

Summary of Safety and Effectiveness Data (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Stent, Superficial Femoral
Device Trade Name:	Zilver Flex® 35 Vascular Stent
Device Procode:	NIP
Applicant's Name and Address:	Cook Ireland, Ltd. O'Halloran Rd. National Technology Park Limerick, Ireland
Date of Panel Recommendation:	None
Premarket Approval (PMA) Application Number:	P050017/S024
Date of FDA Notice of Approval:	07/01/2025

Premarket Approval Application (PMA) P050017 was approved on June 26, 2006 for the Zilver® Vascular Stent as an adjunct to percutaneous transluminal angioplasty (PTA) in the treatment of symptomatic vascular disease of the iliac arteries up to 100 mm in length, with a reference vessel diameter of 5 to 9 mm. The SSED to support the iliac artery indication is available on the CDRH website and is incorporated by reference here. The line extension, Zilver Flex® 35 Vascular Stent, was approved on July 5, 2011.

This application (P050017/S024) for the Zilver Flex® 35 Vascular Stent adds the indication for the treatment of symptomatic lesions in the native above-the-knee femoropopliteal arteries.

II. INDICATIONS FOR USE

The Zilver Flex® 35 Vascular Stent is intended for use as an adjunct to percutaneous transluminal angioplasty (PTA) in the treatment of symptomatic vascular disease of the iliac arteries up to 100 mm in length with a reference vessel diameter of 5 to 9 mm. Patients should be suitable candidates for PTA and/or stent treatment.

The Zilver Flex® 35 Vascular Stent is intended to improve the luminal diameter in the treatment of de novo or restenotic symptomatic lesions in the native above-the-knee femoropopliteal arteries with reference vessel diameters from 4 mm to 7 mm and lesion lengths up to 190 mm.

III. CONTRAINDICATIONS

The Zilver Flex® 35 Vascular Stent is contraindicated for use in:

- Patients who cannot receive appropriate antiplatelet and/or anticoagulant therapy.
- Patients with lesions that prevent complete angioplasty balloon inflation or proper placement of the stent or stent delivery system.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Zilver Flex[®] 35 Vascular Stent labeling (Instructions for Use).

V. DEVICE DESCRIPTION

The Zilver Flex[®] 35 Vascular Stent (the Zilver Flex stent) is a self-expanding nitinol (nickel titanium alloy) stent preloaded onto a delivery system. To facilitate fluoroscopic visualization of the stent, 4 radiopaque gold markers are positioned on each end of the device (Figure 1). Upon deployment, the Zilver Flex stent is designed to establish patency in the stented region. The Zilver Flex stent is available in the diameters and lengths described in Table 1.

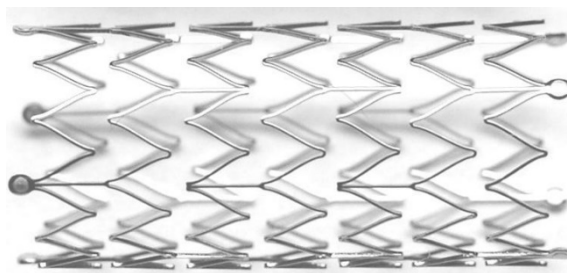
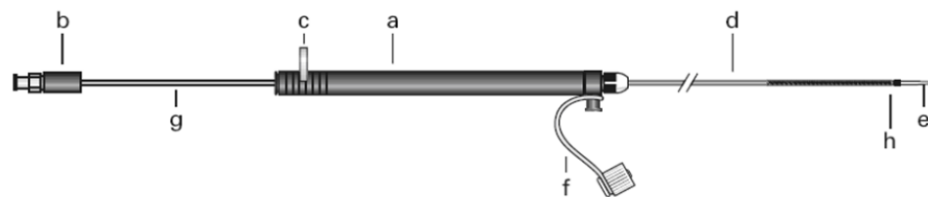


Figure 1: Image of the Zilver Flex stent

The Zilver Flex stent comes preloaded in a 2.0 mm (6Fr) delivery system. The 6Fr delivery system is available in 80 cm and 125 cm lengths. Both delivery systems are compatible with a 0.035 inch wire guide (Figure 2). The delivery system is used to deliver the stent to the appropriate anatomic location. When in position, the stent is deployed by retracting the handle while holding the hub on the metal cannula stationary (i.e., the “pin & pull” technique).



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

Figure 2: Schematic drawing of the Zilver Flex stent delivery system

Table 1. Sizes of Zilver Flex stent

Zilver Flex stent above-the-knee femoropopliteal artery indication											
Stent length (mm)		20	30	40	60	80	100	120	140	170	200
Delivery system length (cm)		80 and 125									
Stent outer diameter (mm)	5	X	X	X	X	X	X	X	X	X	X
	6	X	X	X	X	X	X	X	X	X	X
	7	X	X	X	X	X	X	X	X	X	X
	8	X	X	X	X	X	X	X	X	X	X
Zilver Flex stent iliac artery indication											
Stent length (mm)		20	30	40	60	80	100				
Delivery system length (cm)		80 and 125									
Stent outer diameter (mm)	6	X	X	X	X	X	X				
	7	X	X	X	X	X	X				
	8	X	X	X	X	X	X				
	9	X	X	X	X	X	X				
	10	X	X	X	X	X	X				

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of superficial femoral and proximal popliteal artery atherosclerotic disease:

- Non-invasive treatment (exercise and/or drug therapy)
- Minimally invasive treatment (balloon angioplasty, drug coated balloon angioplasty, endovascular stent placement of a drug-coated stent, directional atherectomy)
- Surgical treatment (surgical bypass)

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

VII. MARKETING HISTORY

The Zilver Flex stent is currently approved in the United States as an adjunct to percutaneous transluminal angioplasty (PTA) in the treatment of symptomatic vascular disease of the iliac arteries up to 100 mm in length, with a reference vessel diameter of 5 to 9 mm (P050017/S006).

Outside of the United States, the Zilver Flex stent for above-the-knee femoropopliteal arteries is commercially available in the following countries:

Argentina, Australia, Belarus, Brazil, Bulgaria, China, Colombia, Costa Rica, Croatia, Czechia, Ecuador, Egypt, El Salvador, Finland, France, Guatemala, Hong Kong, India, Israel, Italy, Japan, Korea, Kuwait, Lithuania, Macedonia, Malaysia, Mexico, Morocco, New Zealand, Palestine, Paraguay, Peru, Poland, Portugal, Romania, Russia, Saudi Arabia, Singapore, Slovakia, Spain, Taiwan, Thailand, UAE, Uruguay, Vietnam, Lebanon, United Kingdom.

