SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Drug-Eluting Peripheral Stent
Device Trade Name:	Zilver PTX Drug-Eluting Peripheral Stent
Device Procode:	NIU
Applicant's Name and Address:	Cook Medical Incorporated 750 Daniels Way Bloomington, IN 47404
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P100022/S020
Date of FDA Notice of Approval:	December 28, 2016

The original PMA (P100022) was approved on November 14, 2012 and is indicated for improving luminal diameter for the treatment of *de novo* or restenotic symptomatic lesions in native vascular disease of the above-the-knee femoropopliteal arteries having reference vessel diameter from 4 mm to 7 mm and total lesion lengths up to 140 mm per limb and 280 mm per patient. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the Zilver PTX Drug-Eluting Peripheral Stent.

II. INDICATIONS FOR USE

The Zilver® PTX® Drug-Eluting Stent is indicated for improving luminal diameter for the treatment of *de novo* or restenotic symptomatic lesions in native vascular disease of the above-the-knee femoropopliteal arteries having reference vessel diameter from 4 mm to 7 mm and total lesion lengths up to 300 mm per patient.

III. CONTRAINDICATIONS

- Women who are pregnant, breastfeeding, or plan to become pregnant in the next 5 years should not receive a Zilver PTX Drug-Eluting Stent. It is unknown whether paclitaxel will be excreted in human milk, and there is a potential for adverse reaction in nursing infants from paclitaxel exposure.
- Patients who cannot receive recommended anti-platelet and/or anti-coagulant therapy.
- Patients judged to have a lesion that prevents proper placement of the stent or stent delivery system.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Zilver PTX Drug-Eluting Peripheral Stent labeling.

V. DEVICE DESCRIPTION

The Zilver® PTX® Drug-Eluting Peripheral Stent (Zilver PTX stent) is a self- expanding nitinol stent coated on its outer surface with the drug paclitaxel (without any polymer, binder, or excipient) at a dose density of 3 μg/mm^2.

Device Component Description

The Zilver PTX stent is preloaded in a 6 Fr delivery system. Upon deployment, the Zilver PTX stent is designed to establish and maintain patency in the stented region. To facilitate fluoroscopic visualization of the stent, 4 radiopaque gold markers are positioned on each end of the device (**Figure 1**).

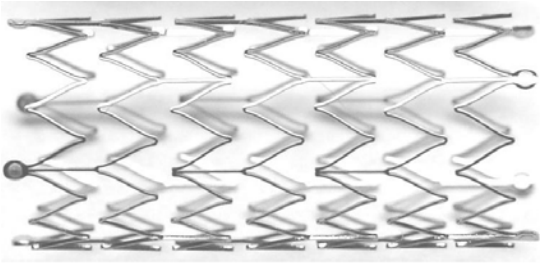
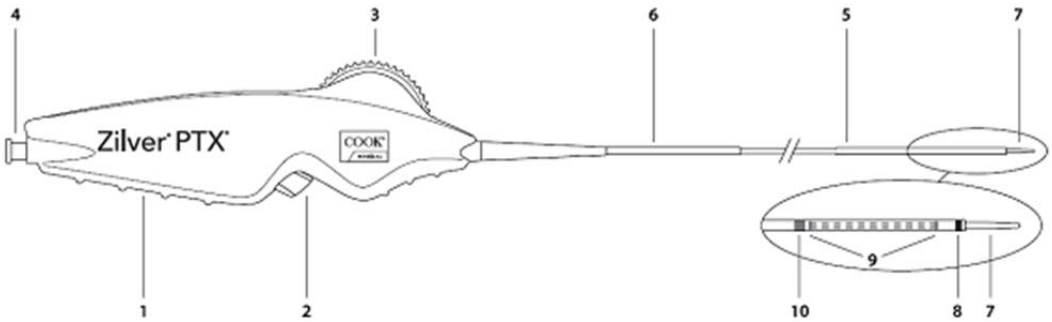
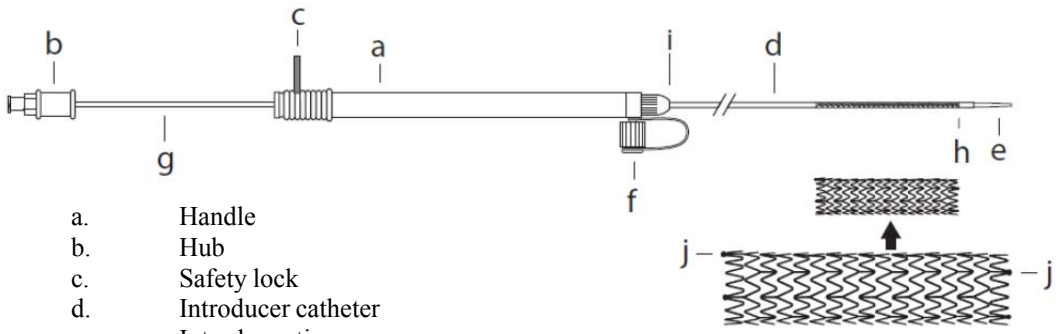


