlusion of inflow or outflow tract (ipsilateral tibial, popliteal, or femoral veins or inferior vena cava); if thrombus is treated by thrombolysis or thrombectomy before stenting the target lesion, the treatment must have resulted in <20% residual stenosis/obstruction. • Lesion with malignant obstruction • Symptomatic pulmonary embolism ≤30 days before stenting • Previous stenting of target vessel • Lesion located within or beyond a bypass graft • Total venous occlusion that cannot be dilated to allow for passage of the delivery system or wire guide Exclusion criteria based on venographic results • Iliofemoral venous segment unsuitable for treatment with available sizes of the study device
Sample size	243
Follow-up period	Immediately after the procedure, 30 days, 6 and 12 months, and 2 and 3 years post-procedure Primary safety endpoint, 30 days post-procedure Primary efficacy endpoint, 12 months post-procedure
Primary endpoints	Efficacy: the rate of 12-Month primary quantitative patency Definition of primary quantitative patency: A treated venous segment continuously retaining a minimum lumen diameter (MLD) that is >50% of the immediately post-stenting MLD since the index procedure (uninterrupted or intervention-free) as demonstrated by core lab-assessed venography. Primary quantitative patency failures are defined as meeting any of the conditions below: • Loss of quantitative patency • Occlusion of treated segment • Surgical bypass of treated segment • Amputation of the extremity because of venous outflow occlusion Safety: the rate of 30-Day freedom from major adverse events Definition of major adverse events: Procedural bleeding requiring transfusion, procedure- or device-related death, clinically driven target lesion reintervention, clinical migration (movement of a stent requiring surgical or endovascular intervention), new symptomatic pulmonary embolism, or procedure-related perforation requiring open surgical repair, or flow-limiting dissection of the target vessel
Secondary endpoint	Change in VCSS from baseline to 1 and 12 months post-procedure
Other endpoints	Procedural success, procedure-related adverse events (e.g., bleeding, death, perforation requiring surgery), post-procedural clinically driven reintervention of stented venous segment; stent migration, and changes in clinical symptoms from baseline (VCSS, Venous Disability Score [VDS], Chronic Venous Insufficiency Questionnaire [CIVIQ]-20 score, and CEAP C classification)

The primary efficacy endpoint of the VIVO study was the "12-month primary quantitative patency rate." Primary quantitative patency was defined as a treated venous segment continuously retaining a minimum lumen diameter (MLD) that is >50% of the immediate post-stenting MLD since the index procedure (uninterrupted or intervention-free) as demonstrated by core lab-assessed venography. Primary quantitative patency failure was defined as any one of the conditions including loss of quantitative patency, occlusion of treated segment, surgical bypass of treated segment, and amputation of the extremity because of venous outflow occlusion. The performance goal of the primary efficacy endpoint was determined based on 39 literature reports on the treatment outcomes with arterial or biliary stents in the treatment of symptomatic iliofemoral venous outflow obstruction, which were extracted by exhaustive search of literature reports published between 2000 and 2014. The performance goal was determined regardless of whether the data pertained to acute- or chronic-phase patients because there was no statistical difference in treatment outcomes between these phases. The 12-month primary quantitative patency rate was calculated to be 86%. With a margin of 10%, the performance goal of the primary efficacy endpoint was determined as 76%.

The primary safety endpoint was "30-day freedom from major adverse event (MAE) rate." As with the primary efficacy endpoint, the performance goal was determined based on literature data. The weighted average of freedom from MAE rate was calculated to be 97% based on 95% in patients in the acute phase and 98% in patients in the chronic phase. With a margin of 10%, the performance goal of the primary safety endpoint was determined as 87%.

A total of 218 subjects were needed to verify the efficacy hypothesis of the "12-month primary quantitative patency rate of 76%" and the safety hypothesis of the "30-day freedom from MAE rate of 87%," with a one-sided significance level of 0.025 and a power of 90%. Allowing for 10% dropout, 243 subjects were enrolled. The protocol specified the use of the data from the intent-to treat (ITT) population consisting of all 243 subjects for the analysis (Table 5).

Table 5. Disposition of subjects in the VIVO study (ITT population)

Follow-up	Number of follow-up subjects	Percentage of subjects with eligible data			Reason for follow-up failure			
		Clinical*2 evaluation	Venography	Ultrasonography*3	Death	Loss to follow-up	Dropout	Others
Baseline*1	243	100% (243/243)	-	-	0	0	0	0
Peri-procedure	243	-	100% (243/243)	97.5% (237/243)	0	2	0	0
1 month	241	98.8% (238/241)	-	-	0	1	0	0
6 months	236	94.5% (223/236)	-	-	0	4	3	1*5
12 months	228	92.5% (211/228)	86.0%*4 (196/228)	89.5% (204/228)	1	7	9	0
2 years	211	94.3% (199/211)	-	94.3% (199/211)	3	3	7	0
3 years	198	94.9% (188/198)	-	94.4% (187/198)	0	4	4	2*6

*1 A total of 351 patients provided consent, including 108 patients who failed screening.
*2 VCSS, VDS, and CEAP C classification were determined in 243 subjects at baseline, and 233 subjects at 1 month post-procedure, 216 subjects at 6 months post-procedure, 202 subjects at 12 months post-procedure, 190 subjects at 2 years post-procedure, and 173 subjects at 3 years post-procedure. CIVIQ-20 was assessed in 236 subjects at baseline, and 210 subjects at 1 month post-procedure, 192 subjects at 6 months post-procedure, 170 subjects at 12 months post-procedure, 157 subjects at 2 years post-procedure, and 134 subjects at 3 years post-procedure.
*3 A total of 231 subjects during procedure, 178 subjects at 12 months post-procedure, 158 subjects at 2 years post-procedure, and 83 subjects at 3 years post-procedure had necessary data for patency assessment. The patency rate was evaluable.
*4 Venographic data of 7 subjects were not collected within the specified time frame and excluded from the primary efficacy analysis.
*5 The subject underwent surgical removal of the stent after stent migration.
*6 One subject completed all of the required imaging procedures at 3 years but did not complete the final clinical evaluation. The other subject was hospitalized because of stroke and did not complete the requirements for the 3-year follow-up.

Originally, the study was designed with 70% patients in the acute phase and 30% patients in the chronic phase based on the literature reports. However, the design was changed during the patient enrollment period so that study participants would consist of approximately 30% patients in the acute phase and 70% patients in the chronic phase, based on the latest literature review results and the input from physicians that stent therapy is required more frequently among patients in the chronic phase than those in the acute phase. An additional analysis was performed in the subjects of the VIVO study grouped into "the acute DVT group," "the PTS group," and "the nonthrombotic iliac vein lesions (NIVL) group." For this additional analysis, the groups were defined as follows based on the subject's baseline information:

- Acute DVT group: "Current or previous DVT" and "acute thrombosis (≤30 days)"
- PTS group: "Current or previous DVT" and "chronic thrombosis/post thrombotic syndrome (>30 days)" or "acute thrombosis + chronic thrombosis/post thrombotic syndrome"
- NIVL group: "No DVT" and no thrombosis as confirmed by baseline lesion morphology at the study site

6.A.2) Patient characteristics

For the VIVO study, Table 6 presents patient characteristics, Table 7 baseline lesion characteristics, Table 8 stent sizes used in the study, and Table 9 the details of the index procedure.

Table 6. Patient characteristics

Patient characteristics	Percentage of subjects (number of subjects/total number of subjects) or mean ± standard deviation (SD)			
	ITT population (N = 243)	Acute DVT (N = 59)	PTS (N = 105)	NIVL (N = 79)
Age (years)	53.0 ± 15.3	52.5 ± 15.2	52.0 ± 15.7	54.7 ± 14.9
BMI	31.3 ± 8.5	32.5 ± 9.7	31.5 ± 8.4	30.2 ± 7.8
Sex				
Male	30.0% (73/243)	28.8% (17/59)	27.6% (29/105)	34.2% (27/79)
Female	70.0% (170/243)	71.2% (42/59)	72.4% (76/105)	65.8% (52/79)
Race				
Caucasian	81.5% (198/243)	83.1% (49/59)	86.7% (91/105)	73.4% (58/79)
Black	11.9% (29/243)	13.6% (8/59)	11.4% (12/105)	11.4% (9/79)
Asian	3.3% (8/243)	3.4% (2/59)	1.9% (2/105)	3.8% (3/79)
Hispanic/Latin	2.9% (7/243)	0% (0/59)	0% (0/105)	10.1% (8/79)
Indigenous/Caucasian	0.4% (1/243)	0% (0/59)	0% (0/105)	1.3% (1/79)
VCSS*[1]	8.0 ± 4.2	6.9 ± 2.8	8.1 ± 4.4	8.5 ± 4.8
VDS*[2]				
0	5.3% (13/243)	5.1% (3/59)	4.8% (5/105)	6.3% (5/79)
1	28.0% (68/243)	32.2% (19/59)	25.7% (27/105)	27.8% (22/79)
2	41.6% (101/243)	16.9% (10/59)	49.5% (52/105)	49.4% (39/79)
3	25.1% (61/243)	45.8% (27/59)	20.0% (21/105)	16.5% (13/79)
CEAP C classification*[3]				
C0	0.4% (1/243)	0% (0/59)	1.0% (1/105)	0% (0/79)
C1	0.8% (2/243)	1.7% (1/59)	0% (0/105)	1.3% (1/79)
C2	3.3% (8/243)	0% (0/59)	1.9% (2/105)	7.6% (6/79)
C3	66.7% (162/243)	84.7% (50/59)	70.5% (74/105)	48.1% (38/79)
C4a	16.9% (41/243)	11.9% (7/59)	14.3% (15/105)	24.1% (19/79)
C4b	3.7% (9/243)	1.7% (1/59)	3.8% (4/105)	5.1% (4/79)
C5	2.9% (7/243)	0% (0/59)	3.8% (4/105)	3.8% (3/79)
C6	5.3% (13/243)	0% (0/59)	4.8% (5/105)	10.1% (8/79)
CIVIQ-20*[4]	44.6 ± 23.5	51.7 ± 21.3	43.0 ± 23.3	41.3 ± 24.5

*1 VCSS: "Pain," "location of varicose vein," "venous edema," "pigmentation," "inflammation," "induration," "number of active ulcers," "active ulcer duration," "active ulcer size," and "use of compression therapy" are scored by severity (0 = none, 1 = mild, 2 = moderate, 3 = severe) and totaled (the highest score, 30).

*2 VDS: 0 = asymptomatic, 1 = symptomatic but able to perform daily activities without compression therapy, 2 = able to perform daily activities only with compression and/or limb elevation, 3 = unable to perform daily activities even with compression and/or limb elevation.

*3 CEAP C classification: C0 = no sign of disease, C1 = reticular or telangiectasia varicose veins, C2 = varicose veins, C3 = edema, C4a = eczema, C4b = lipodermatosclerosis, C5 = healed ulcers, C6 = active ulcers

*4 CIVIQ-20: A self-administered questionnaire form consisting of 20 items. Items in each of the pain, physical, psychological, and social domains are answered on a 5-point scale (the highest score, 100). The figures are based on data from 236 subjects in the ITT population, 57 subjects in the acute DVT group, 103 subjects in the PTS group, and 76 subjects in the NIVL group.