The device has never been withdrawn from the market in any country for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- abrupt stent closure
- allergic reaction to anticoagulant and/or antithrombotic therapy or contrast medium
- allergic reaction to nickel
- amputation
- angina/coronary ischemia
- arrhythmia
- arterial aneurysm
- arterial rupture
- arteriovenous fistula
- atheroembolization (blue toe syndrome)
- death
- embolism
- fever
- hematoma/hemorrhage
- hypersensitivity reactions
- hypotension/hypertension
- infection/abscess formation at access site
- intimal injury/dissection
- ischemia requiring intervention (bypass or amputation of toe, foot or leg)
- myocardial infarction (MI)
- occlusion
- pain/discomfort
- pseudoaneurysm formation

- pulmonary embolism
- renal failure
- restenosis of the stented artery
- septicemia/bacteremia
- stent malapposition
- stent migration
- stent strut fracture
- stroke
- thrombosis
- tissue necrosis
- vasospasm
- worsened claudication/rest pain.

For the specific adverse events that occurred in the clinical studies, please see Section X, below.

IX. SUMMARY OF NON-CLINICAL STUDIES

The following non-clinical studies were leveraged from P050017, P100022, P200023 and subsequent supplements:

- Biocompatibility
- Select stent and delivery system bench testing
- Pre-clinical animal studies

Testing repeated to evaluate the new indications and device sizes is described below.

A. Non-clinical Bench Testing

Comprehensive non-clinical bench testing was performed on the Zilver Flex stent and delivery system to verify that the performance attributes are sufficient for the device to perform as intended and minimize the risk of adverse events under anticipated clinical conditions. This test plan was developed in accordance with FDA's (2010) guidance *Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems* and the (2015) guidance, *Select Updates for Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery System*, and ISO 25539-2 (2020), *Cardiovascular implants —Endovascular devices — Part 2: Vascular Stents*. The testing detailed in Table 2 verified that the Zilver Flex stent and delivery system met their product performance and design specifications and would perform as intended under anticipated clinical conditions. Non-clinical bench testing was leveraged from P050017 and subsequent supplements, except for the following tests:

Table 2. Summary of testing of the Zilver Flex stent and delivery system

Test method	Description of test	Acceptance criteria	Results
Stent corrosion resistance (fretting corrosion)	To determine the potential for fretting corrosion of the stent.	Mean breakdown potential > 600 mV _{SCE} and minimum breakdown potential > 300 mV _{SCE} .	Pass
Stent Dimensional Verification	To characterize the unconstrained dimensions of the stent.	The stent recovers to its specified, unconstrained diameter and expanded stent length.	Pass
Percent Surface Area (unconstrained)	To characterize the metal to lumen ratio of the stent.	N/A	Stented vessel covered surface characterized for each stent size using computer aided techniques
Percent Surface Area (constrained)			
Foreshortening	To determine the foreshortening of the stent from the catheter constrained diameter to use diameter	All test articles shall have < 20% length change	Pass
Stent Integrity	To evaluate the integrity of the stent after deployment	The stent must not exhibit strut fractures upon deployment; no cracks visible on the stent surface greater than 10 µm when viewed at a minimum magnification of 56X.	Pass
Accelerated Durability Testing	To evaluate the accelerated durability of stents after 10-year fatigue cycling.	No stent fractures before 10 years of non-pulsatile loading for each fatigue mode (i.e, axial, bend, or torsional fatigue testing).	Pass
Delivery System Dimensional Verification	Verify dimensional characteristics of the delivery system.	The maximum sheath outer diameter and delivery system working length will be within design specifications and compatible with a 0.035" wire guide.	Pass
Delivery, Deployment and Retraction	To confirm the delivery system meets it prespecified acceptance criteria with respect to its delivery, deployment, and retraction under simulated use conditions.	The delivery system must track through a simulated anatomical model, deliver the stent and be withdrawn remaining fully intact. The stent must be fully deployed.	Pass
Delivery System Bond Strength	To evaluate the tensile strength of the delivery system bonds.	The delivery system must be able to withstand forces which may be experienced clinically.	Pass

B. Packaging Testing

Verification testing was performed to demonstrate that the Zilver Flex stent and delivery system packaging can withstand distribution and maintain sterility throughout the shelf life of the Zilver Flex stent and delivery system. Packaging integrity verification testing included visual assessment, bubble leak testing and seal strength testing at manufacture and after aging to the product's shelf life.

C. Shelf-Life Testing

Shelf-life testing was performed to establish the expiration date of the Zilver Flex stent and delivery system. Non-clinical functional testing of the device after aging included delivery, deployment and retraction testing, deployment force, flexibility and kink resistance, and delivery system tensile strength. The testing supports a 3-year shelf life.

D. Sterilization

The Zilver Flex stent and delivery system is sterilized by a validated ethylene oxide (EtO) sterilization process to achieve a minimal sterility assurance level (SAL) of 10^{-6} . The methods used to validate the sterilization cycle are in accordance with EN ISO 11135:2014, *Sterilization of health care products - Ethylene oxide - Requirements for development, validation, and routine control of a sterilization process for medical devices*. The EtO and ECH residuals levels were in accordance with ISO 10993-7: 2008/Amd 1:2019, *Biological evaluation of medical devices-Ethylene oxide sterilization residual* and the amount of bacterial endotoxins was verified to be within the specification limit for the Zilver Flex stent and delivery system.

X. SUMMARY OF PRIMARY CLINICAL EVIDENCE

Clinical data from the Zilver PTX randomized controlled trial (RCT), the Zilver Flex Vascular Stent study, and the Zilver Flex Post-market Study (PMS) in Japan provide evidence to support the safety and effectiveness of the Zilver Flex stent in the treatment of above-the-knee femoropopliteal arteries. Among these studies, the patient populations were generally consistent (i.e., inclusion and exclusion criteria were generally consistent for the Zilver PTX RCT and Zilver Flex Vascular Stent study and no exclusion criteria for the Zilver Flex Japan PMS but enrollment of symptomatic patients) as were the outcome measures. The device sizes used in these three clinical studies span the range, both in stent diameter and in stent length, of the additional indicated stent sizes. In total, 353 patients were treated with a Zilver Flex stent across the three clinical studies consistent with the proposed indication for use.

A. Study Designs

Summary of Zilver PTX Randomized Controlled Trial

Patients were treated between March 2005 and August 2008 with follow-up through 5 years complete on December 2013. Long-term safety and effectiveness of the Zilver Flex stent for the treatment of *de novo* or restenotic lesions of the above-the-knee femoropopliteal artery were evaluated in Zilver PTX RCT, which was used to support the approval of the Zilver PTX Drug-eluting Peripheral stent under P100022 (approved on November 14, 2012).