Figure 1: Photograph of the Zilver stent

Both a thumbwheel delivery system and a pin and pull delivery system are available in 80 cm and 125 cm lengths and compatible with a 0.035 inch wire guide. The Zilver PTX thumbwheel delivery system, approved in P100022/S014, utilizes a 6 French (Fr) tri-axial delivery catheter, consisting of an inner catheter, stent retraction sheath, and stability sheath, and a thumbwheel-operated handle. Schematics of both delivery systems are provided in **Figure 2**.



1 – Ergonomic thumbwheel-operated handle
2 – Safety lock
3 – Thumbwheel
4 – Luer hub/FLLA (flushing port)
5 – Retraction sheath
6 – Stability sheath
7 – Tip of delivery system inner catheter
8 – Radiopaque marker band on retraction sheath
9 – Gold radiopaque markers on stent
10 – Stent stop



a. Handle
b. Hub
c. Safety lock
d. Introducer catheter
e. Introducer tip
f. Side-arm flushing port
g. Metal cannula
h. Radiopaque marker on the delivery system
i. Strain relief
j. Gold radiopaque markers on the stent

Figure 2: Schematic drawing of the Zilver PTX stent and delivery system

Table 1 shows the available diameters and lengths of the Zilver PTX stent.

Table 1: Sizes of Zilver PTX stents

Stent Outer Diameter (mm)	**Stent Length (mm)**						
	20	30	40	60	80	100	120
6	✓	✓	✓	✓	✓	✓	✓
7	✓	✓	✓	✓	✓	✓	✓
8	✓	✓	✓	✓	✓	✓	✓

Drug Component Description

Paclitaxel is extracted from the bark, branches, or needles of the yew tree, then purified and concentrated by column chromatography, crystallization, and recrystallization. Zilver PTX stents are coated with paclitaxel API (active pharmaceutical ingredient) using a proprietary process. No excipients, polymers, carriers, binding agents, other materials, or other device modifications are involved. The chemical description of paclitaxel is provided in **Figure 3**.

Paclitaxel

- Synonyms: Taxol, Taxol A, Hunxol I, Paclitaxelum
- IUPAC systematic name: *β-(benzoylamino)-α-hydroxy-,6,12b-bis(acetyloxy)-12-(benzoyloxy) 2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca(3,4)benz(1,2-b)oxet-9-yl ester,(2aR-(2a-α,4-β,4a-β,6-β,9-α(α-R*,β-S*),11-α,12-α,12a-α,2b-α))-benzenepropanoic acid*
- CAS registry number: 33069-62-4
- Chemical formula: $C_{47}H_{51}NO_{14}$
- Structure of paclitaxel:

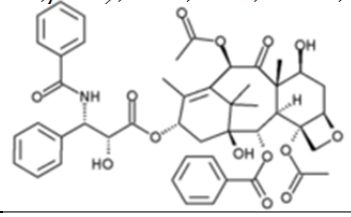


Figure 3: Chemical description of paclitaxel

Paclitaxel is known to bind to microtubules and inhibit their molecular disassembly into tubulin, thus arresting mitosis. This action can prevent the smooth muscle cell proliferation and migration known to occur during the restenotic process in arteries. Several studies in animal models have shown that paclitaxel applied locally reduces restenosis by inhibiting smooth muscle cell proliferation and neointimal hyperplasia.