Table 7. Baseline lesion characteristics (core lab assessment)

Lesion characteristics	Percentage of subjects (number of subjects/total number of subjects) or mean ± SD			
	ITT population (N = 243)	Acute DVT (N = 59)	PTS (N = 105)	NIVL (N = 79)
Target lesion				
Left	86.0% (209/243)	93.2% (55/59)	81.9% (86/105)	86.1% (68/79)
Right	14.0% (34/243)	6.8% (4/59)	18.1% (19/105)	13.9% (11/79)
Target lesion*1				
Common iliac vein	88.1% (214/243)	91.5% (54/59)	86.7% (91/105)	87.3% (69/79)
External iliac vein	51.9% (126/243)	45.8% (27/59)	75.2% (79/105)	25.3% (20/79)
Common femoral vein	22.6% (55/243)	20.3% (12/59)	38.1% (40/105)	3.8% (3/79)
Femoral vein	2.1% (5/243)	3.4% (2/59)	2.9% (3/105)	0% (0/79)
Lesion extending into the inferior vena cava	2.9% (7/243)	3.4% (2/59)	3.8% (4/105)	1.3% (1/79)
Lesion extending below level of the lesser trochanter	4.6% (11/238)	6.8% (4/59)	6.7% (7/104)	0% (0/75)
Lesion length (mm)*2	98.6 ± 69.8	91.7 ± 62.3	126.3 ± 75.1	64.8 ± 48.8
Presence of thrombus (baseline)	40.0% (96/240)	67.8% (40/59)	51.4% (54/105)	2.6% (2/76)
Total obstruction	22.3% (52/233)	21.1% (12/57)	38.8% (40/103)	0% (0/73)

*1 The number of lesion locations totaled more than the total number of subjects enrolled due to some lesions involving multiple veins.
*2 The figures are based on data from 232 subjects in the ITT population, 56 subjects in the acute DVT group, 103 subjects in the PTS group, and 73 subjects in the NIVL group.

Table 8. Stent sizes used in the study

Diameter (mm)	Length (mm)			
	40	60	100	140
10	0	1	0	0
12	0	1	0	0
14		28	61	63
16		32	111	68

Table 9. Details of index procedure

Characteristics	Percentage of subjects (number of subjects/total number of subjects) or mean ± SD (number of subjects, range)		
Pre-dilatation			
Pre-dilatation performed	64.6% (157/243)		
Mean maximum pressure in each subject (atm)	10.2 ± 4.8 (152, 2-24)		
Post-dilatation			
Post-dilatation performed	96.7% (235/243)		
Mean maximum pressure in each subject (atm)	9.9 ± 4.5 (226, 3-30)		
Additional procedure	Timing of additional procedure Percentage (number of subjects/total number of subjects undergoing additional procedure)		
	Pre-stenting	Post-stenting	Pre- and post-stenting
Thrombolysis	31.7% (33/104)	0% (0/15)	20.0% (1/5)
Thrombectomy	12.5% (13/104)	40.0% (6/15)	0% (0/5)
Thrombolysis + thrombectomy	32.7% (34/104)	0% (0/15)	60.0% (3/5)
IVC filter placement	9.6% (10/104)	6.7% (1/15)	0% (0/5)
Others*	13.5% (14/104)	53.3% (8/15)	20.0% (1/5)

* Other additional procedures were mainly angioplasty/venous angioplasty, including placement of stents other than the study device, right cervical vein access used to assist balloon removal, and inferior vena cava (IVC) filter placement.

6.A.3) Study results

6.A.3).(a) Primary efficacy endpoint

Of the 243 subjects enrolled in the study, 189 subjects with venographic primary quantitative patency outcome data available (venographic data immediately after the procedure and 12 months post-procedure) were included in the analysis of the primary efficacy endpoint of the "12-month primary quantitative patency rate." A total of 54 subjects had no venographic primary patency data available at 12 months (320-410 days) post-procedure (Table 10).

Table 10. Reasons for missing venographic primary quantitative patency data

Reasons for missing venographic primary quantitative patency data	N = 54
Failure to return for 12-month follow-up	30*1
No venography at 12 months	10
Target lesion required reintervention within 12 months post-procedure despite quantitative patency >50%	6
Venographic data not within the acceptable time frame of 12-month follow-up	4
Missing MLD measurements at baseline or 12-months	3
Technical failure	1*2

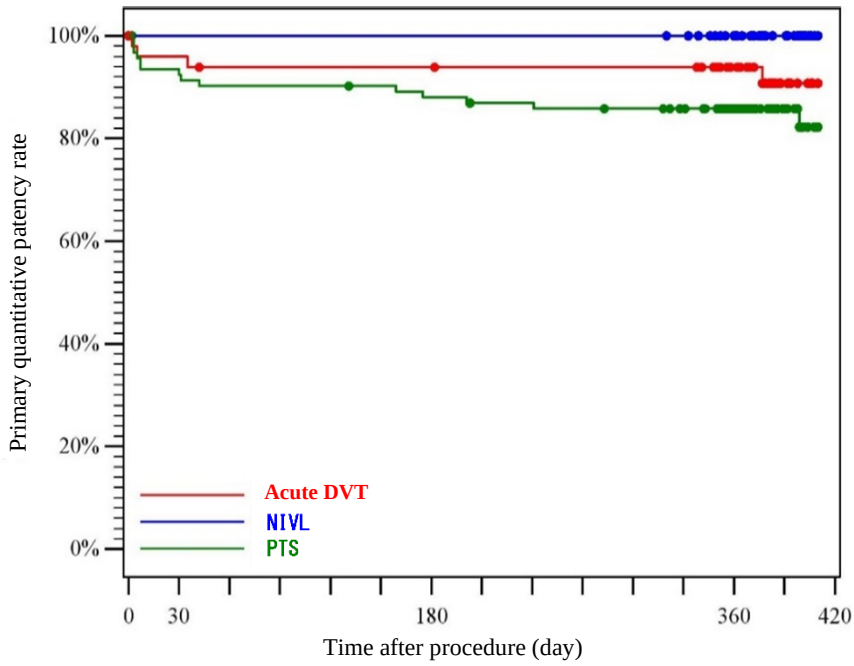
*1 Four of them visited the study site afterward for long-term follow-up.
*2 The subject was excluded from the analysis because the stent was placed in a collateral vessel.

The primary efficacy endpoint of the "12-month primary quantitative patency rate," calculated following protocol-specified multiple imputation for missing primary efficacy outcome data, was 89.9% (95% CI, 85.1%, 93.4%). The lower limit of the 95% confidence interval was 85.1%, which is greater than the protocol-defined performance goal of 76% ($P < 0.0001$). The 12-month primary quantitative patency rate in the 189 subjects in the analyzable population alone was 89.9% (170 of 189 subjects; 95% CI, 84.7%, 93.8%), which is greater than the protocol-defined performance goal of 76% ($P < 0.0001$) (Table 11). The 12-month primary quantitative patency rate in the acute DVT group, the PTS group, and the NIVL group was 93.9%, 85.8%, and 100%, respectively, suggesting that it tended to exceed the performance goal of 76% (Figure 3). The primary endpoint in the acute DVT group, the PTS group, and the NIVL group in the analyzable population was 89.1% (41 of 46 subjects), 83.1% (69 of 83 subjects), and 100% (60 of 60 subjects), respectively. A total of 19 subjects failed to achieve the primary efficacy endpoint. For all of them, the reason for the failure was occlusion or stenosis of the treated segment. These subjects underwent reintervention (thrombectomy, thrombolysis, balloon angioplasty, and/or stent placement) as necessary (Table 12). The mean MLD of veins with the Zilver Vena Stent implanted was 5.9 ± 5.1 mm (n = 188) at baseline, 11.6 ± 3.3 mm (n = 189) immediately after the procedure, and 10.4 ± 3.6 mm (n = 183) at 12 months post-procedure, indicating that the venous lumen diameter was maintained.

Table 11. Twelve-month primary quantitative patency rate

Endpoint	ITT population*1 (N = 243)	Analyzable population*2 (N = 189)
12-Month primary quantitative patency rate	89.9%	89.9% (170/189)
95% CI, *P*- value	85.1%-93.4%, < 0.0001	84.7%-93.8%, < 0.0001

*1 All enrolled subjects
*2 Subjects whose venographic data immediately after the procedure and at 12 months post-procedure are available



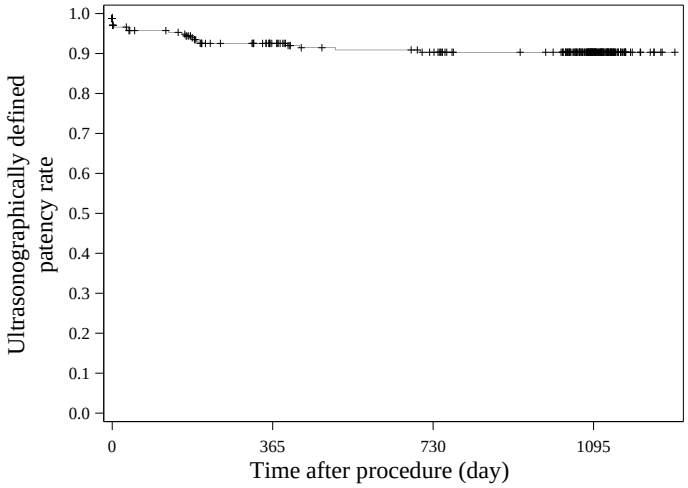
Time after procedure (day)	Acute DVT			PTS			NIVL		
		Number at risk	Cumulative number of events		Number at risk	Cumulative number of events		Number at risk	Cumulative number of events
0	100%	49	0	100%	93	0	100%	60	0
365	93.9% ± 3.4%	34	3	85.8% ± 3.6%	51	13	100%	47	0
410	90.7% ± 5.2%	0	4	82.2% ± 6.9%	0	14	100%	0	0

Figure 3. Twelve-month primary quantitative patency rate by disease type

Table 12. List of subjects who did not achieve the primary efficacy endpoint

	Reason	Adjudication by CEC	Treatment
PTS			
1	Obstruction	Procedure-related Technique-related	Thrombectomy, thrombolysis, balloon angioplasty, and stenting
2	Obstruction	Not performed*[1]	No treatment
3	Obstruction	Procedure-related	Thrombolysis, thrombectomy, balloon angioplasty, and stenting
4	Stenosis	Related to target vessel failure and revascularization of the target lesion	Balloon angioplasty
5	Obstruction	Not performed*[2]	No treatment
6	Obstruction	Related to target vessel failure and revascularization of the target lesion	Balloon angioplasty, stenting, and thrombectomy
7	Obstruction	Procedure-related	Thrombolysis, thrombectomy, balloon angioplasty, and stenting
8	Obstruction	Procedure-related Related to target vessel failure and revascularization of the target lesion	Thrombectomy and thrombolysis
9	Obstruction	Technique-related	Endovascular treatment (failure to insert a cannula into the occluded iliac venous stent)
10	Obstruction	Procedure-related Related to target vessel failure and revascularization of the target lesion	Thrombectomy, thrombolysis, balloon angioplasty, and stenting
11	Obstruction	Related to target vessel failure and revascularization of the target lesion	Balloon angioplasty and thrombolysis
12	Stenosis	Technique-related Related to target vessel failure and revascularization of the target lesion Related to medication that was allowed to be used	Balloon angioplasty and thrombolysis
13	Obstruction	Procedure-related Related to target vessel failure and revascularization of the target lesion	Balloon angioplasty, thrombectomy, and thrombolysis
14	Obstruction	Related to target vessel failure and revascularization of the target lesion	Thrombectomy, thrombolysis, balloon angioplasty, and stenting
Acute DVT			
15	Obstruction	Adjunct therapy-related	Thrombectomy and thrombolysis
16	Obstruction	Related to target vessel failure and revascularization of the target lesion	Thrombectomy, thrombolysis, and balloon angioplasty
17	Stenosis	Procedure-related Related to target vessel failure and revascularization of the target lesion	Balloon angioplasty
18	Obstruction	Not performed*[3]	No treatment (concurrent disease present)
19	Obstruction	Related to target vessel failure and revascularization of the target lesion	Balloon angioplasty, stenting, thrombectomy, and thrombolysis

*1 The investigator assessed that the occlusion was related to May-Thurner syndrome but not related to the study device or procedure.
*2 The investigator assessed that the occlusion was possibly related to the study device and procedure, and previous May-Thurner syndrome.
*3 The investigator assessed that the occlusion was unlikely related to the study device or procedure but related to the underlying disease.



Time after procedure (day)	ITT population	Number at risk	Cumulative number of events
0	98.8% ± 0.7%	231	3
365	92.5% ± 1.8%	178	17
730	90.3% ± 2.2%	158	21
1095	90.3% ± 2.2%	83	21

Figure 4. Three-Year patency rate (ultrasonography)

The Kaplan-Meier estimate for the 3-year ultrasonographically defined patency rate[i] was 92.5% at 365 days and 90.3% at 1095 days (Figure 4).