The study was a prospective, multicenter RCT evaluating Zilver PTX stent versus PTA, and patients who experienced acute PTA failure underwent secondary randomization with the Zilver PTX stent or the Zilver Flex stent. The RCT enrolled 479 patients at 55 investigational sites. A total of 57 lesions in 55 patients received a Zilver Flex stent following PTA failure and randomization to bare metal stent treatment. Patients were treated with Zilver Flex stents with 5-8 mm diameters and 20-80 mm lengths with total lesion lengths up to 140 mm per limb and 280 mm per patient.

Summary of Zilver Flex Vascular Stent Study

Patients were treated between February 2009 and November 2010 with follow-up through 5 years complete on November 2015. The safety and long-term effectiveness of the Zilver Flex stent for the treatment of *de novo* or restenotic lesions of the above-the-knee femoropopliteal artery were evaluated in a prospective, single-arm post-approval clinical study in Germany. The specific objective of the study was to evaluate the long-term effectiveness of the Zilver Flex stent for use in the above-the-knee femoropopliteal artery for treatment of arteriosclerotic stenosis and total occlusions that have been recanalized. Patient selection criteria for this study were consistent with the criteria used to select patients enrolled in the Zilver PTX RCT, with the exception that there was no limitation on lesion length. Patients with *de novo* or restenotic lesions in the above-the-knee femoropopliteal artery were eligible to receive up to two study stents per lesion. Patients with up to two lesions, one in each limb, could be treated with the study device. A total of 112 lesions in 110 patients at three sites were treated with Zilver Flex stents with 5-8 mm diameters and 40-200 mm lengths in lesion lengths up to 200 mm.

Summary of Zilver Flex Post-Market Study in Japan

Patients were treated between July 2012 and January 2015 with follow-up through 3 years complete on December 2017. The Zilver Flex Japan PMS was a prospective, single-arm post-market clinical study in Japan was conducted to collect real-world data and to evaluate the long-term safety and effectiveness of the Zilver Flex Stent in above-the-knee femoropopliteal artery. Based on complete data of consecutively enrolled cases, 188 patients with 200 lesions treated with Zilver Flex stents with 6-8 mm diameters and 20-140 mm lengths were included in this analysis.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the Zilver PTX RCT and Zilver Flex Vascular stent study had the following general inclusion and exclusion criteria:

Select Inclusion Criteria:

- Patient has up to 2 documented stenotic or occluded atherosclerotic lesions of the above-the-knee femoropopliteal artery, up to one in each limb
- Patient has reference vessel diameter of 4-9 mm
- Patient has a *de novo* or restenotic lesion(s) with >50% stenosis documented angiographically and no prior stent in the target lesion

- Patient has symptoms of peripheral arterial disease classified as Rutherford Classification 2 or greater

Select Exclusion Criteria:

- Patient is <18 years of age
- Patient has significant stenosis (>50%) or occlusion of inflow tract (proximal ipsilateral, iliofemoral, or aortic lesions) not successfully treated before the index procedure (success is measured as <30% residual stenosis)
- Patient has had previous stenting of the target vessel
- Patient lacks at least one patent vessel runoff with <50% stenosis throughout its course
- Patient has untreated angiographically-evident thrombus in the target lesion
- Patient has lesions requiring atherectomy (or ablative devices), cutting balloons, cryoplasty balloons, or any other advanced device to facilitate stent delivery

The Zilver Flex Japan PMS had no exclusion criteria and enrolled consecutive patients with symptomatic peripheral arterial disease (PAD) involving the above-the-knee femoropopliteal arteries.

2. Follow-up schedule

Patients in the Zilver PTX RCT and the Zilver Flex Vascular Stent Study were followed annually through 5 years. Patients in the Zilver Flex Japan PMS were followed annually through 3 years.

Key timepoints used for assessment in this panel-track supplement are shown below:

- 30-day primary safety outcomes
- 12-month safety outcomes
- 12-month primary effectiveness outcome
- 12-month effectiveness outcomes

3. Clinical Endpoints

The clinical and statistical analysis plan were prespecified and discussed with FDA via the Pre-submission process prior to conducting the analysis for the subject PMA supplement. With regard to safety, the published VIVA performance goal¹ was used to evaluate the safety of the Zilver Flex stent for the above-the-knee femoropopliteal arteries in the as-treated patient population. In this approach, safety was assessed by comparing the combined rate of freedom from all-cause death, index limb amputation, or target vessel revascularization (TVR) at 30 days post-procedure for the Zilver Flex stent to the VIVA performance goal of 88%. The analysis was a one-sided test to demonstrate that the freedom from all-cause death, amputation, or TVR for the Zilver Flex stent is greater than the VIVA performance goal of 88%.

With regard to effectiveness, the SPEED Objective Performance Goal (OPG)² for the SFA was used to evaluate the effectiveness of the Zilver Flex stent for the above-the-knee femoropopliteal arteries in the as-treated patient population. In this approach,

effectiveness was assessed by comparing the 1-year freedom from TLR rate for all patients with an SFA lesion treated with the Zilver Flex stent to the SPEED OPG of 83.2%, with a margin of 5%, making the null proportion equal to 78.2%. The analysis was a one-sided exact test of proportions to demonstrate that the 1-year freedom from TLR for the Zilver Flex stent is greater than the derived performance goal.

B. Accountability of the Study Cohorts

The three clinical studies (e.g., the Zilver PTX RCT, the Zilver Flex Vascular Stent Study, and the Zilver Flex Post Market Study in Japan) enrolled similar patients based on the inclusion and exclusion criteria and collected similar data (i.e., study endpoints were similar and adverse event data collected was similar). For variables that were common across all three clinical studies, the individual datasets were vertically appended into the appropriate analysis dataset. All patients treated with a Zilver Flex device were included in the analyses; all analyses were performed on the as-treated population. Table 3 shows the patient accountability for each study as well as for the combined clinical cohort through 12-month follow-up. Table 4 shows the patient, lesion, and stent counts for each study as well as for the combined clinical cohort. In total, 353 patients were treated with 533 Zilver Flex stents. Table 5 details the analyses populations for each endpoint.