Table 2 presents the stent sizes and the nominal total quantity of paclitaxel on each stent based on the established dose density of 3µg/mm^2.

Table 2: Paclitaxel total quantity by stent size (for dose density of 3 µg/mm^2)

Stent Size (diameter x length, mm)	Total Paclitaxel (µg/stent)
6 x 20	171
7 x 20	171
8 x 20	178
6 x 30	298
7 x 30	298
8 x 30	267
6 x 40	383
7 x 40	383
8 x 40	356
6 x 60	552
7 x 60	552
8 x 60	579
6 x 80	722
7 x 80	722
8 x 80	757
6 x 100	934
7 x 100	934
8 x 100	935
6 x 120	1103
7 x 120	1103
8 x 120	1112

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

- Non-invasive treatment (exercise and/or drug therapy)
- Minimally invasive treatment (balloon angioplasty, endovascular stent placement of a non-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 PTX stent was approved in the United States on November 14, 2012 with the indication to improve luminal diameter for the treatment of *de novo* or restenotic symptomatic lesions in native vascular disease of the above-the-knee femoropopliteal arteries having reference vessel diameter from 4 mm to 7 mm and total lesion lengths up to 140 mm per limb and 280 mm per patient.

The Zilver PTX stent is commercially available in the European Union, Argentina, Algeria, Australia, Bahrain, Belarus, Brazil, Canada, Chile, Colombia, Costa Rica, Ecuador, Egypt, El Salvador, Guatemala, Hong Kong, Israel, Japan, Jersey, Korea, Kuwait, Lebanon, Macau, Malaysia, Martinique, Mexico, New Zealand, Nicaragua, Norway, Oman, Panama, Peru, Puerto Rico, Reunion, Russia, Saudi Arabia, Taiwan, Thailand, Turkey, Ukraine, UAE, Uruguay, Venezuela, Serbia, Yugoslavia.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Allergic reaction to anticoagulant and/or antithrombotic therapy or contrast medium
- Allergic reaction to nitinol
- Arterial aneurysm
- Arterial rupture
- Arterial thrombosis
- Arteriovenous fistula
- Atheroembolization (Blue Toe Syndrome)
- Death
- Embolism
- Hematoma/hemorrhage
- Hypersensitivity reactions
- Infection
- Infection/abscess formation at access site
- Ischemia requiring intervention (bypass or amputation of toe, foot, or leg)
- Pseudoaneurysm formation
- Renal failure
- Restenosis of the stented artery
- Stent embolization
- Stent malapposition
- Stent migration
- Stent strut fracture
- Vessel perforation or rupture
- Worsened claudication/rest pain

Although systemic effects are not anticipated, refer to the Physicians' Desk Reference for

more information on the potential adverse events observed with paclitaxel.

Potential adverse events, not described in the above source, may be unique to the paclitaxel drug coating:

- Allergic/immunologic reaction to the drug coating
- Alopecia
- Anemia
- Blood product transfusion
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage, or necrosis
- Myalgia/arthralgia
- Myelosuppression
- Peripheral neuropathy

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

IX. SUMMARY OF PRE-CLINICAL STUDIES

The design of the Zilver PTX stent was not changed from the currently-marketed device. Therefore, the potential effects of the modified indication formed the basis for the preclinical test strategy. An additional animal study and an additional magnetic resonance imaging study were performed as described in **Table 3**. All other pre-clinical data previously reviewed under P100022 and subsequent supplements were found to be adequate to support the increased lesion length indication in the current PMA Supplement. Please see the SSED for the original PMA for other pre-clinical study details.

