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
Applicant's Name and Address:	Cook Incorporated 750 Daniels Way Bloomington, IN 47404
Date of Panel Recommendation:	October 13, 2011
Premarket Approval Application (PMA) Number:	P100022
Date of FDA Notice of Approval:	November 14, 2012

II. INDICATIONS FOR U

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 9 mm and total lesion lengths up to 140 mm per limb and 280 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 (Instructions for Use).

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 $\mu g/mm^2$.

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).

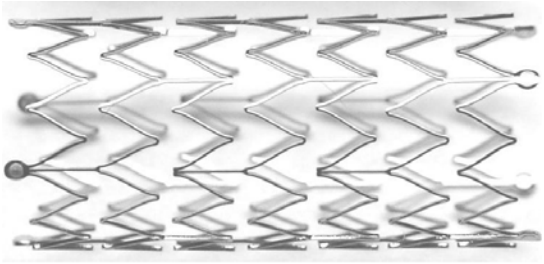
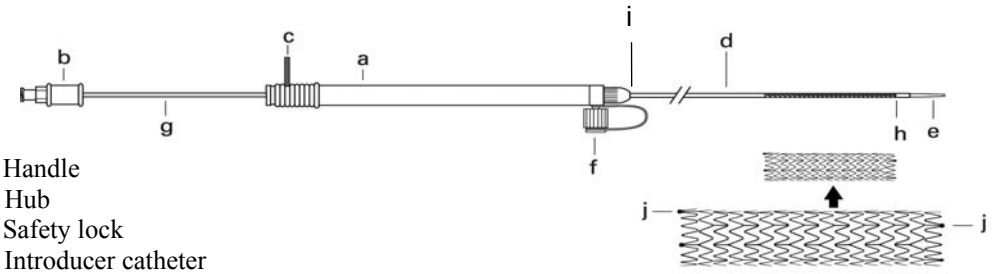


Figure 1: Photograph of the Zilver stent

The delivery system is available in 80 cm and 125 cm lengths and is compatible with a 0.035 inch wire guide (Figure 2). The delivery system is identical to that used with the currently approved Zilver Vascular Stent (P050017).



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
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. Paclitaxel is the same API as used in the currently approved TAXUS® Express^{2}® Paclitaxel-Eluting Coronary Stent System (P030025), TAXUS® Liberté® Paclitaxel-Eluting Coronary Stent System (P060008), and ION™ Paclitaxel-Eluting Platinum Chromium Coronary Stent System (P100023). The chemical description of paclitaxel is provided in Figure 3.

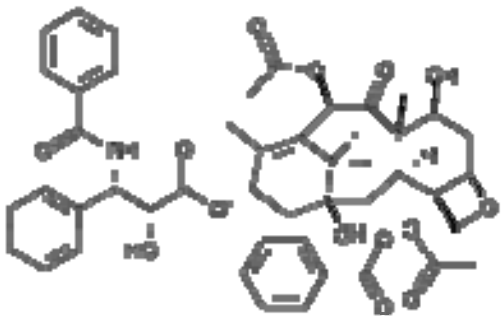
Paclitaxel
• Synonyms: Taxol, Taxol A, Hunxol I, Paclitaxelum • IUPAC systematic name: *β-(benzoylamino)-α-hydroxy-,6,12b-bis(acetyloxy)-12-(benzoyloxy) 2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca(3,4)benz(1,2-b)oxet-9-yl ester,(2aR-(2a-α,4-β,4a-β,6-β,9-α(α-R*,β-S*),11-α,12-α,12a-α,2b-α))-ben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

Figure 3: Chemical description of paclitaxel

The exact mechanism by which a Zilver PTX stent affects neointimal production has not been established. 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. Clinical studies of the TAXUS® stent and the V-Flex Plus™ Paclitaxel Coated Stent have demonstrated that paclitaxel reduces restenosis in coronary vasculature.