Table 3. Patient accountability by study through 12-month (410 days) follow-up

	Zilver PTX RCT	Zilver Flex Vascular Stent Study	Zilver Flex Japan PMS	Combined Cohort
Number of Patients	55	110	188	353
30 days				
Evaluable	55	109	179	343
LTFU/Withdrawal	0	1	9	10
Death	0	0	0	0
12 months				
Evaluable	50	104	140	294
LTFU/Withdrawal	4	4	38	46
Death	1	2	10	13

LTFU: Lost-to-follow-up

Table 4. Patient, lesion, and stent counts by study

Measure	Zilver PTX RCT	Zilver Flex Vascular Study	Zilver Flex Japan PMS	Combined Cohort
Number of patients	55	110	188	353
Number of study lesions	57	112	200	369
Number of Zilver Flex stents implanted	85	177	271	533

Table 5. Safety and effectiveness outcomes assessed

Outcome Assessed	Definition	Number Evaluated
<i>Safety Outcomes</i>		
Primary safety: 30-day safety	Freedom from all-cause death, amputation, or TVR at 30 days post-procedure.	353 patients
12-month stent integrity	Freedom from stent fracture through 12 months.	533 stents
12-month all-cause mortality	Death through 12 months.	353 patients
<i>Effectiveness Outcomes</i>		
Primary effectiveness: 12-month freedom from TLR	Freedom from reintervention performed for a $\geq 50\%$ stenosis within ± 5 mm of the study lesion after recurrent clinical symptoms of PAD.	352 patients – straight rate
		352 patients – KM estimate
12-month primary patency ^a	Assessed by duplex ultrasound (peak systolic velocity ratio (PSVR) ≤ 2.4) and/or angiography ($< 50\%$ stenosis) and the absence of reintervention within the study lesion post-index procedure. In the absence of a duplex ultrasound with a PSVR, a best available assessment of patency was used.	369 lesions
12-month clinical improvement	An improvement in Rutherford score by at least 1 class between pre-procedure and the 12-month clinical assessment.	262 patients
12-month clinical benefit	Freedom from persistent or worsening symptoms of ischemia (i.e., claudication, rest pain, ulcer or tissue loss) after the initial study treatment.	353 patients

^a Duplex ultrasound patency assessments were not required in the Zilver Flex Japan PMS. Therefore, 12-month primary patency, based on best available data (i.e., core laboratory-reported imaging when available, otherwise site-reported imaging), was also assessed for 169 lesions in the Zilver PTX RCT and in the Zilver Flex Vascular Stent study. When duplex ultrasound and angiography were both available and evaluable and a failure was identified by either imaging modality, then patency was deemed a failure.

C. Study Population Demographics and Baseline Parameters

Baseline Patient, Lesion, and Stent Data

Table 6 summarizes baseline patient demographics for each study as well as for the combined clinical cohort. The mean age of the patients in the combined clinical cohort was 70.4 ± 10 years, and the majority (71.1%) of patients were male and had claudication (Rutherford classification 0-3, 77.8%) at baseline. The baseline patient demographics and medical history for the combined clinical cohort are similar to those observed in patients with PAD.

Table 6. Demographics and medical history

Baseline Variable	Zilver PTX RCT (N = 55)	Zilver Flex Vascular Study (N = 110)	Zilver Flex Japan PMS (N = 188)	Combined Cohort (N = 353)
Age (years, mean $\pm$ SD (N, range))	66.7 $\pm$ 10.8 (55, 40 - 89)	66.4 $\pm$ 9.5 (110, 44 - 86)	73.8 $\pm$ 8.8 (188, 45 - 94)	70.4 $\pm$ 10 (353, 40 - 94)
Sex				
Male	76.4% (42/55)	68.2% (75/110)	71.3% (134/188)	71.1% (251/353)
Female	23.6% (13/55)	31.8% (35/110)	28.7% (54/188)	28.9% (102/353)

Baseline Variable	Zilver PTX RCT (N = 55)	Zilver Flex Vascular Study (N = 110)	Zilver Flex Japan PMS (N = 188)	Combined Cohort (N = 353)
Ethnicity				
Asian	20.4% (10/49) ¹	0% (0/110)	100% (188/188)	57.1% (198/347)
Black	8.2% (4/49) ¹	0% (0/110)	0% (0/188)	1.2% (4/347)
Hispanic/Latino	4.1% (2/49) ¹	0% (0/110)	0% (0/188)	0.6% (2/347)
Caucasian/White	67.3% (33/49) ¹	100% (110/110)	0% (0/188)	41.2% (143/347)
Cardiac				
Cardiac arrhythmia	9.1% (5/55)	10.0% (11/110)	N/A	9.7% (16/165)
Congenital heart disease	N/A	0.9% (1/110)	N/A	0.9% (1/110)
Coronary artery disease (CAD)	N/A	32.7% (36/110)	45.2% (85/188)	40.6% (121/298)
Congestive heart failure (CHF)	14.5% (8/55)	1.8% (2/110)	N/A	6.1% (10/165)
Myocardial infarction (MI)	18.2% (10/55)	12.7% (14/110)	N/A	14.5% (24/165)
Diabetes	43.6% (24/55)	35.5% (39/110)	48.9% (92/188)	43.9% (155/353)
Type I	8.3% (2/24)	0% (0/39)	4.5% (4/89) ¹	3.9% (6/152)
Type II	91.7% (22/24)	100% (39/39)	95.5% (85/89) ¹	96.1% (146/152)
Hypercholesterolemia	74.5% (41/55)	61.8% (68/110)	50.0% (94/188)	57.5% (203/353)
Hypertension	78.2% (43/55)	80.9% (89/110)	78.2% (147/188)	79.0% (279/353)
Carotid disease	18.2% (10/55)	N/A	45.2% (85/188)	39.1% (95/243)
Renal disease	10.9% (6/55)	N/A ^b	41.0% (77/188)	34.2% (83/243)
Chronic renal failure	N/A	1.8% (2/110)	85.7% (66/77)	36.4% (68/187)
Pulmonary disease	12.7% (7/55)	9.1% (10/110) ^c	6.9% (13/188) ^c	8.5% (30/353)
Existing tissue loss (amputations, gangrene, ischemic ulcers)	7.3% (4/55)	7.3% (8/110)	N/A	7.3% (12/165)
Smoking				
Never	14.5% (8/55)	17.3% (19/110)	33.0% (62/188)	25.2% (89/353)
Quit/Past	47.3% (26/55)	48.2% (53/110)	42.0% (79/188)	44.8% (158/353)
Current	38.2% (21/55)	34.5% (38/110)	25.0% (47/188)	30.0% (106/353)
Rutherford Classification ^a				
0-3	90.9% (50/55)	89.8% (97/108) ^a	66.3% (116/175) ^a	77.8% (263/338)
4-6	9.1% (5/55)	10.2% (11/108) ^a	33.7% (59/175) ^a	22.2% (78/338)

^a Data were not available for all patients.

^b In the Zilver Flex Vascular Stent Study, data were not collected for renal disease; however, data were collected for renal failure.

^c Rates represent chronic obstructive pulmonary disease.