Table 3: Additional non-clinical tests to support modified indication

Test	Purpose/Objective	Acceptance Criteria	Test Results
One-month Study of Zilver® Stents Coated with Paclitaxel in Domestic Swine Peripheral Arteries – An Evaluation of Regional Effects	Characterize the regional responses associated with the implantation of multiple Zilver PTX stents with a total Paclitaxel dose of approximately 10,500 μg in a single limb: • Angiography • Complete necropsy with detailed evaluation of downstream, hindlimb tissues • Histopathology • Animal health and clinical pathology	Characterization Study	Support the regional (per limb) safety of the Zilver PTX stent for a total stented length up to 360 mm.

Magnetic Resonance Imaging (MRI) compatibility	Evaluate the safety and compatibility of the Zilver PTX stent for a total stented length of approximately 395 mm by assessment of the MRI-related heating (ASTM F2182) at 1.5 Tesla and 3 Tesla field strengths.	Characterization Study	The device was established as MR Conditional.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a retrospective analysis to establish a reasonable assurance of safety and effectiveness to expand the Indication for Use of the Zilver PTX stent to include treatment of lesions up to 300 mm in length. Data from this retrospective analysis were the basis for the PMA Supplement approval decision. A summary of the retrospective analysis is provided below.

A. Study Design

Patients were treated between April 7, 2006 and June 18, 2008 at 30 sites in Europe Canada, and South Korea. The database for this PMA supplement reflected data collected through April 15, 2011 and included 665 patients.

The analysis was a retrospective analysis of the longer lesion patient cohorts from the Zilver PTX single-arm clinical study (SAS), a multi-center trial at 30 sites in Europe, Canada, and South Korea. These analyses include three subgroups of patients from the SAS with lesion lengths up to 140 mm, > 140 mm to 240 mm, and > 240 mm to 300 mm to support expanding the indication for use to include treatment of lesions up to 300 mm in length. All patients and lesions in the Zilver PTX SAS were included in the proposed analyses, with the exception of lesions where data on the length was missing, lesions > 300 mm, and lesions enrolled for treatment of in-stent restenosis (ISR), since treatment of ISR is not included in the currently approved indication.

There was no control group or prospectively-defined performance goal for this retrospective analysis. An independent Clinical Events Committee (CEC) and Data Safety Monitoring Board (DSMB) were established for this study to provide oversight and review.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the Zilver PTX SAS was limited to patients who met the following inclusion criteria:

   - Patient has signed and dated the informed consent.
   - Patient has documented stenotic or occluded atherosclerotic lesions of the above-the-knee femoropopliteal artery which meet all of the inclusion criteria and none of the exclusion criteria.
   - Patient has a reference vessel diameter ranging from 4-9 mm in diameter.
   - Patient has a *de novo* or restenotic lesion(s) with > 50% stenosis documented angiographically.

- Patient has symptoms of peripheral arterial disease classified as Rutherford category 2 or greater.
- Patient agrees to follow-up including:
    - clinical status assessment at 1 month, 6 months, 12 months, and 2 years,
    - ultrasound at 6 months and 12 months,
    - x-rays at 6 and 12 months, and
    - telephone contact at 3, 9, and 18 months.

Patients were not permitted to enroll in the Zilver PTX SAS if they met any of the following exclusion criteria:

- Patient is pregnant or breast-feeding.
- Patient is simultaneously participating in another investigational drug or device study. The patient must have completed the follow-up phase for the primary endpoint of any previous study at least 30 days prior to enrollment in this study.
- Patient has significant stenosis (> 50%) or occlusion of inflow tract (proximal ipsilateral, iliofemoral, or aortic lesions) not successfully treated before this procedure (success is measured as < 30% residual stenosis).
- Patient lacks at least one patent vessel of runoff with < 50% stenosis throughout its course.
- Patient has undergone an unsuccessful arterial interventional treatment of the legs (i.e., the treatment resulted in > 30% residual stenosis of a treated lesion) within 30 days prior to the study procedure.
- Patient has experienced complications of an arterial access site in the legs within 30 days prior to the study procedure.
- Patient has any planned surgical or interventional procedure within 30 days after the study procedure.
- Patient has a medical condition or disorder that would limit life expectancy to less than 1 year or that may cause noncompliance with the protocol or confound the data analysis.
- Patient has a known left ventricular ejection fraction < 25%.
- Patient has a New York Heart Association Classification of 4.
- Patient has had a myocardial infarction within the last 90 days.
- Patient in whom antiplatelet and/or anticoagulant therapy is contraindicated.
- Patient has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions.
- Patient has known hypersensitivity or contraindication to aspirin, antiplatelet medication, contrast dye, paclitaxel, or nitinol that, in the opinion of the investigator, cannot be adequately premedicated.
- Patient has a target lesion located within a synthetic graft.
- Patient has an untreated systemic or local infection, or infection treated for less than 10 days prior to the procedure.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 1 month, 6 months, 12 months, and 24 months postoperatively.

Preoperatively, the following clinical evaluations were performed: baseline Rutherford classification, bilateral ankle-brachial index (ABI), functional status assessment (Walking Impairment Questionnaire (WIQ) and Quality of Life (QOL) Questionnaire), complete blood count (CBC) and blood chemistry, and diagnostic angiography. Postoperatively, the objective parameters measured during the study included:

- *Post-procedural*: Angiography (after stent implantation) and ultrasound subset, bilateral ABI, x-ray, and CBC and blood chemistry prior to discharge.
- *1 month (30 ± 15 days):* Clinical assessment with WIQ, QOL, bilateral ABI, Rutherford, and CBC and blood chemistry.
- *3 months (90 days):* Telephone contact.
- *6 months (180 ± 30 days):* Clinical assessment with WIQ, QOL, bilateral ABI, Rutherford, x-ray, ultrasound subset, and CBC and blood chemistry.
- *9 months (270 ± 30 days):* Telephone contact.
- *12 months (365 ± 45 days):* Clinical assessment with WIQ, QOL, bilateral ABI, Rutherford, x-ray, ultrasound subset, and CBC and blood chemistry.
- *18 months (545 days):* Telephone contact.
- *2 years (730 ± 60 days):* Clinical assessment with WIQ, QOL, bilateral ABI, Rutherford, and CBC and blood chemistry.

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

3. Clinical Endpoints

With regards to safety, the following primary endpoints were assessed: freedom from all-cause death, amputation, or target vessel revascularization (TVR) at 30 days post-procedure. Secondary endpoints included freedom from all-cause death or amputation at 12 and 24 months post-procedure.

With regards to effectiveness, the following primary endpoint was assessed: primary patency at 12 months post-procedure. The secondary endpoint of freedom from target lesion revascularization (TLR) at 12 and 24 months post-procedure was also evaluated.

There were no success/failure criteria for this retrospective analysis

B. Accountability of PMA Cohort

A total of 787 patients with 900 lesions were enrolled in the SAS, and 665 patients with 755 lesions were included in this analysis. Lesions that were treated for in-stent restenosis (ISR), had a lesion length > 300 mm, or missing lesion length information

were excluded from the analyses. Of the patients included, 493 patients had 574 lesions up to 140 mm in length, 110 patients had 116 lesions > 140 mm to 240 mm in length, and 62 patients had 65 lesions > 240 mm to 300 mm in length.

Clinical follow-up at 12 months was completed for 444 patients with lesions ≤ 140 mm, 95 patients with lesions > 140 mm to 240 mm, and 54 patients with lesions > 240 mm to 300 mm. At 24 months, 399, 82, and 47 patients completed clinical follow-up for the respective lesion length groups.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a study performed in the U.S. Characteristics of the subjects and lesions analyzed are provided in the **Tables 4 and 5**.