Table 2 presents the stent sizes and the nominal total quantity of paclitaxel on each stent based on the established dose density of 3 μg/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	174
7 x 20	174
8 x 20	180
6 x 30	261
7 x 30	261
8 x 30	270
5 x 40	390
6 x 40	390
7 x 40	390
8 x 40	360
6 x 60	564
7 x 60	564
8 x 60	540
6 x 80	738
7 x 80	738
8 x 80	762

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, 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 is commercially available in the following countries:

Afghanistan, Algeria, Albania, Andorra, Argentina, Austria, Bahrain, Belgium, Belarus, Benin, Bosnia-Herzegovina, Botswana, Brazil, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Chile, Congo Dem. Rep., Congo Republic, Cyprus, Czech Republic, Denmark, Dom. Rep., Equatorial Guinea,

Estonia, Ethiopia, Finland, former Yugoslav Republic, France, Gabon, Gambia, Ghana, Germany, Greece, Guinea, Hong Kong, Hungary, Iceland, Iran, Ireland, Italy, Jordan, Kenya, Latvia, Lebanon, Liechtenstein, Lithuania, Luxembourg, Madagascar, Malawi, Malaysia, Mali, Malta, Mauritania, Mauritius, Moldova, Monaco, Morocco, Mozambique, New Zealand, Niger, Nigeria, the Netherlands, Norway, Oman, Pakistan, Peru, Poland, Portugal, Qatar, Romania, Russia, Rwanda, San Marino, Saudi Arabia, Senegal, Serbia Montenegro, Sierra Leone, Singapore, Somalia, South Africa, South Korea, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Tanzania, Thailand, Togo, Tunisia, Turkey, UAE, Uganda, UK, Ukraine, Vatican City, Yemen, Zambia

As of May 31, 2011, approximately 4,472 Zilver PTX stents have been distributed outside the U.S. No products have 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) 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 IDE clinical study, please see Section X, below.

IX. SUMMARY OF PRE-CLINICAL STUDIES

A. Laboratory Studies

Biocompatibility

A thorough panel of biocompatibility testing was performed on the Zilver PTX stent and delivery system in accordance with ISO 10993 and 21 CFR 58 Good Laboratory Practice (GLP) requirements to demonstrate that the components are

non-toxic. Specifically, the Zilver PTX stent was assessed by tests considered appropriate under ISO 10993-1 for a permanent (> 30 days) implantable blood-contacting device. Similarly, biocompatibility of the Zilver PTX delivery system was assessed by tests considered appropriate under ISO 10993-1 for a limited-contact (< 24 hours) externally communicating device within circulating blood.

Table 3 and Table 4 summarize the test results for the Zilver PTX stent and delivery system, respectively.

Table 3: Summary of biocompatibility testing on Zilver PTX stent

Test Name	Purpose of Test	Test Results
Subchronic Intravenous Toxicity Study (Aqueous extract)	Determine whether the test article would cause systemic toxicity	No evidence of systemic toxicity from the test article extracts injected intravenously into rats
In vitro Hemolysis Study (Modified ASTM-Extraction Method)	Determine whether test article would cause *in vitro* hemolysis	The test article extract was considered to be nonhemolytic
In vitro Hemolysis Study (Direct contact)	Determine whether test article direct contact would cause *in vitro* hemolysis	The test article in direct contact was considered to be hemocompatible
Cytotoxicity Study Using the ISO Elution Method (1X MEM Extract)	Determine whether test article would cause cytotoxicity and cell lysis	The test article extract showed no evidence of causing cell lysis or toxicity
ISO Muscle Implantation Study-2 Week	Determine the potential for toxic response to test articles implanted in direct contact with muscle tissue	No evidence of macroscopic or microscopic reaction to the implanted test article
ISO Muscle Implantation Study-12 Week		
C3a Complement Activation Assay (Serum extract)	Evaluate the test article's potential to activate the C3a complement system	The test article extract was considered to be non activator of the complement system
Plasma Recalcification Time Coagulation Study (Plasma extract)	Determine whether test article would cause a change in degree of inhibition or promotion of clotting time	The test article extract had no significant effect on recalcification time compared to the negative control
USP and ISO Systemic Toxicity Study (Aqueous and cottonseed oil extract)	Determine whether the test article would cause acute systemic toxicity	There was no mortality or evidence of significant systemic toxicity over the 72 hour test period from the test article extracts compared to the control blank extracts
ISO Intracutaneous Study (Aqueous and sesame oil extract)	Determine whether test article would cause local dermal irritation or toxic effects	There was no evidence of significant irritation over the 72 hour test period from the test article extracts injected intracutaneously into rabbits compared to the control blank extracts
Genotoxicity: Bacterial Reverse Mutation Study (DMSO Extract)	Determine whether test article would cause mutagenic changes in *S. typhimurium* and *E. coli* tester	The test article extract was considered non-mutagenic to *S. typhimurium* and *E. coli* tester