A total of 369 lesions were treated in the 353 patients. Baseline lesion characteristics are based on best available angiographic imaging data (core laboratory-reported data for the Zilver PTX RCT and the Zilver Flex Vascular Study; site-reported data for the Zilver Flex Japan PMS) for each study as well as for the combined clinical cohort are shown in Table 7. Site-reported lesion characteristics for each study as well as for the combined clinical cohort are shown in Table 8. The average lesion length based on best available data was 107.3 ± 81.3 mm for the 369 lesions in the combined clinical cohort, 45.8% of the lesions were classified as total occlusions, and 33.1% of lesions were severely calcified.

Table 7. Baseline lesion characteristics (best available)

Lesion Characteristic	Zilver PTX RCT (N = 57)	Zilver Flex Vascular Study (N = 112)	Zilver Flex Japan PMS (N = 200)	Combined Cohort (N = 369)
Calcification				
None	3.5% (2/57)	16.1% (18/112)	29.0% (58/200)	21.1% (78/369)
Little	26.3% (15/57)	N/A	N/A	4.1% (15/369)
Mild	N/A	1.8% (2/112)	42.0% (84/200)	23.3% (86/369)
Moderate	31.6% (18/57)	9.8% (11/112)	19.5% (39/200)	18.4% (68/369)
Severe	38.6% (22/57)	72.3% (81/112)	9.5% (19/200)	33.1% (122/369)
Inflow tract stenosis ¹				
None	51.9% (28/54)	6.3% (5/79)	N/A	24.8% (33/133)
≤50%	35.2% (19/54)	82.3% (65/79)		63.2% (84/133)
>50%	13.0% (7/54)	11.4% (9/79)		12.0% (16/133)
Patent runoff vessels ^a				
0	12.1% (4/33)	15.9% (11/69)	10.1% (20/199)	11.6% (35/301)
1	66.7% (22/33)	30.4% (21/69)	31.7% (63/199)	35.2% (106/301)
2	15.2% (5/33)	36.2% (25/69)	29.6% (59/199)	29.6% (89/301)
3	6.1% (2/33)	17.4% (12/69)	28.6% (57/199)	23.6% (71/301)
Total occlusion	43.9% (25/57)	65.2% (73/112)	35.5% (71/200)	45.8% (169/369)
Lesion length (mm, mean ± SD (n, range))	60.3 ± 37.9 (57, 7 - 160)	128.0 ± 87.2 (112, 10.8 - 393)	109.1 ± 81.8 (200, 10 - 320)	107.3 ± 81.3 (369, 7 - 393)
RVD (mm, mean ± SD (n, range))	5.0 ± 0.9 (57, 2.9 - 7.7)	5.2 ± 0.9 (112, 3.3 - 7.4)	5.7 ± 0.9 (200, 2 - 8.4)	5.4 ± 1.0 (369, 2 - 8.4)
Percent diameter stenosis (%, mean ± SD (n, range))	84.9 ± 16.0 (57, 56.5 - 100)	91.3 ± 13.5 (112, 52.6 - 100)	91.6 ± 10.1 (200, 41.1 - 100)	90.5 ± 12.4 (369, 41.1 - 100)
In-stent restenosis	N/A	N/A	8.0% (16/200)	8.0% (16/200)

^a Data was not available for all lesions.

Table 8. Baseline lesion characteristics (site-reported)

Lesion Characteristic	Zilver PTX RCT (N = 57)	Zilver Flex Vascular Study (N = 112)	Zilver Flex Japan PMS (N = 200)	Combined Cohort (N = 369)
Previous intervention in study vessel				
None	94.6% (53/56) ^a	92.0% (103/112)	85.5% (171/200)	88.9% (327/368)
PTA	1.8% (1/56) ^a	0% (0/112)	0% (0/200)	0.3% (1/368)
Other	3.6% (2/56) ^a	0% (0/112)	0% (0/200)	0.5% (2/368)
Yes	N/A	8.0% (9/112)	14.5% (29/200)	10.3% (38/368)
Calcification				
None	35.1% (20/57)	1.8% (2/112)	29.0% (58/200)	21.7% (80/369)
Little	26.3% (15/57)	25.0% (28/112)	N/A	11.7% (43/369)
Mild	N/A	N/A	42.0% (84/200)	22.8% (84/369)
Moderate	21.1% (12/57)	51.8% (58/112)	19.5% (39/200)	29.5% (109/369)
Severe	17.5% (10/57)	21.4% (24/112)	9.5% (19/200)	14.4% (53/369)
Inflow tract stenosis				

Lesion Characteristic	Zilver PTX RCT (N = 57)	Zilver Flex Vascular Study (N = 112)	Zilver Flex Japan PMS (N = 200)	Combined Cohort (N = 369)
None	64.9% (37/57)	83.0% (93/112)	N/A	76.9% (130/169)
≤50%	26.3% (15/57)	9.8% (11/112)		15.4% (26/169)
>50%	8.8% (5/57)	7.1% (8/112)		7.7% (13/169)
Patent runoff vessels				
0	0% (0/57)	0% (0/112)	10.1% (20/199) ^a	5.4% (20/368)
1	22.8% (13/57)	18.8% (21/112)	31.7% (63/199) ^a	26.4% (97/368)
2	26.3% (15/57)	27.7% (31/112)	29.6% (59/199) ^a	28.5% (105/368)
3	50.9% (29/57)	51.8% (58/112)	28.6% (57/199) ^a	39.1% (144/368)
>3	0% (0/57)	1.8% (2/112)	0% (0/199) ^a	0.5% (2/368)
Total occlusion	42.1% (24/57)	61.6% (69/112)	35.5% (71/200)	44.4% (164/369)
Lesion length (mm, mean ± SD (n, range))	73.9 ± 38.1 (57, 10 - 140)	142.4 ± 89.1 (112, 7 - 360)	109.1 ± 81.8 (200, 10 - 320)	113.8 ± 82.1 (369, 7 - 360)
RVD (mm, mean ± SD (n, range))	5.0 ± 0.8 (57, 3 - 6.3)	5.4 ± 0.8 (112, 3 - 7.5)	5.7 ± 0.9 (200, 2 - 8.4)	5.5 ± 0.9 (369, 2 - 8.4)
Percent diameter stenosis (%, mean ± SD (n, range))	81.9 ± 22.7 (57, 0 - 100)	94.8 ± 8.2 (112, 60 - 100)	91.6 ± 10.1 (200, 41.1 - 100)	91.1 ± 13.1 (369, 0 - 100)
In-stent restenosis	N/A	N/A	8.0% (16/200)	8.0% (16/200)

^a Data was not available for all patients.

A total of 533 Zilver Flex stents were implanted during the index procedure in the combined clinical cohort. The number of stents placed in each individual study and for the combined clinical cohort are shown in Table 9. In the combined clinical cohort, a mean number of 1.6 ± 0.8 stents were implanted per patient and a mean number of 1.4 ± 0.7 stents were implanted per lesion.