Table 4: Demographics and medical history

Demographic		**Lesion Length ≤ 140 mm (n=493 patients)**	**Lesion Length > 140 mm to 240 mm (n=110 patients)**	**Lesion Length > 240 mm to 300 mm (n=62 patients)**
Age (years)		66.9 ± 9.6	66.9 ± 9.5	66.4 ± 9.2
Gender	Male	75.1% (370/493)	74.5% (82/110)	82.3% (51/62)
	Female	24.9% (123/493)	25.5% (28/110)	17.7% (11/62)
Height (cm)		66.5 ± 3.2	66.1 ± 3.2	67.2 ± 3.4
Weight (kg)		172.9 ± 31.5	174.3 ± 37.3	177.1 ± 32.3
Diabetes		36.9% (182/493)	39.1% (43/110)	19.4% (12/62)
Diabetes type	Type I	8.2% (15/182)	9.3% (4/43)	25.0% (3/12)
	Type II	91.8% (167/182)	90.7% (39/43)	75.0% (9/12)
Hypercholesterolemia		54.0% (266/493)	62.7% (69/110)	59.7% (37/62)
Hypertension		78.3% (386/493)	82.7% (91/110)	75.8% (47/62)
Carotid disease		10.3% (51/493)	8.2% (9/110)	11.3% (7/62)
Renal disease		10.3% (51/493)	13.6% (15/110)	3.2% (2/62)
Pulmonary disease		8.5% (42/493)	9.1% (10/110)	8.1% (5/62)
Congestive heart failure		8.8% (43/491)	14.5% (16/110)	14.5% (9/62)
Previous MI		14.3% (70/490)	20.0% (22/110)	19.4% (12/62)
Smoking status	Never smoked	17.4% (86/493)	18.2% (20/110)	9.7% (6/62)
	Quit	45.2% (223/493)	40.0% (44/110)	50.0% (31/62)
	Still smokes	34.3% (169/493)	39.1% (43/110)	35.5% (22/62)
	Unknown	3.0% (15/493)	2.7% (3/110)	4.8% (3/62)

Table 5: Lesion characteristics

Characteristic	**Lesion Length ≤ 140 mm (n=574 lesions)**	**Lesion Length > 140 mm to 240 mm (n=116 lesions)**	**Lesion Length > 240 mm to 300 mm (n=65 lesions)**
Lesion length (mm)	55.3 ± 34.4	185.7 ± 28.3	265.8 ± 18.0
Proximal RVD (mm)	5.3 ± 0.8	5.4 ± 0.9	5.8 ± 1.0
Distal RVD (mm)	5.2 ± 0.8	5.2 ± 0.8	5.4 ± 1.0
MLD in lesion (mm)	1.0 ± 0.9	0.4 ± 0.7	0.1 ± 0.2
Percent diameter stenosis (%)	80.7 ± 17.1	93.4 ± 12.9	99.2 ± 3.2
Previous treatment of study lesion	11.0% (63/574)	12.1% (14/116)	15.4% (10/65)

Characteristic		Lesion Length ≤ 140 mm (n=574 lesions)	Lesion Length > 140 mm to 240 mm (n=116 lesions)	Lesion Length > 240 mm to 300 mm (n=65 lesions)
Calcification	None	18.5% (106/574)	13.8% (16/116)	9.2% (6/65)
	Little	32.6% (187/574)	39.7% (46/116)	23.1% (15/65)
	Moderate	30.7% (176/574)	29.3% (34/116)	36.9% (24/65)
	Severe	18.3% (105/574)	17.2% (20/116)	30.8% (20/65)
Total occlusion		26.1% (150/574)	70.7% (82/116)	92.3% (60/65)
Other stenosis in artery	None	68.6% (394/574)	61.2% (71/116)	63.1% (41/65)
	≤ 50%	18.5% (106/574)	28.4% (33/116)	30.8% (20/65)
	> 50%	11.8% (68/574)	8.6% (10/116)	3.1% (2/65)
Inflow tract stenosis	None	78.7% (452/574)	65.5% (76/116)	64.6% (42/65)
	≤ 50%	18.1% (104/574)	31.0% (36/116)	27.7% (18/65)
	> 50%	0.9% (5/574)	0% (0/116)	0% (0/65)
Patent runoff vessels	1	18.5% (106/574)	16.4% (19/116)	16.9% (11/65)
	2	32.1% (184/574)	43.1% (50/116)	43.1% (28/65)
	3	48.1% (276/574)	38.8% (45/116)	35.4% (23/65)
	> 3	0.7% (4/574)	0% (0/116)	1.5% (1/65)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of 660 patients available for the 30-day evaluation. The key safety outcomes for this study are presented below in **Table 6**.