Test Name	Purpose of Test	Test Results
Genotoxicity: Bacterial Reverse Mutation Study (Saline Extract)	*typhimurium* and *E. coli* strains	strains
Genotoxicity: *In vitro* Chromosomal Aberration Study in Mammalian Cells (McCoy's 5A medium extract)	Determine whether test article would cause genotoxicity in Chinese hamster ovary (CHO) cells	The test article extract was considered non-mutagenic to CHO cells under both the metabolic activated and non-activated conditions
Genotoxicity: *In vivo* mouse peripheral blood micronucleus study (Saline extract)	Determine the potential of the test article to cause in vivo genotoxicity	The saline test article extract did not induce micronuclei formation, whereas the sesame oil test article extract induced micronuclei formation. Appropriate justification based on the exposure route and paclitaxel quantity delivered from Zilver PTX stent implantation was provided to ensure that this result was not considered to be a clinical concern
Genotoxicity: *In vivo* mouse peripheral blood micronucleus study (Sesame oil extract)		
ISO Maximization Sensitization Study (Aqueous and sesame oil extract)	Investigate the potential for delayed dermal contact sensitization	The test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig
USP Pyrogen Study – Material Mediated	Determine whether the test article would induce a pyrogenic response following intravenous injection	The test article extract was considered as non-pyrogenic. The rise in temperature during the 3 hour observation period after extract injection in rabbits was within acceptable USP limits
In vivo Thromboresistance/ *In vivo* Thrombogenicity	Determine whether the placement of test article would cause thrombosis during simulated clinical use	Thrombogenicity evaluated as part of the *in vivo* animal studies showed no evidence of thromboses in vessels implanted with Zilver® PTX™ stents

Table 4: Summary of biocompatibility testing on Zilver PTX stent delivery system

Test Name	Purpose of Test	Test Results
In vitro Hemolysis Study (Modified ASTM-Extraction Method)	Determine whether test article would cause *in vitro* hemolysis	The test article extract was considered to be nonhemolytic
Cytotoxicity Study Using the ISO Elution Method (1X MEM Extract)	Determine whether test article would cause cytotoxicity and cell lysis	The test article extract showed no evidence of causing cell lysis or toxicity
USP and ISO Systemic Toxicity Study (Aqueous and cottonseed oil extract)	Determine whether the test article would cause acute systemic toxicity	There was no mortality or evidence of significant systemic toxicity over the 72 hour test period from the test article extracts compared to the control blank extracts
ISO Intracutaneous Study (Aqueous and cottonseed oil extract)	Determine whether test article would cause local dermal irritation or toxic effects	There was no evidence of significant irritation over the 72 hour test period from the test article extracts injected intracutaneously into rabbits compared to the control blank extracts
Genotoxicity: Bacterial Reverse Mutation Study (DMSO Extract)	Determine whether test article would cause mutagenic changes in *S. typhimurium* and *E. coli* strains	The test article extract was considered non-mutagenic to *S. typhimurium* and *E. coli* tester strains
ISO Maximization Sensitization Study (Aqueous and cottonseed oil extract)	Investigate the potential for delayed dermal contact sensitization	The test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig
USP Pyrogen Study – Material Mediated	Determine whether the test article would induce a pyrogenic response following intravenous injection	The test article extract was considered as non-pyrogenic. The rise in temperature during the 3 hour observation period after extract injection in rabbits was within acceptable USP limits

Evidence of safety in terms of chronic toxicity, carcinogenicity, and reproductive toxicity studies of the Zilver PTX stent, was provided based on extensive clinical history of the stent materials, no chemicals of concern from the stent and coating process, and small starting quantities of the paclitaxel drug coating.

The test results show that the Zilver PTX stent and delivery system are biocompatible and non-pyrogenic, thereby indicating that the Zilver PTX stent is safe and acceptable for clinical use.

Non-Clinical Testing

Comprehensive *in vitro* laboratory testing was performed on the Zilver PTX 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 "Guidance for Industry and FDA Staff: Non-clinical tests and recommended labeling for intravascular stents and associated delivery systems".

Under circumstances where *in vitro* non-clinical laboratory tests were conducted on the uncoated, bare Zilver stents, appropriate rationale was provided based on the stent platform being unchanged and the evaluation of the uncoated stent being fully representative of the coated stent for the purpose of these tests. Additional testing was conducted to support the integrity and stability of the coating on the Zilver PTX stent as shown in Section D: Coating testing and Section F: Stability testing, respectively.