Table 9. Zilver Flex stents implanted by study

Measure	Zilver PTX RCT	Zilver Flex Vascular Study	Zilver Flex Japan PMS	Combined Cohort
Number of Zilver Flex stents implanted	85	177	271	533
Mean number of stents implanted per patient	1.9 ± 1.0	1.6 ± 0.7	1.4 ± 0.8	1.6 ± 0.8
Mean number of stents implanted per lesion	1.5 ± 0.5	1.6 ± 0.6	1.4 ± 0.7	1.4 ± 0.7

Details regarding the stent sizes implanted in the combined clinical cohort and each individual study are provided in Table 10. Both the 6 mm and the 7 mm stent diameters were equally used (42.8%, 228/533 stents for each stent length) across the three clinical studies. The most common stent length was 80 mm (38.8%, 207/533 stents).

Table 10. Zilver Flex stents implanted

Combined Clinical Cohort (Zilver PTX RCT, Zilver Flex Vascular Study, Zilver Flex Japan PMS)								
Diameter (mm)	Stent Length (mm)^a							
	20	30	40	60	80	140	200	Total
5.0	0 (0, N/A, N/A)	0 (0, N/A, N/A)	1 (0, 1, N/A)	0 (0, N/A, N/A)	6 (0, 6, N/A)	21 (N/A, 21, N/A)	0 (N/A, 0, N/A)	28
6.0	1 (0, N/A, 1)	0 (0, N/A, N/A)	46 (6, 16, 24)	23 (6, N/A, 17)	90 (31, 18, 41)	61 (N/A, 39, 22)	7 (N/A, 7, N/A)	228
7.0	1 (1, N/A, 0)	0 (0, N/A, N/A)	46 (4, 16, 26)	27 (8, N/A, 19)	94 (23, 15, 56)	57 (N/A, 21, 36)	3 (N/A, 3, N/A)	228
8.0	0 (0, N/A, 0)	0 (0, N/A, N/A)	21 (2, 6, 13)	5 (2, N/A, 3)	17 (2, 2, 13)	6 (N/A, 6, 0)	0 (N/A, 0, N/A)	49
Total	2	0	114	55	207	145	10	533

^a In the Zilver PTX RCT, the 140 and 200 mm stent lengths were not available. In the Zilver Flex Vascular Study, the 20, 30, and 60 mm stent lengths were not available. In the Zilver Flex Japan PMS, the 30 and 200 mm stent lengths and the 5 mm stent diameter were not available. These are noted as “N/A” in the table above.

D. Safety and Effectiveness Results

1. Primary Safety Endpoint

The primary safety endpoint is the combined rate of freedom from all-cause death, amputation, or TVR at 30 days post-procedure. As reported in Table 11, 98.0% of patients (346/353) treated with the Zilver Flex stent remained free from death, amputation, or TVR through 30 days. The combined rate of freedom from all-cause death, amputation, or TVR at 30 days post-procedure compares favorably to the established VIVA performance goal of 88%, with a p -value < 0.01 indicating that the performance goal for safety was met. Through 30 days, there were four amputations and three TVR events (seven unique patients) in the 353 patients; there were no deaths.

Table 11. Primary safety endpoint

Primary Safety Endpoint	VIVA Performance Goal (%)	Zilver Flex Stent (% [n, 95% CI])	p -value
Freedom from all-cause death, amputation, or TVR at 30 days	88%	98.0% (353, 96.0% – 99.2%)	<0.01

Additional Safety Outcomes

Vascular Adverse Events

Vascular adverse events prospectively defined in the study protocols were identified by the investigative sites. Table 12 presents the vascular adverse events through 12-month follow-up (i.e., through 410 days) for the combined clinical cohort. The table includes the event rate per patient as well as the total number of a particular event. Note that a single patient could experience multiple events within an event category. Percutaneous or surgical reintervention of the study vessel was the most common vascular adverse event (16.7%, 59/353) and restenosis or occlusion of the study lesion (14.4%, 51/353) also commonly occurred. These events are expected adverse events within this patient population. Additional details on target lesion revascularization (TLR) are addressed below.

Table 12. Vascular adverse events reported through 12-month (410 days) follow-up

Adverse Event	Combined Cohort (N = 353)	
	% (n)	Events
Embolism distal to the treated study vessel	0.3% (1/353)	1
Gangrene	2.3% (8/353)	11
Hematoma	0% (0/353)	0
Ischemia	3.1% (11/353)	14
Ischemic ulcer	1.7% (6/353)	14
Pseudoaneurysm or AV Fistula	0.3% (1/353)	1
Percutaneous or surgical reintervention of study vessel ^a	16.7% (59/353)	78
Restenosis or occlusion of the study lesion ^b	14.4% (51/353)	63
Study limb amputation ^c	2.8% (10/353)	17
Thrombosis	1.7% (6/353)	8
Worsened claudication/rest pain	2.5% (9/353)	12

^a Percutaneous and surgical reinterventions were classified as secondary interventions and not as adverse events in the Zilver Flex Vascular Study and the Zilver Flex Japan PMS. The rate in the table reflects all occurrences of the event type across all three studies, regardless of how the data were reported in each study.

^b Restenosis and occlusion were evaluated by angiography and were not classified as adverse events in the Zilver PTX RCT. The rate in the table reflects all occurrences of restenosis and occlusion regardless of how the data were reported in each study.

^c Amputations were classified as treatments for adverse events and were a result of gangrene, stenosis or occlusion of a non-study lesion, and infection in Zilver Flex Vascular Study and the Zilver Flex Japan PMS. The rate in the table reflects any amputation (i.e., amputation of a toe).

Device- or Procedure-related Vascular Adverse Events

Table 13 presents the device- or procedure-related vascular adverse events through 12-month follow-up (i.e., through 410 days) based on all available data for the combined clinical cohort. Device- or procedure-relatedness data is not available for events reported in the Zilver Flex Vascular Study; therefore, the analysis conservatively assumed that all vascular adverse events in the Zilver Flex Vascular Study were related events. The table includes the event rate per patient as well as the total number of patients who have experienced a particular event.

Table 13. Device- or procedure-related vascular adverse events reported through 12-month (410 days) follow-up

Adverse Event	Combined Cohort ^a (N = 353)	
	% (n)	Events
Embolism distal to the treated study vessel	0% (0/353)	0
Gangrene	1.1% (4/353)	6
Hematoma	0% (0/353)	0
Ischemia	2.5% (9/353)	12
Ischemic ulcer	0.6% (2/353)	7
Pseudoaneurysm or AV Fistula	0% (0/353)	0
Percutaneous or surgical reintervention of study vessel ^b	13.0% (46/353)	59
Restenosis or occlusion of the study lesion ^c	11.9% (42/353)	50
Study limb amputation ^d	1.7% (6/353)	13
Thrombosis	0.8% (3/353)	4
Worsened claudication/rest pain	1.1% (4/353)	6

^a Adverse events in the Zilver Flex Vascular study were not CEC-adjudicated, thus relatedness data is not available; the rates shown in the table represent the total number of reported vascular events through 12 month follow-up.