Table 6: Analysis of primary safety endpoint

Measure	Lesion Length	Result	
		Kaplan-Meier Estimate*	% (n/N)
Freedom from all-cause death, amputation, or TVR at 30 days post-procedure	≤ 140 mm	98.8%	98.8% (482/488)
	> 140 mm to 240 mm	97.3%	97.3% (107/110)
	> 240 mm to 300 mm	96.8%	96.8% (60/62)

* 11 events occurred, 4 patients were censored, and 645 patients remained at risk at 30 days.

Adverse events observed for patients treated with longer lesion lengths were captured and categorized. There were no concerning safety trends across lesion lengths or compared to the pivotal cohorts used to support P100022.

2. Effectiveness Results

The analysis of effectiveness was based on the 701 lesions in 593 patients evaluable at the 12-month time point. Fifty-four lesions that did not have patency information were excluded from the analysis. Key effectiveness outcomes are presented in **Table 7**.

Table 7: Analysis of primary effectiveness endpoint

Measure	Lesion Length	Result	
		Kaplan-Meier Estimate*	% (n/N)
Primary patency at 12 months post-procedure	≤ 140 mm	91.3%	91.6% (488/533)
	> 140 mm to 240 mm	73.2%	73.6% (81/110)
	> 240 mm to 300 mm	73.5%	74.1% (43/58)

* 89 events occurred, 42 lesions were censored, and 570 lesions remained at risk at 12 months.

3. Additional Outcomes

Additional analyses of longer-term safety, longer-term safety and effectiveness, and device integrity were performed to provide further information supporting the performance of the Zilver PTX stent in lesions up to 300 mm. Longer-term safety, assessed by freedom from all-cause death and amputation, and longer-term safety and effectiveness, assessed by freedom from TLR, were both shown to have clinically acceptable rates through 24 months. The rates of freedom from all-cause death or amputation at 12 and 24 months were 98.3% and 98.1% for lesions up to 140 mm, 96.3% and 92.9% for lesions > 140 mm to 240 mm, and 98.4% and 98.4% for lesions > 240 mm to 300 mm. The rates of freedom from TLR at 12 and 24 months were 92.9% and 88.1% for lesions up to140 mm, 75.6% and 71.3% for lesions > 140 mm to 240 mm, and 84.9% and 74.7% for lesions > 240 mm to 300 mm.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The Zilver PTX SAS included 129 investigators of which none were full-time or part-time employees of the sponsor and 6 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: 6
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

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

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Results from a Japanese post-market surveillance study further support the safety and effectiveness of the Zilver PTX stent for the treatment of lesions > 140 mm. The Japanese post-market surveillance study had no inclusion/exclusion criteria and enrolled 905 patients who were treated with the Zilver PTX stent. Patient medical history included a high incidence of diabetes (58.8%), hypercholesterolemia (60.8%), hypertension (85.4%), renal disease (43.6%), and renal failure (35.5%). Critical limb ischemia (Rutherford classification 4-6) was present in 21.2% of limbs. Lesions treated in the study had a mean length of 146 ± 96 mm, 41.5% of lesions were classified as total occlusions, and 18.6% of lesions entered the study with in-stent restenosis. Freedom from TLR was 90.9%, 83.6%, and 79.8% at 1, 2, and 3 years, respectively.