6.A.3).(b) Secondary endpoint

For the secondary endpoint of the "change in VCSS from baseline to 1 and 12 months post-procedure," the secondary hypothesis at 1 and 12 months post-procedure was tested by paired t-test (null hypothesis, the change in VCSS at a specific time point relative to baseline in subjects treated with the Zilver Vena Stent is not significantly different from 0). The mean VCSS was 8.0 ± 4.2 at baseline. The mean change in VCSS from baseline (negative values denoting improvement) was −3.0 (95% CI, −3.5, −2.6) at 1 month and −4.2 (95% CI, −4.7, −3.7) at 12 months ($P < 0.0001$ for both) (Table 13). The null hypothesis for 1 and 12 months post-procedure was rejected. Improvement in clinical symptoms was maintained through 3 years post-procedure.

Table 13. Changes in VCSS from baseline

Evaluation point	N	Mean change (95% CI)	*P*-value*
Baseline	243	–	
1 month	233	−3.0 (−3.5, −2.6)	< 0.0001
6 months	216	−3.8 (−4.3, −3.3)	< 0.0001
12 months	202	−4.2 (−4.7, −3.7)	< 0.0001
2 years	190	−4.2 (−4.8, −3.7)	< 0.0001
3 years	173	−4.1 (−4.6, −3.5)	< 0.0001

* The *P*-values at 1 and 12 months post-procedure were adjusted for multiple comparisons using the Holm' procedure in accordance with the protocol. The *P*-values at 6 months, and 2 and 3 years post-procedure were not adjusted for multiple comparisons.

[i] Absence of blood flow in the target lesion, in the segment proximal or distal to the target lesion in ultrasonogram was defined as no ultrasonographically-defined patency.

6.A.3).(c) Other endpoints

Figures 5 to 7 present the results of VDS, CEAP C classification, and CIVIQ-20, showing that improvement in clinical symptoms tended to be maintained through 3 years post-procedure as with VCSS.

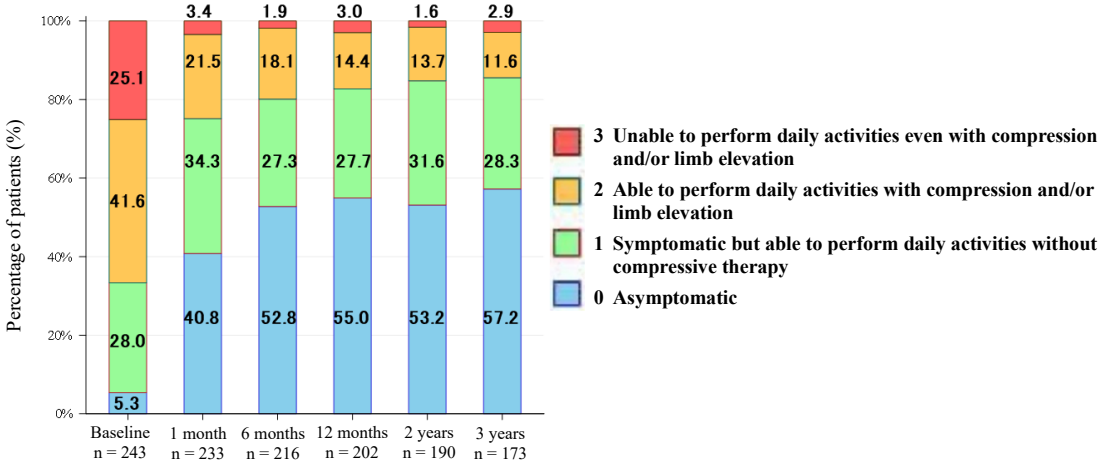


Figure 5. VDS through 3 years post-procedure

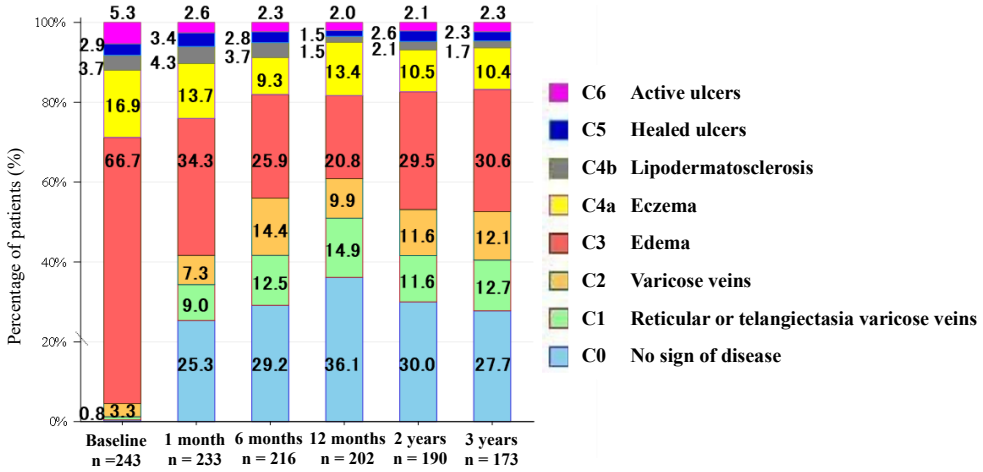


Figure 6. CEAP C classification through 3 years post-procedure

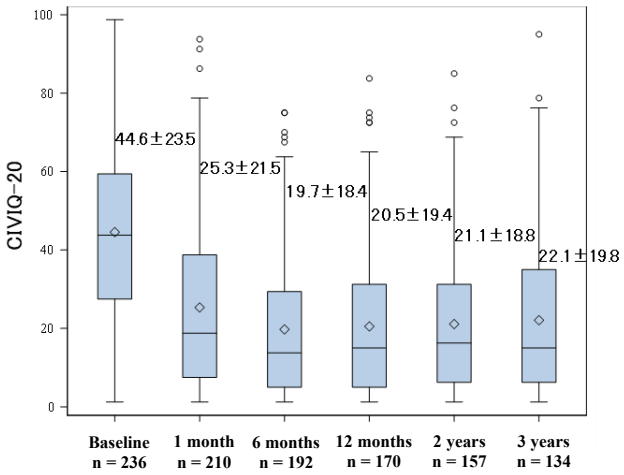


Figure 7. CIVIQ-20 scores through 3 years post-procedure

6.A.3).(d) Primary safety endpoint

The primary safety endpoint of the "30-day freedom from MAE rate" was 96.7% (232 of 240 subjects; 95% CI, 93.5%, 98.6%). The lower limit of the 95% confidence interval (93.5%) exceeded the protocol-defined performance goal of 87% ($P < 0.0001$) (Table 14). Of the 243 subjects enrolled in the VIVO study, 2 subjects were lost to follow-up without a MAE within 30 days post-procedure (last contact, 13 and 21 days post-procedure), and 1 subject was excluded from the analysis because the stent was placed in the collateral vessel. MAEs reported at 30 days post-procedure were 7 events of "clinically driven target lesion reintervention" in 7 subjects, and 1 event of "new symptomatic pulmonary embolism" in 1 subject. The 30-day freedom from MAE rate was 94.9% (56 of 59 subjects) in the acute DVT group, 95.1% (98 of 103 subjects) in the PTS group, and 100% (78 of 78 subjects) in the NIVL group. Table 15 lists MAEs reported in 3 years post-procedure, including those in 8 subjects who did not achieve the primary safety endpoint. Subjects with new symptomatic pulmonary embolism (8 events in 7 subjects) reported in 3 years post-procedure were discharged from the study sites after medical therapy, except for 1 subject who received thrombolysis.

Table 14. Thirty-day freedom from MAE rate

Endpoint	N = 240
30-Day freedom from MAE rate	96.7% (232/240)
95% accurate CI, *P*-value	93.5%-98.6%, < 0.0001
- Clinically driven target lesion reintervention	2.9% (7/240)
- New symptomatic pulmonary embolism	0.4% (1/240)
- Clinical migration	0.0% (0/240)
- Procedural bleeding requiring transfusion	0.0% (0/240)
- Procedure- or device-related death	0.0% (0/240)
- Procedure-related perforation requiring open surgical repair	0.0% (0/240)
- Flow-limiting dissection of the target vessel	0.0% (0/240)

Table 15. Causes and outcomes of MAEs reported in 3 years post-procedure

	Onset day	MAE	Adjudication by CEC	Treatment	Outcome
Acute DVT					
1	2	Clinically driven target lesion reintervention	Related to target vessel failure and revascularization of the target lesion	Thrombectomy, thrombolysis, and balloon angioplasty	The blood flow in the collateral vessel was not assessed. The stented segment was revascularized.
2	5	Clinically driven target lesion reintervention	Related to target vessel failure and revascularization of the target lesion	Balloon angioplasty, stenting, thrombectomy, and thrombolysis	The blood flow in the collateral vessel was reduced. The stented segment was revascularized.
3	30	New symptomatic pulmonary embolism (low-risk pulmonary embolism)	Adjunct therapy-related (baseline INR, 0) Related to no optimal anticoagulant therapy given	No treatment	The MAE resolved.
4	384	Clinically driven target lesion reintervention	Related to the procedure, target vessel failure, and revascularization of the target lesion	Balloon angioplasty	The blood flow in the collateral vessel was reduced. The stented segment was revascularized.
5	508	Clinically driven target lesion reintervention	Related to the procedure, target vessel failure, and revascularization of the target lesion	Balloon angioplasty, thrombectomy, and thrombolysis	The blood flow in the collateral vessel was reduced. The stented segment was revascularized.

6	518	New symptomatic pulmonary embolism (low-risk pulmonary embolism)	Unrelated to the device or procedure. Related to previous DVT at enrollment	Medical therapy Switching of drug	Discharged
	1,051	New symptomatic pulmonary embolism (low-risk pulmonary embolism)	Related to trauma or discontinuation of anticoagulant therapy	Medical therapy Switching of drug	Discharged
PTS					
7	2	Clinically driven target lesion reintervention	Procedure-related	Thrombolysis, thrombectomy, and balloon angioplasty	The blood flow in the collateral vessel was not assessed. The stented segment was revascularized.
	830	New symptomatic pulmonary embolism (low-risk pulmonary embolism)	Unrelated to the device or procedure. Related to the underlying disease	Medical therapy Switching to apixaban after drip infusion of heparin	Discharged
8	3	Clinically driven target lesion reintervention	Related to procedure and technique (severe stenosis in the common femoral vein left untreated at the initial treatment)	Thrombectomy, thrombolysis, balloon angioplasty, and stenting	The blood flow in the collateral vessel was reduced. The stented segment was revascularized.
9	7	Clinically driven target lesion reintervention	Technique-related. Related to target vessel failure and revascularization of the target lesion. Related to medication required by the protocol	Balloon angioplasty and thrombolysis	The blood flow in the collateral vessel was reduced. The stented segment was revascularized.
10	7	Clinically driven target lesion reintervention	Related to the procedure, target vessel failure, and revascularization of the target lesion	Balloon angioplasty, thrombectomy, and thrombolysis	The blood flow in the collateral vessel was not reduced, but the stented segment was revascularized.
11	30	Clinically driven target lesion reintervention	Related to target vessel failure and revascularization of the target lesion	Thrombectomy, thrombolysis, balloon angioplasty, and stenting	The blood flow in the collateral vessel was reduced. The stented segment was revascularized.
12	31	Clinically driven target lesion reintervention	Procedure-related (obstruction already suspected at 1 day post-procedure)	Balloon angioplasty, stenting, thrombectomy, and thrombolysis	The blood flow in the collateral vessel was reduced. The stented segment was revascularized.
13	157	New symptomatic pulmonary embolism (low-risk pulmonary embolism)	Procedure-related (related to stent thrombosis, a history of factor V Leiden deficiency, which is a risk factor)	Medical therapy Systemic anticoagulant therapy	Discharged
	159	Clinically driven target lesion reintervention	Related to the procedure, target vessel failure, and revascularization of the target lesion	Thrombectomy and thrombolysis failed and were followed by venous intimal excision, patch formation of the left CFV, balloon angioplasty, stenting, and thrombectomy on 245 days post-procedure.	The blood flow in the collateral vessel was reduced. The stented segment was revascularized.
14	175	Clinically driven target lesion reintervention	Technique-related	Unsuccessful cannulation of the occluded stent	Unsuccessful
15	420	Clinically driven target lesion reintervention	Related to target vessel failure and revascularization of the target lesion	Balloon angioplasty, thrombectomy, and thrombolysis	The blood flow in the collateral vessel was reduced. The stented