^b Percutaneous and surgical reinterventions were classified as secondary interventions and not as adverse events in the Zilver Flex Vascular Study and the Zilver Flex Japan PMS. The rate in the table reflects all occurrences of device- or procedure-related percutaneous and surgical reinterventions regardless of how the data were reported in each study.

^c Restenosis and occlusion were evaluated by angiography and were not classified as adverse events in the Zilver PTX RCT. The rate in the table reflects all occurrences of device- or procedure-related percutaneous and surgical reinterventions regardless of how the data were reported in each study.

^d Amputations were classified as treatments for adverse events and were a result of gangrene, stenosis or occlusion of a non-study lesion, and infection in Zilver Flex Vascular Study and the Zilver Flex Japan PMS. The rate in the table reflects any device- or procedure-related amputation (i.e., amputation of a toe).

Stent Integrity

Stent integrity was assessed at 12 months post-procedure based on best available data. For stent integrity, best available data is defined as core laboratory-reported imaging when available, otherwise site-reported imaging was used. Based on the Kaplan-Meier estimates for freedom from stent fracture for the combined clinical cohort at 12 months, the rate of freedom from stent fracture was 99.6% (number of patients remaining at risk was 464). No fractures were detected upon procedure completion and only two fractures were detected through 12 months, both fractures were Type I fractures.

All-Cause Mortality

A total of 13 deaths were reported in the combined clinical cohort through 410 days, including one death in the Zilver PTX RCT, two deaths in Zilver Flex Vascular Stent study, and ten deaths in the Zilver Flex Japan PMS. There were no reported CEC-adjudicated, device-, or procedure-related deaths in the combined clinical cohort. Through 12 months, the Kaplan-Meier estimated mortality rate was 3.0%. This mortality rate is low and expected of a PAD patient population.

2. Primary Effectiveness Endpoint

The primary effectiveness endpoint is 12-month freedom from TLR, where TLR was defined as a reintervention performed for $\geq 50\%$ diameter stenosis within ± 5 mm of the study lesion after recurrent clinical symptoms of PAD. At 12 months, 87.2% of patients (307/352) treated with the Zilver Flex stent were free from TLR. The rate of freedom from TLR is high with a lower bound of the 95% confidence interval (CI) exceeding the derived performance goal of 78.2%, indicating that the effectiveness endpoint met the pre-defined criteria (Table 14).

Table 14. Primary effectiveness endpoint

Primary Effectiveness Endpoint	Performance Goal (%)	Zilver Flex Vascular Stent (% [n, 95% CI])
12-month freedom from TLR	78.2%	87.2% (352, 83.3% – 90.5%)

Additional Effectiveness Endpoints

Freedom from TLR through 12 months

The Kaplan-Meier estimates for freedom from TLR through 12 months for the combined clinical cohort are provided in Table 15. TLR was defined as a reintervention performed for a $\geq 50\%$ stenosis of the target lesion after documentation of recurrent clinical symptoms of PAD. Patients who died, withdrew, or were LTFU were censored upon study exit.

Table 15. Kaplan-Meier estimates for freedom from TLR for the combined clinical cohort

Months	Freedom from TLR Estimate	Standard Error	Cumulative Failed	Cumulative Censored	Number Remaining
0	100%	0%	0	0	352
6	98.2%	0.7%	6	26	320
12	89.1%	1.8%	35	40	277

The 12-month Kaplan-Meier estimates for freedom from TLR for the Zilver PTX RCT, Zilver Flex Vascular Study, and Zilver Flex Japan PMS are comparable at 85.8%, 90.8%, and 88.8%, respectively.

Primary Patency

In the Zilver PTX RCT and in the Zilver Flex Vascular Stent study, primary patency, based on best available data, was assessed by duplex ultrasound (peak systolic velocity ratio (PSVR) ≤ 2.4) and/or angiography ($< 50\%$ stenosis) and the absence of reintervention within the study lesion. Duplex ultrasound patency assessments were not required in the Zilver Flex Japan PMS. The Kaplan-Meier estimates for 12-month primary patency for these two clinical studies is provided in Table 16.

Table 16. Kaplan-Meier estimates for primary patency for the Zilver PTX RCT and in the Zilver Flex Vascular Stent studies

Months	Primary Patency Estimate	Standard Error	Cumulative Failed	Cumulative Censored	Number Remaining
0	100%	0%	0	0	169
6	98.8%	0.8%	2	6	161
12	83.0%	3.3%	26	40	103

In the Zilver Flex Japan PMS, primary patency was evaluated by duplex ultrasound at 12 months where physicians considered this standard of care, with loss of patency corresponding to a peak systolic velocity ratio >2.4. In the absence of a duplex ultrasound with a PSVR, a best available assessment of patency was used. Taking all available data into account for the combined clinical cohort, the 12-month primary Kaplan-Meier estimates are provided in Table 17. In this analysis, the 12-month primary patency rate for the Zilver Flex stent was 85.9%.

Table 17. Kaplan-Meier estimates for primary patency for the combined clinical cohort

Months	Primary Patency Estimate	Standard Error	Cumulative Failed	Cumulative Censored	Number Remaining
0	100%	0%	0	0	369
6	98.3%	0.7%	6	29	334
12	85.9%	2.0%	46	74	249

Clinical Improvement: Change in Rutherford Classification

Rutherford classification was assessed at a patient level at pre-procedure and 12 months. Clinical improvement, defined as improvement in Rutherford classification score by at least 1 class between pre-procedure and 12 months, was assessed by a paired data Wilcoxon signed-rank test. Rutherford classification results are presented in Table 18. Prior to the study procedure, most (59.8%, 202/338) patients reported severe claudication or rest pain and were classified as Rutherford class 3, 4, 5, or 6. At 12 months, only 9.9% (27/273) of patients were similarly classified, and 78.4% (214/273) of patients were reported to be asymptomatic or had mild claudication and were classified as Rutherford class 0 or 1. Clinical improvement of at least 1 Rutherford class was achieved in 84.7% of patients (222/262) at 12 months. The changes in Rutherford classification from baseline to 12 months are statistically significant ($p<0.01$) and indicate sustained improvement of the clinical symptoms associated with PAD in patients treated with the Zilver Flex stent.