Of the total 905 patients enrolled in the study, 717 patients with 842 lesions were included in an analysis by lesion length, including 391 patients with 494 lesions up to 140 mm in length, 183 patients with 201 lesions > 140 mm to 240 mm in length, and 143 patients with 147 lesions > 240 mm to 300 mm in length. Average lesion length was 68 ± 34 mm, 187 ± 27 mm, and 266 ± 23 mm in each length group, respectively, and total occlusions were present in 26.3%, 53.2%, and 72.8% of lesions within each group. Freedom from TLR at 1, 2, and 3 years was 95.5%, 91.4%, and 87.8% for lesions up to 140 mm, 92.2%, 83.4%, and 81.4% for lesions > 140 mm to 240 mm, and 88.5%, 78.8%, and 70.4% for lesions > 240 mm to 300 mm. Primary patency at 1 year was 90.5%, 83.2%, and 80.0% for lesions up to140 mm, > 140 mm to 240 mm, and > 240 mm to 300 mm, respectively. The results from this study provide additional evidence to support the use of the Zilver PTX stent in lesions > 140 mm.

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

In accordance with the provisions of section 515(c)(2) 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

Non-clinical and clinical testing support the expansion of the indications for the treatment for lesions up to 300 mm in length. A majority of the preclinical evaluations were leveraged from the original PMA and subsequent supplements. Clinical effectiveness was assessed by evaluation of the primary patency rate at 12 months post-procedure in patients with long lesions treated with the Zilver PTX stent in a multi-center trial at 30 sites in Europe, Canada, and South Korea. The 12-month patency results for lesion length subgroups ≤ 140 mm, > 140 mm to 240 mm, and > 240 mm to 300 mm were 91.3%, 73.2%, and 73.5%, respectively. Although there

trends a reduction of effectiveness in longer lesions, these results are reasonable and expected from a clinical perspective. The overall data support the effectiveness of the Zilver PTX stent in its intended use.

B. Safety Conclusions

The risks of the device were based on non-clinical and clinical testing conducted to support supplement approval for the expansion of the indications for use for lesions up to 300 mm in length. Results from the retrospective analysis of the Zilver PTX single-arm multi-center OUS study demonstrate that the device is acceptable for clinical use. Safety was assessed by evaluation of the combined rate of freedom from all-cause death, amputation, or TVR at 30 days post-procedure for the Zilver PTX stent. At 30 days, 98.8% of patients with lesions ≤ 140 mm, 97.3% of patients with lesions > 140 mm to 240 mm, and 96.8% of patients with lesions > 240 mm to 300 mm remained free from death, amputation, or TVR. Longer term safety is supported by the original pivotal trials results, which demonstrated an 86.6% freedom from major adverse event rate at 24 months. Results and adverse events are in alignment with results from the pivotal clinical trial used to support the original PMA.

C. Benefit-Risk Conclusions

The probable benefits of the Zilver PTX stent are based on data collected in an OUS clinical study conducted to expand the indications, as described above. The results of the Zilver PTX single-arm study show positive clinical outcomes in terms of safety and effectiveness endpoints and outweigh risks when used as intended according to the Instructions for Use.

Additional factors to be considered in determining probable risks and benefits for the Zilver PTX stent for lesions up to 300 mm in length included:

- The data were robust. The study was also overseen by an independent CEC and DSMB.
- Though the retrospective analysis was not pre-specified, the results demonstrated adequate clinical outcomes.

The results were determined to be applicable to the U.S. population based on similarities in baseline demographics and lesion characteristics from this OUS study as compared to the pivotal clinical trial.

D. Patient Perspectives

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

E. Overall Conclusions

In conclusion, given the available information described above, the data support that for treatment of lesions up to 300 mm in length, the probably benefits outweigh the probably risks. The data show that the Zilver PTX stent can be used in lesions up to

300 mm in length and can provide an effective treatment with acceptable patency and freedom from reintervention. The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on December 28, 2016. There are no conditions of approval

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.