					segment was revascularized.
16	441	Clinically driven target lesion reintervention	Related to the procedure, target vessel failure, and revascularization of the target lesion	Balloon angioplasty	The blood flow in the collateral vessel was reduced. The stented segment was revascularized.
17	473	Clinically driven target lesion reintervention	Related to the procedure, target vessel failure (responsible lesions proximal and distal to the target lesion), and revascularization of the target lesion	Balloon angioplasty, stenting, and thrombolysis	The blood flow in the collateral vessel was not reduced, but the stented segment was revascularized.
18	887	New symptomatic pulmonary embolism (low-risk pulmonary embolism)	Unrelated to the device or procedure. Related to the underlying disease	Medical therapy Switching of drug	Discharged
19	890	New symptomatic pulmonary embolism (low-risk pulmonary embolism)	Unrelated to the device or procedure. Related to the underlying disease	Medical therapy Switching to Lovenox and Xarelto	Discharged
20	971	Clinically driven target lesion reintervention	Target vessel failure	Recanalization of the target lesion was attempted but failed to recanalize the occluded segment.	Unsuccessful
21	980	New symptomatic pulmonary embolism (sub-massive pulmonary embolism)	Unrelated to the device or procedure. Related to the underlying disease	Thrombolysis	Discharged
22	1,090	New symptomatic pulmonary embolism (low-risk pulmonary embolism)	Unrelated to the device or procedure. Related to previous DVT at enrollment	Medical therapy Switching of drug	Discharged
NIVL					
23	218	Clinical migration	Technique-related	Hospitalization for sternotomy and stent removal through the pulmonary artery under extracorporeal circulation. The stent removal failed. Re-hospitalization for thoracotomy to remove the stent that had migrated from the pulmonary artery	Successful stent removal

During the 3-year follow-up, a total of 796 adverse events occurred in 204 subjects in the ITT population, including 279 serious adverse events in 109 subjects. A total of 29 serious procedure- or device-related adverse events occurred in 22 subjects in the ITT population (Table 16).

Table 16. Serious device- and/or procedure-related* adverse events in 3 years post-procedure

Event	Number of subjects with event				Number of events	Incidence (N = 243)
	0-30 days (N = 243)	31-365 days (N = 241)	366-730 days (N = 220)	>730 days (N = 207)		
Pulmonary embolism	0% (0/243)	0.4% (1/241)	0% (0/220)	0.5% (1/207)	2	0.8% (2/243)
Obstruction	2.5% (6/243)	1.2% (3/241)	0.5% (1/220)	0% (0/207)	11	4.1% (10/243)
Restenosis	0% (0/243)	1.2% (3/241)	0.5% (1/220)	0.5% (1/207)	6	1.6% (4/243)
Hemorrhage associated with anticoagulant therapy/ antiplatelet therapy	0.4% (1/243)	0% (0/241)	0% (0/220)	0% (0/207)	1	0.4% (1/243)
Deteriorated pain of the target limb	0% (0/243)	0% (0/241)	0.5% (1/220)	0% (0/207)	1	0.4% (1/243)
Multistage regressive changes	0% (0/243)	0.4% (1/241)	0% (0/220)	0% (0/207)	1	0.4% (1/243)
Pleural effusion	0% (0/243)	0.4% (1/241)	0% (0/220)	0% (0/207)	1	0.4% (1/243)
In-stent thrombus	0% (0/243)	0.8% (2/241)	0.9% (2/220)	0% (0/207)	4	1.6% (4/243)
Stent migration	0% (0/243)	0.4% (1/241)	0% (0/220)	0% (0/207)	1	0.4% (1/243)
Thrombus	0% (0/243)	0% (0/241)	0% (0/220)	0.5% (1/207)	1	0.4% (1/243)

* Study site-assessed causal relationship

Table 17 presents all deaths in 3-years post-procedure. There was no device- or procedure-related death.

Table 17. A list of deaths in 3 years post-procedure

	Date of occurrence	Cause of death	Relationship*
1	131	Sepsis	Unrelated
2	387	Acute lymphoblastic leukemia	Unrelated
3	720	Secondary neoplasm malignant in liver and intrahepatic biliary tract	Unrelated
4	772	Suicide	Unrelated
5	943	Cardio-respiratory arrest secondary to acute myeloid leukemia	Unrelated

* Clinical Events Committee (CEC)-assessed causal relationship

6.B Outline of the review conducted by PMDA

6.B.(1) Clinical positioning of the Zilver Vena Stent

The applicant's explanation about the clinical positioning of the Zilver Vena Stent:

The standard first-line therapy for symptomatic iliofemoral venous outflow obstruction is conservative therapy (e.g., lifestyle changes, anticoagulant therapy, and compression therapy) in the US and Japan. Stenting therapy is considered for persistent and/or severer symptoms. Thus there is no large difference in the clinical positioning of stent therapy between the US and Japan.

The "appropriate use criteria for chronic lower extremity venous disease" prepared by the American Venous Forum in 2020 provide more specific criteria for stent therapy in the treatment of the iliac veins. Specifically, iliofemoral venous stenting is recommended as "appropriate" treatment for CEAP C4 to C6 symptomatic iliofemoral venous outflow obstruction without superficial venous reflux, and "may be appropriate" for CEAP C3 symptomatic iliofemoral venous outflow obstruction due to venous disease and CEAP C4 to C6 symptomatic iliofemoral venous outflow obstruction with untreated superficial venous reflux.[6] In Japan, the drafting of guidelines for proper use of iliofemoral venous stents is

currently underway by the related academic societies. According to the draft guidelines, the treatment is indicated for PTS with appropriately treated superficial veins in all cases classified in CEAP C5 and C6, but eligible CEAP C3 and C4 cases are limited to symptomatic iliofemoral venous outflow obstruction presenting with persistent pain that significantly interferes with daily activities (VCSS pain score 3). Eligible cases of acute DVT are only severe DVT accompanied by arterial ischemia or DVT presenting with persistent pain that significantly interferes with daily activities even after standard therapy (VCSS pain score 3). Thus, the use criteria in Japan set more stringent conditions than those in the US. In both countries, iliofemoral venous stenting is clinically recognized as a treatment for severe cases. In Japan, patients to be treated with the Zilver Vena Stent must meet the eligibility criteria in the draft guidelines for proper use (Table 18).

Table 18. Patient eligibility criteria in the draft guidelines for proper use

PTS	• PTS (>3 months after acute DVT) classified as CEAP C6, CEAP C5 with recurrent ulcers, or CEAP C4 or C3 with persistent pain significantly interfering with daily activities (VCSS pain score 3). • Tested, diagnosed, and treated with compression therapy appropriately at medical organizations accredited for "venous compression treatment of chronic venous insufficiency," and presenting with venous hypertension as likely cause of PTS, which will be improved by compression therapy. • CEAP C3 PTS for which the possibility of pure lymphedema has been ruled out. • An appropriate inflow blood vessel existing downstream to the femoral veins. • A stenotic lesion obviously affecting the hemodynamics (e.g., iliac vein occlusion and formation of collateral circulation) as confirmed by diagnostic imaging. • Superficial veins assessed for morphology and valve incompetence, and appropriately treated.
Acute DVT	• Acute DVT and subacute DVT (within 3 months from onset) including iliac vein occlusion. • (a) Severe DVT associated with arterial ischemia (phlegmasia cerulea dolens, phlegmasia alba dolens, or venous gangrene) or (b) DVT with persistent pain significantly interfering with daily activities despite appropriate conservative therapies including anticoagulant therapy, lower limb elevation, and compression therapy (VCSS pain score 3). • An extramural compressive venous lesion interfering with a blood flow as confirmed by endovascular ultrasonography of the iliac vein after thrombolysis, or thrombus suction, destruction, or removal.

PMDA's view:

The possible causes of symptomatic iliofemoral venous outflow obstruction for which the Zilver Vena Stent is indicated are acute DVT, PTS (including chronic DVT), and NIVL.

The standard of care for symptomatic iliofemoral venous outflow obstruction caused by acute DVT are anticoagulant therapy and lower limb elevation or compression therapy. For the treatment of persistent or severe symptoms, catheter therapy such as CDT and thrombus removal (transcatheter or surgical) are the options. Non-responders to these conventional therapies who have a compressive lesion that may potentially lead to severe clinical symptoms such as pain may require the use of stents like the Zilver Vena Stent, when vascular expansion is clinically necessary. Meanwhile, for patients with PTS presenting with persistent and severe clinical symptoms such as ulcers and pain, despite being treated appropriately for superficial vein incompetence or perforator vein incompetence and undergoing compression therapy or other conservative therapies, arterial stents are used at some medical institutions to improve the venous lumen. The Zilver Vena Stent is also expected to serve the same purpose. NIVL is to be addressed similarly to acute DVT based on the comments from the Expert Discussion that cases of symptomatic iliofemoral venous outflow obstruction caused by anatomical retraction alone without

a thrombotic event are extremely rare in Japan, and that NIVL is recognized as a compressive lesion in acute DVT.

In all of these disease types, the Zilver Vena Stent is indicated for patients who do not respond to conventional therapies with a risk of serious pathological outcomes such as pulmonary embolism and venous necrosis. In view of current limited evidence about improved clinical symptoms and prevented recurrence of thrombus by stenting in patients with symptomatic iliofemoral venous outflow obstruction and about the risk of long-term placement of a metal stent in the vein, the eligibility criteria in the draft guidelines for proper use, which are more stringent than the exclusion criteria in the VIVO study (CEAP C classification ≥3, or VCSS pain score ≥2), are considered appropriate.

Taking into consideration the comments from the Expert Discussion, PMDA concluded that the Zilver Vena Stent is of clinical significance as a new treatment option for patients with severe symptomatic iliofemoral venous outflow obstruction who are poorly responding to conventional therapies, when they are selected based on their expected risk-benefit balance with stenting, as proposed in the draft guidelines for proper use.

6.B.(2) Extrapolation of the results of the VIVO study to Japanese population

The applicant's explanation about the extrapolation of the results of the VIVO study to the Japanese population:

There is no morphological difference in the iliofemoral vein between Caucasians and Japanese. The etiology of DVT is also similar between the ethnic groups, while its incidence is lower in Japanese than in Caucasians. There is no ethnic difference in the natural history of the disease after onset. For these reasons, the ethnic differences are unlikely to affect safety and efficacy evaluation of the Zilver Vena Stent.

The VIVO study included subjects who had undergone thrombolysis, thrombectomy, or both as additional procedure before and after stenting (Table 9). Although no device has been approved for use in mechanical thrombectomy in Japan, the fact remains that stenting is performed after thrombectomy for the treatment of acute DVT, and such difference in medical environment between Japan and the foreign countries will not affect the safety and efficacy of the Zilver Vena Stent.

Anticoagulant therapy, according to the Japanese guidelines,[1] "should be continued or discontinued during the extended treatment phase, i.e., 3 to 6 months following the acute phase, depending on the patient's risk and symptoms." This recommendation is consistent with the criteria for anticoagulant therapy in the VIVO study, thus the data from subjects who underwent anticoagulant therapy in the study can be extrapolated to the Japanese population. The use of antiplatelets, namely, aspirin and clopidogrel, after endovascular treatment of the coronary and peripheral arteries is also practiced in Japan. Thus the extrapolation of data pertaining to the use of antiplatelets is possible.[7]

PMDA's view:

The target population of the Zilver Vena Stent in Japan is considered small. In light of the product's high medical need, it is acceptable to evaluate the efficacy and safety of the Zilver Vena Stent using the results

of the VIVO study conducted in the US and other country, on the basis of the applicant's explanation and for the following reasons:

- Ethnic differences including genetic factors, lifestyles, etc. were reflected not only in the incidence of DVT that causes symptomatic iliofemoral venous outflow obstruction but also in the proportion of disease types (acute, DVT, PTS, and NIVL). Nevertheless, the evaluation is possible in the subjects who met the expected eligibility criteria in Japan based on the results of the additional disease type-based analysis.
- Approximately half the subjects enrolled in the VIVO study were on conservative therapies (anticoagulant therapy and compressive therapy) at baseline. The optimal conservative therapy is selected according to the baseline characteristics and pathological conditions of each patient. Given this, and taking into consideration the comments from the Expert Discussion, it is unlikely that whether the subjects underwent a conservative therapy affected the vascular patency in the VIVO study.