Table 18. Rutherford classification for the combined clinical cohort

Rutherford Category	Percent Patients (number/total number)	
	Pre-procedure (n=338)	12-months ^a (n=273)
0	0.3% (1/338)	50.9% (139/273)
1	3.8% (13/338)	27.5% (75/273)
2	36.1% (122/338)	11.7% (32/273)
3	37.6% (127/338)	6.6% (18/273)
4	8.6% (29/338)	0% (0/273)
5	11.2% (38/338)	3.3% (9/273)
6	2.4% (8/338)	0% (0/273)

^a $p < 0.01$ compared to pre-procedure; statistically significant.

Clinical Benefit

Clinical benefit was defined as freedom from persistent or worsening symptoms of ischemia (i.e., claudication, rest pain, ulcer, or tissue loss) after the initial study treatment. Table 19 provides the Kaplan-Meier estimates for clinical benefit for the combined clinical cohort. The 12-month clinical benefit Kaplan-Meier rate is 93.5% for the Zilver Flex stent.

Table 19. Kaplan-Meier estimates for clinical benefit for the combined clinical cohort

Months	Clinical Benefit Estimate	Standard Error	Cumulative Failed	Cumulative Censored	Number Remaining
0	100%	0.0%	0	0	353
6	98.2%	0.7%	6	26	321
12	93.5%	1.4%	21	41	291

Effectiveness Measures Through 36 Months

Table 20 reports the longer term outcomes for freedom from TLR and the rate of clinical benefit for the combined clinical cohort at 24 and 36 months. The 36-month Kaplan-Meier estimates for freedom from TLR for the Zilver PTX RCT, Zilver Flex Vascular Study, and Zilver Flex Japan PMS and are comparable at 76.1%, 75.0%, and 83.6%, respectively.

Table 20. Kaplan-Meier estimates of long-term outcomes

Measure	Kaplan-Meier Estimate	Standard Error	Cumulative Failed	Cumulative Censored	Number Remaining
24-month Outcomes					
Freedom from TLR	82.1%	2.3%	56	68	228
Clinical benefit	90.4%	1.8%	30	74	249
36-month Outcomes					
Freedom from TLR	79.2%	2.8%	63	134	155
Clinical benefit	89.6%	1.9%	32	142	179

3. Subgroup Analysis

Although the study was not powered for this purpose, patient sex, Rutherford Classification (4-6 [critical limb ischemia (CLI)] vs 0-3), and stent length (140 mm or 200 mm vs ≤ 80 mm) were evaluated to determine if there was an effect on the primary effectiveness result (rate of freedom from TLR) in a Cox Proportional Hazards model. There was no difference between males vs. females or patients with CLI on freedom from TLR through the 3-year visit; however, longer stents had a statistically significant greater likelihood to experience TLR, which is typical in this patient population.

No subgroup analysis on race or ethnicity was performed. However, the three clinical studies (e.g., the Zilver PTX RCT, the Zilver Flex Vascular Stent Study, and the Zilver Flex Post Market Study in Japan) enrolled similar patients based on the inclusion and exclusion criteria. The Zilver Flex Post Market Study only enrolled patients in Japan. Results from each individual study are reflective of the results of the combined patient cohort.

4. Pediatric Extrapolation

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

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The clinical trials included 544 principal and sub-investigators none of which were full-time or part-time employees of the sponsor and 15 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 15
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

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

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

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

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The nonclinical engineering testing conducted on the stent and delivery system demonstrated that the performance characteristics of the device met the product specifications. The shelf-life testing has established acceptable performance for a labeled shelf life up to 3 years.

Combined data from three previously-completed Cook-sponsored clinical studies where above-the-knee femoropopliteal artery lesions were treated with the Zilver Flex stent were used to support device effectiveness. The primary effectiveness endpoint was the 12-month freedom from TLR, defined as a reintervention performed for $\geq 50\%$ diameter stenosis within ± 5 mm of the study lesion after recurrent clinical symptoms of PAD. In the Zilver Flex stent group, the point estimate for freedom from TLR at 12 months was determined to be 87.2% (95% CI: 83.3%, 90.5%). The lower bound (83.3%) is greater than the predetermined performance goal (78.2%). Although the Zilver Japan PMS accounted for greater than 50% of the sample size, the patients disease characteristics and the effectiveness outcomes were generally comparable across the three studies, demonstrating that the results are generalizable for the US patient population. The results support the effectiveness of the Zilver Flex stent for the treatment of above-the-knee femoropopliteal lesions.

B. Safety Conclusions

The biocompatibility testing and animal testing support reasonable assurance of the safety of the device for the intended use.

Combined data from three previously completed Cook sponsored clinical studies where above-the-knee femoropopliteal artery lesions were treated with the Zilver Flex stent were used to support device safety. The primary safety endpoint was defined as freedom from all-cause death, amputation, or TVR at 30 days. Freedom from all-cause death, amputation, or TVR at 30 days was determined to be 98.0% in the Zilver Flex stent group which compared favorably to the VIVA performance goal of 88%¹ ($p < 0.01$). The results support the safety of the Zilver Flex stent for the treatment of above-the-knee femoropopliteal lesions.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in three clinical studies. The probable benefits of the Zilver Flex stent and delivery system include improving or restoring blood flow in patients with peripheral arterial disease to improve the patient symptoms and quality of life.

The probable risks of the device are also based on data collected in three clinical studies. Overall, the frequency and types of the adverse events reported throughout the clinical studies are in alignment with what might be expected in the studied patient population and therapeutic area. No unanticipated adverse device effects were reported in the study.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for using the Zilver Flex Stent to improve the luminal diameter in the treatment of de novo or restenotic symptomatic lesions in the native above-the-knee femoropopliteal arteries with reference vessel diameters from 4 mm to 7 mm and lesion lengths up to 190 mm.

1. Patient Perspectives: This supplement did not include specific information on patient perspectives for this device.

D. Overall Conclusions

The non-clinical and clinical data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The results of a prospectively planned analysis from data collected across three clinical studies in which above-the-knee femoropopliteal artery lesions were treated with the Zilver Flex stent demonstrate that the device is safe and effective when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on 07/01/2025.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

1. Rocha-Singh KJ, Jaff MR, Crabtree TR, et al; for VIVA Physicians, Inc. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. *Catheter Cardiovasc Interv.* 2007;69:910-919.
2. Bertges DJ, White R, Cheng Y-C, et al; for the Registry Assessment of Peripheral Interventional Devices (RAPID) and Superficial Femoral Artery-Popliteal Evidence Development (SPEED) Study Group. Registry assessment of peripheral interventional devices objective performance goals for superficial femoral and popliteal artery peripheral vascular interventions. *J Vasc Surg.* 2021;73:1702-1714.