The applicant must make clear to users through training, etc. that the results from subjects with acute DVT in the VIVO study include the results after mechanical thrombectomy. The applicant should also continue to investigate the use of anticoagulants or antiplatelets via a use-result survey, etc. as a post-marketing safety measures aiming for the proper use of these therapies, as described later in Section "6.B.(4) Efficacy and safety of the Zilver Vena Stent."

6.B.(3) Design of the VIVO study

6.B.(3).1) Justification for the evaluation different disease types in 1 study

Stenting is performed in patients with acute DVT, PTS, and NIVL that require intervention with the same purpose of the improvement of the lumen of target vein in a stenotic or obstructive lesion. However, the expected clinical outcomes of the intervention vary slightly, and thus the clinical efficacy and safety of the Zilver Vena Stent should normally be evaluated by disease type. Nevertheless, with the feasibility of the study and the product's medical needs taken into account, and for the following reasons, PMDA concluded that it was acceptable to determine the common performance goal based on vascular patency rate and to evaluate the Zilver Vena Stent by integrating the 3 disease types as 1 population:

- All disease types are manifested by symptomatic iliofemoral venous outflow obstruction. The clinical performance of the Zilver Vena Stent is evaluable based on the vascular patency at the target lesion.
- Literature reports[8,9,10] suggest the possibility that improved vascular lumen at the target lesion will lead to the improvement of clinical symptoms in all disease types.
- The point estimates of the primary quantitative patency rate were acceptable in each of 3 disease types in the study, as described later in Section "6.B.(4) Efficacy and safety of the Zilver Vena Stent."

6.B.(3).2) Justification of the performance goal

As described in Section "6.A.1) Methodology," the performance goal of the primary efficacy endpoint was derived from 39 literature reports on the outcomes with arterial or biliary stents in the treatment of symptomatic iliofemoral venous outflow obstruction. The 12-month primary quantitative patency rate was calculated to be 86%. With a margin of 10%, the performance goal of the primary efficacy endpoint of 76% was determined. The performance goal of the primary safety endpoint was also derived from the same literature reports. The weighted average rate of freedom from MAE was calculated to be 97%

using 95% in patients in the acute phase and 98% in patients in the chronic phase. With a margin of 10%, the performance goal of the primary safety endpoint of 87% was determined.

Severe symptomatic iliofemoral venous outflow obstruction, for which the Zilver Vena Stent is indicated, is conventionally treated with medication, catheter therapy, or surgical thrombectomy. Arterial stents have been used out of necessity for patients who do not respond to these conventional therapies. The Japanese and foreign guidelines also recommend venous stent therapy based on the treatment outcomes with arterial stents, which have been accepted as results from patients who are refractory to therapies other than venous stenting.[1,11,12] Therefore, in order to demonstrate the equivalence of the Zilver Vena Stent and arterial stents, it is reasonable to determine the performance goals of the Zilver Vena Stent based on the literature on treatment using arterial stents.

The efficacy performance goal of 76% does not substantially differ from the outcomes of stenting for the treatment of symptomatic iliofemoral venous outflow obstruction reported in 4 Japanese literature articles,[13,9,14,15] the results of meta-analysis,[10] and the outcomes with similar medical devices[16,17,18] (Table 19). Taking into consideration the comments from Expert Discussion, PMDA concluded that the performance goal was clinically reasonable. The safety performance goal of 87% was also derived from the same literature articles as those used to determine the efficacy performance goal. The mentioned meta-analysis showed the freedom rate from major hemorrhage, pulmonary embolism, pre- and post-procedural deaths, and early thrombosis of 90.8% in acute DVT, 91.4% in PTS, and 98.4% in NIVL.[10] On the basis of these, PMDA concluded that the performance goal was acceptable for the VIVO study.

Table 19. Primary patency rate in Japanese and foreign literature reports

	Overall	Acute DVT	PTS	NIVL
Funatsu et al. (Japanese report)[13]	-	84%	-	-
Matsuda et al. (Japanese report)[9]	-	80%	-	-
Igari et al. (Japanese report)[14]	-	75%	-	-
Hoshino et al. (Japanese report)[15]	-	-	93%	-
Razavi et al.[10]	-	87%	79%	96%
Dake et al. (Venovo)[16]	88.6%	-	81.7%	97.1%
Murphy et al. (Abre)[17]	88%	87.1%	79.8%	98.6%
Razavi et al. (VICI)[18]	84%	-	79.8%	96.2%

6.B.(3).3) Justification for primary efficacy analysis method

Missing data from subjects without venographic primary quantitative patency data immediately after the procedure and 12 months post-procedure, which are necessary for primary efficacy analysis, were addressed by multiple imputation for the analysis in the ITT population, as defined in the protocol.

The applicant's justification for this primary efficacy analysis method:
As per the protocol, the primary analysis of the primary efficacy endpoint, i.e., the primary quantitative patency rate, involved the ITT population consisting of all 243 subjects enrolled in the VIVO study. Of the 243 subjects, 189 subjects with venographic data immediately after the procedure and 12 months post-procedure were included in the analyzable population for the primary quantitative patency rate. Of these, 19 subjects did not achieve primary quantitative patency (Table 11). For the ITT analysis, the outcome for subjects with a missing primary efficacy outcome was imputed per the protocol, by random sampling from the Bernoulli distribution using the data from the 189 analyzable patients without

covariate adjustment. The imputation was performed 20 times to obtain the pooled results. To assess the effects of missing primary efficacy endpoint data on the analysis results, the data from the analyzable population were also analyzed. Furthermore, a tipping point analysis was performed per the protocol. The analysis, along with the imaging data (ultrasonographic data or venographic data at study sites) mentioned below, revealed the possibility that at least 38 of the 54 subjects with missing data had achieved patency at 12 months post-procedure. The number of subjects who did not achieve patency by that time point is assumed to fall significantly below 27, the predefined threshold of the tipping point analysis, indicating a low likelihood of failure to achieve the primary efficacy endpoint.

- Ultrasonography confirmed blood flow in 17 subjects after 12 months post-procedure.
- Ultrasonography confirmed no blood blow in 3 subjects, in whom, however, venography within 12 months post-procedure confirmed quantitative patency.
- Of 28 subjects with venographic or ultrasonographic data within 12 months post-procedure, 18 subjects were suggested to have patency based on improved imaging data and clinical evaluation scores within 12 months post-procedure.

The imputation for missing data in the ITT analysis was performed per the study protocol. The method is considered reasonable.

PMDA's view:
While it is understandable that the imputation for missing data was performed per the study protocol, the preventive measures against data missing and sample size setting should have been more carefully taken into consideration in study designing. The analysis results with imputed missing primary efficacy data need to be handled with care. However, in view of the satisfactory results yielded from the analyzable population, low likelihood of arbitrary exclusion of subjects from the analysis, and the results based on the tipping point analysis, the efficacy of the Zilver Vena Stent is unlikely to be denied. Thus, the results of the VIVO study are valid for efficacy evaluation of the Zilver Vena Stent.

6.B.(4) Efficacy and safety of the Zilver Vena Stent

6.B.(4).1) Efficacy

6.B.(4).1).(a) Efficacy of the Zilver Vena Stent demonstrated in the VIVO study

As described earlier in Section "6.B.(3).3) Justification for primary efficacy analysis method," the VIVO study is considered to have achieved the primary efficacy endpoint (ITT population). The analyzable population yielded a satisfactory patency rate. In addition, for the following reasons, the results of the VIVO study demonstrated the efficacy of the Zilver Vena Stent in improving and maintaining the lumen of the affected iliofemoral vein:

- The ultrasonographically defined patency rate at 2 and 3 years post-procedure was 90.3%, suggesting long-lasting patency of the target lesion (Figure 4).
- The 12-month primary quantitative patency rate was 93.9% in the acute DVT group, 85.8% in the PTS group, and 100% in the NIVL group. The point estimates exceeded the performance goal of 76%. Satisfactory results were obtained from all groups, including the PTS group that was predicted to be relatively poor responders.

The purpose of the treatment with the Zilver Vena Stent is to maintain the patency of the affected iliofemoral vein, and thereby to improve clinical symptoms. In the VIVO study, the secondary endpoint of the "change in VCSS from baseline to 1 and 12 months post-procedure" was evaluated according to the predefined statistical hypothesis. The study demonstrated improved clinical symptoms, which was maintained through 3 years post-procedure (Table 13). The other clinical measures (VDS, CEAP C classification, and CIVIQ-20) also indicated improved symptoms that tended to be long-lasting as with VCSS (Figures 5 to 7). These findings indicate the clinically significant efficacy of the Zilver Vena Stent in improving the lumen of the affected vein.

On the basis of the above discussion, PMDA concluded that the clinical efficacy of the Zilver Vena Stent had been demonstrated in the subject population of the VIVO study.

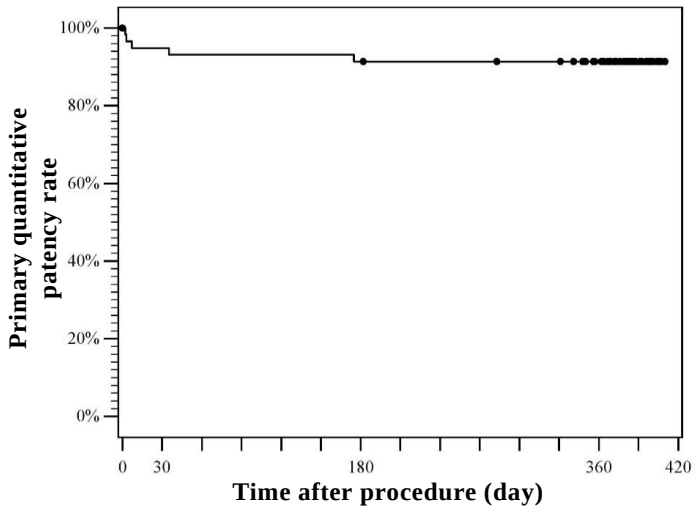
6.B.(4).1).(b) Efficacy of the Zilver Vena Stent in the target patient population in Japan

In the draft guidelines for proper use of iliofemoral venous stents including the Zilver Vena Stent prepared by related academic societies, the treatment is intended for severer cases in Japan than in the VIVO study. The efficacy of the Zilver Vena Stent in this target population was discussed.

Of the 243 subjects in the ITT population of the VIVO study, 70 subjects met the eligibility criteria for the treatment per the draft guidelines for proper use.

- 34 subjects with a VCSS pain score of 3 in the acute DVT group
- 21 subjects with CEAP C3 and VCSS pain score of 3 in the PTS group
- 6 subjects with CEAP C4 and VCSS pain score of 3 in PTS group
- 4 subjects with CEAP C5 in PTS group
- 5 subjects with CEAP C6 in PTS group

The Kaplan-Meier estimate for the primary quantitative patency rate in these 70 subjects was 91.4% through 365 days, which shows a similar trend to the result (89.9%) in the ITT population of the VIVO study (Figure 8).



Follow-up period	Study population	Number at risk	Cumulative number of events
0	100%	58	0
365	91.4% ± 3.7%	41	5
410	91.4% ± 3.7%	0	5

Figure 8. Primary quantitative patency rate in subjects meeting the eligibility criteria in the draft guidelines for proper use

To assess the therapeutic effect on the improvement of clinical symptoms in the subjects in the acute DVT and PTS groups meeting the eligibility criteria, changes in scores on "pain," "venous edema," "pigmentation," and "number of active ulcers," which are key measurements for the evaluation of the disease among the VCSS items, were reviewed. The clinical evaluation scores tended to improve in both groups (Tables 20 and 21). Subjects with most serious active ulcers also had an ulcer healing rate comparable to that previously reported with stent therapy in the treatment of symptomatic iliofemoral venous outflow obstruction (51%-62%)[8,19,20] (Table 22).

Table 20. Changes in clinical symptoms in subjects with acute DVT meeting the eligibility criteria in the draft guidelines for proper use

	Mean ± SD (range)	**12 months**				**3 years**			
		Change from baseline			**Mean ± SD (range)**	**Change from baseline**			**Mean ± SD (range)**
*[1,2]	Enrollment	Improved	Unchanged	Deteriorated		Improved	Unchanged	Deteriorated	
Pain	3 ± 0 (3-3)	79.4% (27/34)	2.9% (1/34)	0% (0/34)	0.4±0.7 (0-3)	73.5% (25/34)	2.9% (1/34)	0% (0/34)	0.5 ± 0.8 (0-3)
Edema	2.6 ± 0.7 (0-3)	76.5% (26/34)	5.9% (2/34)	0% (0/34)	0.4 ± 0.7 (0-2)	67.6% (23/34)	5.9% (2/34)	2.9% (1/34)	0.5 ± 0.8 (0-3)
Pigmentation	0.4 ± 0.9 (0-3)	11.8% (4/34)	64.7% (22/34)	5.9% (2/34)	0.1 ± 0.4 (0-2)	11.8% (4/34)	55.9% (19/34)	8.8% (3/34)	0.2 ± 0.6 (0-2)
Number of ulcers	0 ± 0 (0-0)	–	82.4% (28/34)	0% (0/34)	0 ± 0 (0-0)	–	76.5% (26/34)	0% (0/34)	0 ± 0 (0-0)
Missing		17.6% (6/34)				23.5% (8/34)			

*1 The severity score of each symptom was classified as follows:
"Pain": 0 = none, 1 = occasional (not restricting regular daily activities), 2 = daily (interfering with but not preventing regular daily activities), 3 = daily (limiting most regular daily activities)
"Venous oedema": 0 = none, 1 = limited to foot and ankle, 2 = extending beyond ankle but not beyond knee, 3 = extending beyond knee
"Pigmentation": 0 = none or focal, 1 = limited around medial or lateral malleolus, 2 = extending to the distal third of lower leg, 3 = extending beyond the distal third of lower leg
"Number of active ulcers": 0 = 0, 1 = 1, 2 = 2, 3 = ≥3
*2 Subjects with missing data did not undergo assessments because of reintervention.

Table 21. Changes in clinical symptoms in subjects with PTS meeting the eligibility criteria in the draft guidelines for proper use

	Mean ± SD (range)	12 months				3 years			
		Change from baseline			Mean ± SD (range)	Change from baseline			Mean ± SD (range)
CEAP C3 and VCSS pain score of 3 (N = 21)*1,2									
	Enrollment	Improved	Unchanged	Deteriorated		Improved	Unchanged	Deteriorated	
Pain	3 ± 0 (3-3)	81.0% (17/21)	0% (0/21)	0% (0/21)	0.6 ± 0.7 (0-2)	66.7% (14/21)	4.8% (1/21)	0% (0/21)	1.2 ± 0.9 (0-3)
Edema	2.6 ± 0.7 (0-3)	76.2% (16/21)	4.8% (1/21)	0% (0/21)	0.6 ± 0.9 (0-3)	57.1% (12/21)	14.3% (3/21)	0% (0/21)	0.9 ± 1.1 (0-3)
Pigmentation	0.3 ± 0.9 (0-3)	4.8% (1/21)	66.7% (14/21)	9.5% (2/21)	0.1 ± 0.3 (0-1)	4.8% (1/21)	57.1% (12/21)	9.5% (2/21)	0.1 ± 0.4 (0-1)
Number of ulcers	0 ± 0 (0-0)	0% (0/21)	81.0% (17/21)	0% (0/21)	0 ± 0 (0-0)	0% (0/21)	71.4% (15/21)	0% (0/21)	0 ± 0 (0-0)
Missing		19.0% (4/21)				28.6% (6/21)			
CEAP C4 and VCSS pain score of 3 (N = 6)*1,2									
	Enrollment	Improved	Unchanged	Deteriorated		Improved	Unchanged	Deteriorated	
Pain	3 ± 0 (3-3)	66.7% (4/6)	0% (0/6)	0% (0/6)	0.8 ± 0.5 (0-1)	33.3% (2/6)	16.7% (1/6)	0% (0/6)	1.7 ± 1.5 (0-3)
Edema	2.7 ± 0.5 (2-3)	66.7% (4/6)	0% (0/6)	0% (0/6)	1.3 ± 1 (0-2)	33.3% (2/6)	16.7% (1/6)	0% (0/6)	2 ± 0 (2-2)
Pigmentation	1.2 ± 1.2 (0-3)	33.3% (2/6)	0% (0/6)	33.3% (2/6)	1 ± 1.4 (0-3)	16.7% (1/6)	16.7% (1/6)	16.7% (1/6)	1 ± 1.7 (0-3)
Number of ulcers	0 ± 0 (0-0)	0% (0/6)	66.7% (4/6)	0% (0/6)	0 ± 0 (0-0)	0% (0/6)	50.0% (3/6)	0% (0/6)	0 ± 0 (0-0)
Missing		33.3% (2/6)				50.0% (3/6)			
CEAP C5 (N = 4)*1,2									
	Enrollment	Improved	Unchanged	Deteriorated		Improved	Unchanged	Deteriorated	
Pain	2.3 ± 0.5 (2-3)	50.0% (2/4)	25.0% (1/4)	0% (0/4)	1.3 ± 1.2 (0-2)	50.0% (2/4)	0% (0/4)	0% (0/4)	1 ± 0 (1-1)
Edema	2.3 ± 0.5 (2-3)	50.0% (2/4)	0% (0/4)	25.0% (1/4)	1.3 ± 1.5 (0-3)	25.0% (1/4)	25.0% (1/4)	0% (0/4)	1 ± 1.4 (0-2)
Pigmentation	2 ± 0 (2-2)	0% (0/4)	75.0% (3/4)	0% (0/4)	2 ± 0 (2-2)	50.0% (2/4)	0% (0/4)	0% (0/4)	1 ± 0 (1-1)
Number of ulcers	0 ± 0 (0-0)	0% (0/4)	75.0% (3/4)	0% (0/4)	0 ± 0 (0-0)	0% (0/4)	25.0% (1/4)	25.0% (1/4)	0.5 ± 0.7 (0-1)
Missing		25.0% (1/4)				50.0% (2/4)			
CEAP C6 (N = 5)*1,2									
	Enrollment	Improved	Unchanged	Deteriorated		Improved	Unchanged	Deteriorated	
Pain	2.4 ± 0.9 (1-3)	80.0% (4/5)	20.0% (1/5)	0% (0/5)	1.2 ± 1.1 (0-2)	80.0% (4/5)	0% (0/5)	0% (0/5)	0.8 ± 0.5 (0-1)
Edema	2 ± 1.2 (0-3)	60.0% (3/5)	20.0% (1/5)	20.0% (1/5)	1.4 ± 0.9 (0-2)	40.0% (2/5)	20.0% (1/5)	20.0% (1/5)	1.3 ± 1 (0-2)
Pigmentation	2 ± 1.2 (0-3)	40.0% (2/5)	40.0% (2/5)	20.0% (1/5)	2 ± 0.7 (1-3)	20.0% (1/5)	40.0% (2/5)	20.0% (1/5)	2.5 ± 0.6 (2-3)
Number of ulcers	1 ± 0 (1-1)	40.0% (2/5)	40.0% (2/5)	20.0% (1/5)	1 ± 1.2 (0-3)	60.0% (3/5)	20.0% (1/5)	0% (0/5)	0.3 ± 0.5 (0-1)
Size of ulcer	2 ± 0.7 (1-3)	60.0% (3/5)	40.0% (2/5)	0% (0/5)	1.2 ± 1.3 (0-3)	80.0% (4/5)	0% (0/5)	0% (0/5)	0.5 ± 1 (0-2)
Missing		0% (0/5)				20.0% (1/5)			

*1 The severity score of each symptom was classified as follows:
"Pain": 0 = none, 1 = occasional (not restricting regular daily activities), 2 = daily (interfering with but not preventing regular daily activities), 3 = daily (limiting most regular daily activities)
"Venous oedema": 0 = none, 1 = limited to foot and ankle, 2 = extending beyond ankle but not beyond knee, 3 = extending beyond knee
"Pigmentation": 0 = none or focal, 1 = limited around medial or lateral malleolus, 2 = extending to the distal third of lower leg, 3 = extending beyond the distal third of lower leg
"Number of active ulcers": 0 = 0, 1 = 1, 2 = 2, 3 = ≥3
"Diameter of active ulcer": 0 = none, 1 = <2 cm, 2 = 2 to 6 cm 3 = >6 cm
*2 Subjects with missing data did not undergo assessments because of reintervention.

Table 22. List of outcome of ulcers in subjects with active ulcers

	VCSS active ulcer variables*1	Evaluation point						Outcome of active ulcer*5
		Enrollment	1 month	6 months	12 months	2 years	3 years	
1*2	Number	3	3	-	-	-	-	Unhealed
	Size	3	3	-	-	-	-	
2	Number	1	1	1	1	1	0	Unhealed
	Size	2	2	2	2	2	0	(healed in 3 years)
3	Number	1	1	1	1	1	1	Unhealed
	Size	3	3	2	3	3	2	
4	Number	1	3	2	3	0	0	Unhealed
	Size	2	2	1	2	0	0	(healed in 3 years)
5	Number	1	1	1	1	Death	Death	Unhealed
	Size	2	1	1	1	Death	Death	
6	Number	1	0	0	0	0	0	Healed
	Size	2	0	0	0	0	0	
7	Number	1	1	1	-*3	0	2	Unhealed
	Size	2	2	2	-*3	0	1	
8*4	Number	0	0	0	0	0	-	-
	Size	0	0	0	0	0	-	
9	Number	1	0	0	0	0	0	Healed
	Size	1	0	0	0	0	0	
10	Number	1	0	3	3	1	2	Unhealed
	Size	2	0	2	3	2	2	
11	Number	1	1	0	0	0	0	Healed
	Size	1	1	0	0	0	0	
12	Number	1	0	0	0	0	0	Healed
	Size	1	0	0	0	0	0	
13	Number	1	1	0	0	0	0	Healed
	Size	2	1	0	0	0	0	

*1 The severity score of each symptom was classified as follows:
"Number of active ulcers": 0 = 0, 1 = 1, 2 = 2, 3 = ≥3
"Diameter of active ulcer": 0 = none, 1 = <2 cm, 2 = 2 to 6 cm, 3 = >6 cm
*2 The subject underwent amputation below the knee joint because of osteomyelitis. The investigator assessed and attributed it to the patient's medical history and not to the venous disease.
*3 Assessments were not performed because the target leg was covered for skin transplantation.
*4 Although the subject was assessed as CEAP C6 at enrollment, the number of active ulcers was recorded as 0 in the VCSS assessment. The subject dropped out before the 3-year follow-up because of other underlying illnesses.
*5 "Healed" denotes cases with the number and size of ulcers of 0 at 12 months post-procedure and thereafter, and "Unhealed" denotes otherwise.

PMDA's view:

In Japan, the Zilver Vena Stent is indicated for patients with intractable disease for which there is no other effective treatment option. The VIVO study demonstrated the efficacy of the Zilver Vena Stent with improved vascular patency and clinical symptoms, as summarized below, in the subjects meeting the expected eligibility criteria in Japan, albeit limited number. For these reasons and taking into consideration the comments from Expert Discussion, the Zilver Vena Stent will have promising clinical efficacy in Japan.

- The study subjects meeting the expected eligibility criteria in Japan also achieved the primary patency, which tended to be similar to that in the ITT population, suggesting that the Zilver Vena Stent is expected to provide satisfactory primary patency in the target population in Japan.
- In 57 of the 70 subjects in the acute DVT and PTS groups, excluding those with missing data, pain improved at 12 months post-procedure, except for 3 subjects with the VCSS pain score of 3 remaining unchanged. The improvement lasted through 3 years post-procedure in many subjects.

- In 49 of the 61 subjects in the acute DVT group or subjects with CEAP C3 or C4 in the PTS group, excluding those with missing data, venous edema improved at 12 months post-procedure, except for 3 subjects without improvement (no change). In addition, the improvement in clinical symptoms lasted through 3 years post-procedure in many subjects without worsening of CEAP C classification.
- Some subjects in the acute DVT group and those with CEAP C3, C4, or C5 in the PTS group had the progression of pigmentation. Except 1 subject with CEAP C5 in the PTS group had progression to active ulcers in 3 years post-procedure, no other subjects progressed to active ulcers, which is the most severe clinical condition. This outcome is of significance considering that approximately 5% to 10% of DVT cases are reported to progress to severe PTS.[21]
- Of 12 subjects with active ulcers at enrollment, 5 subjects had ulcers healed in 6 months post-procedure without recurrence up to 3 years post-procedure (41.7%, 5 of 12 subjects). A total of 7 subjects had active ulcers healed in 3 years post-procedure (58.3%, 7 of 12 subjects), which is comparable to the results of treatment with arterial stents reported.

Nevertheless, considering the limited number of subjects in the VIVO study meeting the eligibility criteria in Japan, it is important to continue efficacy and safety evaluation of the Zilver Vena Stent in Japan via the use-result survey etc. to ensure the proper use of the product.

6.B.(4).2) Safety

PMDA's view:

The safety profile of the Zilver Vena Stent in the VIVO study, including adverse events, was clinically acceptable since the primary safety endpoint of "the of 30-day freedom from MAE rate" met the protocol-defined performance goal based on the following reasons:

- The results of the primary safety endpoint by disease type was 94.9% (56 of 59 subjects) in the acute DVT group, 95.1% (98 of 103 subjects) in the PTS group, and 100% (78 of 78 subjects) in the NIVL group. The point estimates exceeded the predefined performance goal of 87%.
- The prevention of pulmonary embolism is important to assure the safety of the Zilver Vena Stent. Of 9 cases of pulmonary embolism in 8 subjects over 3 years post-procedure, only 1 case was related to the Zilver Vena Stent or procedure. This was a case with a low-risk pulmonary embolism associated with stent thrombus in a subject with a history of coagulation factor deficiency. The subject was treated with medication and discharged from the study site, and the case was considered clinically acceptable (Table 15).
- The Kaplan-Meier estimate for the 3-year rate of freedom from clinically driven reintervention was 95.8% at 365 days and 92.9% at 1095 days. Reintervention was required at a certain frequency but did not lead to any serious event. Re-interventional endovascular therapies including thrombolysis, thrombectomy, balloon angioplasty and/or stenting produced satisfactory outcomes and are clinically acceptable.
- No serious device- or procedure-related adverse event specific to the Zilver Vena Stent was reported in 3 years post-procedure. No adverse event occurred at a particularly higher incidence than those reported in the literature on stent therapy for symptomatic iliofemoral venous outflow obstruction in and outside Japan[9,10,13-15] (Table 16).

- The deaths in 3 years post-procedure is unlikely to be attributed to treatment with the Zilver Vena Stent, based on their causes (Table 17). One subject underwent amputation below the knee joint, which was due to previous osteomyelitis.

PMDA asked the applicant to explain the safety in the target population of the Zilver Vena Stent in Japan, which is comparable to severe cases in the VIVO study, as described in Section "6.B.(4).1) Efficacy."

The applicant's explanation:
Baseline CEAP C classifications of 23 subjects with 26 MAEs reported in 3 years post-procedure (Table 15) were C1 in 1 subject, C3 in 17 subjects, C4a in 2 subjects, C4b in 1 subject, C5 in 1 subject, and C6 in 1 subject. Of these, 8 subjects met the eligibility criteria per the draft guidelines for proper use. Of the 26 MAEs, 25 excluding clinical migration were clinically driven target lesion reintervention or new symptomatic pulmonary embolism. Although the draft guidelines for proper use in Japan focus on the patient population with severer disease than those in the VIVO study, the events that were identified and included in the safety analysis in the VIVO study are valid for safety evaluation in the target population of the Zilver Vena Stent in Japan.

PMDA's view:
The incidence of MAEs was 3.3% (8 of 240 subjects) in the VIVO study and 2.9% (2 of 69 subjects) in subjects meeting the expected eligibility criteria in Japan at 30 days post-procedure, and 9.6% (23 of 240 subjects) and 11.6% (8 of 69 subjects), respectively, at 3 years post-procedure. The details of the MAEs did not particularly differ between these patient populations. On the basis of these findings, the applicant's explanation that the safety profile of the Zilver Vena Stent was similar in the target population in Japan and the ITT population was acceptable. Nevertheless, only a limited number of subjects in the VIVO study met the expected eligibility criteria in Japan, post-marketing safety evaluation of the Zilver Vena Stent should be continued via a use-result survey, etc., and post-marketing safety measures including additional risk mitigation should be taken thoroughly as necessary.

6.B.(4).3) Stent migration

Stent migration is a potential risk recognized based on early experience with off label use of arterial stents and biliary stents for the treatment of symptomatic iliofemoral venous outflow obstruction. Stent migration to the inferior vena cava, right ventricle, pulmonary artery, etc. was reported with these stents. In 2021, Food and Drug Administration (FDA) issued a class I recall for similar medical devices because of stent migration after deployment. Albeit its low incidence, stent migration may require additional endovascular treatment or surgical stent removal by thoracotomy, which may lead to serious complications. Therefore, to ensure the efficacy and safety of the treatment with the Zilver Vena Stent, the reduction of risk of stent migration is important.

The incidence of stent migration in the VIVO study was 0.82% (2 of 243 subjects). One subject underwent a thoracotomy for stent removal, and the other underwent additional stenting. Stent migration occurred at an incidence of 0.017% ([redacted] events) as a post-marketing malfunction reported abroad as of the end of December 2021. Table 23 is a summary of stent migration reported in the VIVO study and post-marketing setting.

Table 23. Summary of stent migration

	Stent size Diameter × Length (mm)	Re-treatment	Outcome	Cause
VIVO study				
1	16 × 100	Yes	Surgical stent removal	Inappropriate stent size selection
2	16 × 60	No	Placement of additional 18 × 90 mm stent	Inappropriate stent size selection
Post-marketing malfunctions				
[redacted]				

PMDA's view:

Foreign systematic review about iliofemoral venous stents revealed the incidence of stent migration of 0.17%.[22] Compared to this number, the incidence of stent migration with the Zilver Vena Stent (0.017%) is low in the foreign post-marketing experience. The potential risk of stent migration with the Zilver Vena Stent is unlikely to be particularly higher than that of other similar products. The causes of stent migration identified for [redacted] of [redacted] events reported with the Zilver Vena Stent were inappropriate stent size selection ([redacted] events) and off-label stenting in inappropriate vessels ([redacted] events). As reported in Europe and the US, where iliofemoral venous stents have been used, adherence to the proper directions for use, including stent size selection according to the characteristics of veins and lesions, is critical to avoid stent migration. Although the incidence of stent migration in the VIVO study (0.82%) is higher than that reported in the latest literature,[22] the event occurred in limited number of subjects and was attributed to inappropriate size selection and off-label use. The incidence of stent migration can be lowered through risk mitigation measures.

The applicant's explanation about risk mitigation measures for stent migration with the Zilver Vena Stent based on the cause analysis of venous stent migration and its preventative measures taken outside Japan:

The following information about the reduction of stent migration risk was added to foreign instruction manuals in 2022. Accordingly, the same information will be disseminated through the Information on Precautions etc. of the Zilver Vena Stent. In addition, updates on stent migration from the latest literature, how to determine estimated vascular diameters, etc. will be communicated via risk reduction training materials.

- Additional information was added to call for careful attention to both stent length and diameter. It is important to select not only appropriate stent diameter but, as recommended in the VIVO study

protocol, also a stent length long enough to cover the target lesion properly, extending into healthy tissue by 5 to 10 mm, so that venous wall apposition will be secured.

- A precaution was added on stent length selection for NIVL. Literature[22,23] and recent academic meetings have suggested high possibility of stent migration in NIVLs. This is likely attributable to the fact that NIVLs tend to be treated with short stents, resulting in a weak force to grip the normal veins at both sides of the lesion.
- Instructions on venography-based post-procedural stent assessment are more clearly given. Specifically, the stent must be fully expanded to achieve satisfactory apposition to the venous wall along the stent length and, when ≥2 stents are deployed, each stent must be assessed and undergo post-deployment dilation on a one-by-one basis before the next stent is deployed.

The VIVO study protocol recommended the use of stents oversized by 2 to 4 mm with respect to the estimated vascular diameter. In the study, however, stents oversized by 1 mm with respect to the estimated vascular diameter were used in many cases and yielded satisfactory outcomes. The safety and efficacy of stents oversized by 1 to 4 mm were evaluated in nonclinical and clinical studies. Accordingly, the use of stents oversized by 1 to 4 mm with respect to the estimated vascular diameter is recommended in the foreign operating instructions and instructions for use.

PMDA concluded that the risk mitigation measures proposed by the applicant were appropriate because they are consistent with the analysis results of the VIVO study and the information in the 2 latest foreign systematic reviews.[22,24]

6.B.(4).4 Use of anticoagulants and antiplatelets

PMDA asked the applicant to explain the use of antiplatelets and anticoagulants that are required for post-procedural management after placement of the Zilver Vena Stent.

The applicant's explanation:

In the VIVO study, subjects were instructed to take an anticoagulant for ≥6 months and an antiplatelet (clopidogrel or aspirin) for 3 years according to literature reports and discussions with FDA at the time. Table 24 summarizes medications in the VIVO study. Only a low percentage of subjects used anticoagulants after 12 months post-procedure, which likely indicates clinical decisions made for many subjects based on their pathological conditions that they would not need anticoagulants. In contrast, the percentage of subjects who were on antiplatelets was almost consistent after 12 months post-procedure. Approximately 90% of subjects used antiplatelets from 1 to 12 months post-procedure. Of these subjects, 81.8% (162 of 198 subjects) continued antiplatelets up to 3 years post-procedure.

In view of the medications in the VIVO study and available data from published literature, etc.,[25] the use of post-procedural anticoagulant or antiplatelet therapy in patients who have undergone iliofemoral venous stenting has not currently gained consensus. Whether to use an anticoagulant or antiplatelet should be decided for each patient by physicians according to its clinical needs.

Table 24. Use of anticoagulants and antiplatelets in 3 years post-procedure

	Percentage of subjects						
	Baseline	**Immediately after procedure**	**1 month**	**6 months**	**12 months**	**2 years**	**3 years**
Anticoagulants	56.4% (137/243)	93.8% (228/243)	92.9% (224/241)	88.6% (209/236)	61.0% (139/228)	52.1% (110/211)	51.0% (101/198)
Antiplatelets	26.3% (64/243)	81.9% (199/243)	91.7% (221/241)	91.1% (215/236)	89.9% (205/228)	89.6% (189/211)	81.8% (162/198)

PMDA's view on the concurrent use of antiplatelets and anticoagulants after placement of the Zilver Vena Stent:
Of 26 MAEs reported in 3 years post-procedure in the VIVO study, 5 events were considered related to anticoagulants or antiplatelets, including 2 possibly related to the termination of anticoagulant therapy. The remaining 3 events were possibly attributable to anticoagulant therapy unsuitable to the characteristics of patients. Neither the Japanese guidelines[1] explaining anticoagulant therapy for DVT nor the European/US guidelines[26] provides established evidence for pharmacotherapy for symptomatic iliofemoral venous outflow obstruction treated by stenting. Considering that the persistent risk factors for DVT and venous thromboembolism (e.g., malignant tumors, concomitant medications, and genetic factors), risk of hemorrhage etc., which are common to many patients to be treated with the Zilver Vena Stent, vary with patients, no specific anticoagulant or antiplatelet therapy can be recommended for use after the treatment with the Zilver Vena Stent, until a certain level of clinical evidence is available. Currently, therefore, treating physicians are required to have adequate knowledge of anticoagulant therapy, etc. and to make a case-by-case decision on concomitant medication based on individual patient characteristics. Taking into consideration the comments from Expert Discussion, it is important that the Information on Precautions etc. provides information on anticoagulant therapy and antiplatelet therapy performed in the VIVO study, and it is critical for physicians to appropriately address post-procedural management with anticoagulant or antiplatelet therapy for each patient so that an optimal risk-benefit balance is achieved in the treatment with the Zilver Vena Stent.

Information on the use of anticoagulants and antiplatelets in the post-marketing setting should be collected through the use-results survey, etc. and provided promptly to users, i.e., physicians and medical institutions. In addition, the appropriateness of the usage and the necessity of additional risk measures should be constantly discussed.

PMDA's view on the basis of the above discussion 6.B.(4).1) to 6.B.(4).4):
The VIVO study demonstrated the clinical efficacy and safety of the Zilver Vena Stent and suggested, although in limited number of cases, its efficacy and safety in patients who will be treated with the product in Japan. Treatment with the Zilver Vena Stent is intended for patients with a severe symptomatic disease who have to rely on off-label arterial stents because of no effective therapeutic option other than stent therapy. A research study reported a lower risk of complications with venous stents than with arterial stents in the treatment of iliac vein compression syndrome and PTS.[2] Considering that the Zilver Vena Stent has been designated as a device to be early introduced, the product will be highly useful in Japan. The risk-benefit balance of the Zilver Vena Stent in the studied disease can be maintained through efforts to ensure the proper use of the product and safety measures taken

through industry-university-government collaborations, including those mentioned in Section "6.B.(5) Post-marketing safety measures including proper use of the Zilver Vena Stent" and the optimization of registry data on the treatment, which are to be offered by the related academic societies.

On the basis of the clinical positioning of the Zilver Vena Stent, Intended Use should be modified as shown below (the underlined words are added).

Intended Use
The Zilver Vena Venous Stent is used to improve the luminal diameter of the iliofemoral veins for the treatment of symptomatic iliofemoral venous outflow obstruction <u>that is difficult to treat with conventional therapies</u>.

6.B.(5) Post-marketing safety measures including proper use of the Zilver Vena Stent

The Zilver Vena Stent will be the first iliofemoral venous stent to be introduced to Japan. Since there is only limited experience and achievements in the treatment of symptomatic iliofemoral venous outflow obstruction with arterial stents, the following requirements need to be met for effective and safe introduction of the Zilver Vena Stent to Japan. Treating physicians are required to (a) have expertise in the treatment of symptomatic iliofemoral venous outflow obstruction and be able to select patients eligible for the treatment appropriately; (b) have knowledge and skills for diagnosis and procedures essential for safe and proper placement of the Zilver Vena Stent; (c) have knowledge and experience for appropriate decision making on post-procedural anticoagulant or antiplatelet therapy and its administration; and (d) be able to properly deal with complications and adverse events associated with the treatment with the Zilver Vena Stent. The applicant is required to (e) review the guidelines for proper use and take additional safety measures according to the post-marketing treatment outcomes.

The training program proposed by the applicant in response to the requirement (b) (Table 25), which covers the general information regarding venous diseases of the lower limb and the standard directions for use of the Zilver Vena Stent including the results of the VIVO study and stent size selection, is considered reasonable. The requirements (a) to (d) can be addressed by adhering to the guidelines for proper use (Table 26) currently being drafted by 5 related academic societies (JSIR, the Japanese Association of Cardiovascular Intervention and Therapeutics, the Japanese Society for Vascular Surgery, the Japanese College of Angiology, and Japanese Society of Phlebology). PMDA concluded that these requirements, including the training, should be attached as Approval Condition 1.

To fulfill the requirement (e), it is important to continue addressing these activities through industry-university-government collaborations, optimizing the use-results survey of the Zilver Vena Stent and the registry data to be offered by the related academic societies.

Table 25. Outline of training program

Subject (classroom lecture)	Description
Complexity of venous disease	General information on lower limb venous diseases
Results of the VIVO study	Efficacy and safety results, anticoagulant therapy, and antiplatelet therapy
Product description	Standard procedures with the Zilver Vena Stent (product size, stent selection method [including the risk mitigation measures for stent migration], directions for use, and MR safety information)

Table 26. Summary of the draft guidelines for proper use

Requirements for medical facilities	1) Certified for venous compression treatment or affiliated with a facility certified for venous compression treatment. 2) Accepting patients with PTS (CEAP C classification ≥3) or acute DVT. 3) Cooperative in the enrollment of all patients. 4) Certified by the JSIR, the Japanese Association of Cardiovascular Intervention and Therapeutics, or the Japanese Board of Cardiovascular Surgery.
Requirements for physicians	1) IVR specialists, cardiovascular surgery specialists, certified for cardiovascular intervention, or endovascular treatment specialists certified by any of the Japanese Society for Vascular Surgery 2) Completed designated training program.

7. Plan for Post-marketing Surveillance etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

Table 27 presents the summary of the use-results survey plan of the Zilver Vena Stent.

Table 27. Summary of the use-results survey plan

Objectives	Collection and assessment of data pertaining to the safety and efficacy of the Zilver Vena Stent in clinical use in Japan
Survey population	Patients with symptomatic iliofemoral venous outflow obstruction
Survey period	7.5 years (preparation for sale, 1 year; enrollment, 3 years; follow-up, 3 years; analysis, 0.5 years)
Sample size	118 (all patients)
Justification for sample size	The performance goal of the primary safety endpoint was 88%. To assess this hypothesis with a power of 80%, non-inferiority margin of 7%, and α of 0.025, at least 107 patients are needed. Allowing for a dropout of 10%, the sample size of 118 was determined. Considering the incidence of MAEs in the VIVO study (approximately 3%), this sample size is enough to detect at least 1 MAE at a probability of ≥95%.
Survey items	Main endpoints • 30-Day freedom from major adverse event (MAE) rate • 12-Month ultrasonographically defined primary patency rate • Change in VCSS from baseline to 1 and 12 months post-procedure Other endpoints • Patient characteristics • Success in stenting • Adverse events • Clinically driven target venous segment reintervention • Target venous segment reintervention • Stent integrity • Clinical migration • Change in VCSS, VDS, CEAP, and CIVIQ-20 from baseline to each follow-up time point • Anticoagulants and antiplatelets

7.B Outline of the review conducted by PMDA

As described earlier in Section "6.B Outline of the review conducted by PMDA," for the following reasons, the safety and efficacy of Zilver Vena Stent must be evaluated based on data of all patients treated with the product collected until the planned sample size is reached. Proper use of the Zilver Vena Stent should be reviewed, and additional risk mitigation measures should be taken as necessary.

- Because of the limited number of subjects in the VIVO study who met the expected eligibility criteria of the Zilver Vena Stent in Japan, the efficacy and safety of the product should be evaluated in Japan.
- The procedural safety of iliofemoral venous stenting therapy should be assessed with the Zilver Vena Stent, which is characteristically and technically different from arterial stenting.
- There is no protocol established for anticoagulant therapy or antiplatelet therapy after the placement of the Zilver Vena Stent in Japanese population, the safety of these therapies should be confirmed and information on the use of these therapies should be communicated to users promptly.

The planned sample size for the use-results survey proposed by the applicant will allow the collection of MAE data including items critical in the evaluation of an iliofemoral venous stents with a certain degree of accuracy, and is thus acceptable. "Anticoagulants and antiplatelets" was added to the survey items upon the applicant's agreement, and is also appropriate.

PMDA concluded that the draft use-results survey plan proposed by the applicant was appropriate and attached this as Approval Condition 2.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

PMDA's conclusion concerning the results of document-based GLP/GCP inspection and data integrity assessment

The medical device application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

The Zilver Vena Venous Stent is a venous stent intended for use to improve the luminal diameter of the iliofemoral veins for the treatment of symptomatic iliofemoral venous outflow obstruction that is difficult to treat with conventional therapies. PMDA's review on the Zilver Vena Stent focused on (1) its efficacy and safety and (2) post-marketing safety measures. Based on comments raised in the Expert Discussion, PMDA reached the following conclusions:

(1) Efficacy and safety of the Zilver Vena Stent

The VIVO study evaluated the efficacy and safety of the Zilver Vena Stent as a venous stent in patients with symptomatic iliofemoral venous outflow obstruction. The primary efficacy endpoint of the VIVO study of the "12-month primary quantitative patency rate" was 89.9%, which exceeds the protocol-defined performance goal of 76%. The secondary endpoint of "change in VCSS from baseline to 1 and

12 months post-procedure" was −3.0 at 1 month and −4.2 at 12 months, showing a significant decrease from baseline. The Zilver Vena Stent also improved the primary quantitative patency rate and clinical symptoms in subjects meeting the expected eligibility criteria in Japan, indicating promising efficacy of the Zilver Vena Stent in Japan.

The primary safety endpoint of the VIVO study of the "30-day freedom from MAE rate" was 96.7%, which exceeded the protocol-defined performance goal of 87%, demonstrating the clinically acceptable safety of the Zilver Vena Stent. There were no other adverse events specific to the Zilver Vena Stent or events reported with higher incidences than those related to stent therapy using arterial stents for the treatment of symptomatic iliofemoral venous outflow obstruction in and outside Japan. The incidence of stent migration, a concern with iliofemoral venous stenting including that using the Zilver Vena Stent, was 0.82% in the VIVO study and 0.017% in the post-marketing clinical use of the Zilver Vena Stent (as of the end of December 2021). The results are, however, clinically acceptable in view that the risk of stent migration can be reduced by appropriate stent size selection according to the anatomical characteristics of the target lesion.

Patients to be treated with the Zilver Vena Stent are those who suffer severe symptomatic venous diseases that have no effective therapeutic option other than stenting and currently rely on off-label arterial stents. Therefore, the benefits of the treatment with the Zilver Vena Stent outweigh its risk. The submitted data demonstrate the clinical usefulness of the Zilver Vena Stent.

(2) Post-marketing safety measures

For effective and safe introduction of the Zilver Vena Stent as Japan's first iliofemoral venous stent, it is important that treating physicians or medical teams with adequate experience and achievements in the standard treatment of the diseases must have acquired essential knowledge and skills pertaining to the product and procedures through training, etc. and select appropriate patients. The treatment with the Zilver Vena Stent should be performed at medical institutions with a system prepared for necessary emergency response including surgery for rare cases of stent migration, pulmonary embolism, and other complications. To this end, adherence to the guidelines for proper use, currently being drafted by the related academic societies, is crucial, and thus should be attached as Approval Condition 1.

For being the first iliofemoral venous stent to be introduced in Japan, and because of limited number of the VIVO study subjects meeting the expected eligibility criteria in Japan, post-marketing data on adverse events, procedures, patient characteristics, concomitant anticoagulant/antiplatelet therapy, etc. of the Zilver Vena Stent must be gathered from patients in Japan through a use-results survey, and additional risk mitigation measures should be taken as necessary. The use-results survey period should be 7.5 years (preparation for sale, 1 year; enrollment, 3 years; follow-up, 3 years; and analysis, 0.5 years). This condition should be attached as Approval Condition 2.

As a result of the above review, PMDA has concluded that the Zilver Vena Stent may be approved for the intended use shown below.

Intended Use

The Zilver Vena Venous Stent is used to improve the luminal diameter of the iliofemoral veins for the treatment of symptomatic iliofemoral venous outflow obstruction that is difficult to treat with conventional therapies.

Approval Conditions

1. The product must be used for patients eligible for the treatment, who should be selected by physicians with adequate knowledge and experience in the treatment of lower limb venous disease. Before using the product, the physicians must have acquired skills to handle the product and various knowledge including procedure-associated complications, and medical institutions must have a system prepared for the use of the product. To fulfill these requirements, the applicant is required to take necessary measures, such as disseminating the guidelines for proper use jointly prepared with relevant academic societies and offering seminars.
2. The applicant is required to conduct a use-results survey, which is to be continued over a period of time covering all patients treated with the product to obtain post-marketing data from a certain number of patients, report the survey result to the Pharmaceuticals and Medical Devices Agency, and take other measures as appropriate.

The product is not classified as a biological product or a specified biological product. The product is designated as a medical device subject to a use-results survey. The use-results survey period should be 7.5 years.

PMDA has concluded that the application should be subject to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

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