The testing detailed in Table 5 verified that the Zilver PTX stent and delivery system met their product performance and design specifications and would perform as intended under anticipated clinical conditions.

Table 5: Summary of *in vitro* testing of the Zilver PTX stent and delivery system

Test	Description of Test	Specification/ Acceptance Criteria	Test Results
Corrosion resistance	Testing was performed in accordance with ASTM F2129 to demonstrate that the Zilver PTX stents will be adequately able to resist corrosion following implantation.	Breakdown potential (E_B) > 300 mV	The device met the established acceptance criteria.
Fretting corrosion	Testing was performed in accordance with ASTM F2129 to demonstrate that overlapped Zilver PTX stents after 3 month and 10 year simulated use will be adequately able to resist fretting corrosion following implantation.		The device met the established acceptance criteria.

Test	Description of Test	Specification/ Acceptance Criteria	Test Results
Magnetic Resonance Imaging (MRI) compatibility	Testing was performed to evaluate the safety and compatibility of the Zilver PTX stent by assessment of the magnetic field interactions (ASTM F2052), MRI-related heating (ASTM F2182) and image artifacts (ASTM F2119) at 1.5 Tesla and 3 Tesla field strengths.	Magnetically induced deflection of the test article should be less than 45º (as specified in ASTM F2052) and the presence of the stent should not possess an additional unacceptable risk to patients when subjected to 1.5 T and 3 T MRI field strengths.	The device was established as MR Conditional.
Percent vessel covered surface area	Calculation of the percent vessel surface area covered by the expanded Zilver PTX stent following deployment	Characterization study	The vessel surface area covered by the device ranged between 10% to 21%
Tensile testing of stent bars	Characterization of the ultimate tensile strength and tensile strain at failure for the Zilver PTX stent strut	Characterization study	The stent axial bar tensile testing results met the specification for tensile properties of the raw nitinol tubing used for the Zilver PTX stent.
Delivery system profile	Testing was performed to evaluate the maximum outer diameter of the Zilver PTX delivery system and to verify that the outer diameters of the delivery system would be adequate for the intended use with the appropriate sized guiding catheter.	Maximum Outer diameter ≤ 2.11 mm (≤ 0.083 inches)	The device met the established acceptance criteria.
Ease of access	Testing was performed to evaluate the advancement of the Zilver PTX stent and delivery system over the wire guide, followed by stent deployment and withdrawal of the delivery system.	The Zilver PTX stent and delivery system should easily advance over the 0.035” wire guide and be radiographically visible, followed by easy withdrawal of the delivery system.	The device met the established acceptance criteria.
Deployment accuracy	Testing was performed to evaluate the ability of the delivery system to accurately deploy the Zilver PTX stents.	Stent must deploy within ± 4 mm of the target	The device met the established acceptance criteria

Test	Description of Test	Specification/ Acceptance Criteria	Test Results
Deployment force	Testing was performed to evaluate the force required to deploy the Zilver PTX stents from the delivery system.	Deployment force must be < 32 N	The device met the established acceptance criteria
Stent length and length change	Testing was performed to evaluate the Zilver PTX stent length and length change following deployment.	Deployed stent length must be within + 2/- 5 mm of nominal, labeled length and change in length between undeployed and deployed stents must be within ± 25%	The device met the established acceptance criteria
Stent diameter	Testing was performed to evaluate diameter and uniformity of diameter at three locations (proximal, middle and distal) on the Zilver PTX stent following deployment.	Stent Diameter must be within ± 0.3 mm of the nominal diameter for 5-9 mm diameter stents and within ± 0.4 mm of the nominal diameter for 10 mm diameter stents	The device met the established acceptance criteria
Stent integrity	Testing was performed to evaluate the integrity of the Zilver PTX stents following deployment.	No cracks or fractures visible at 50 to 63X magnification	The device met the established acceptance criteria
Radial force	Testing was performed to evaluate the normalized radial force exerted by the Zilver PTX stent as a function of the stent diameter.	At operating diameter (1 mm less than nominal diameter of the stent) radial force should be between 0.14 N/mm and 0.62 N/mm	The device met the established acceptance criteria
Flex/Kink evaluation	Testing was performed to evaluate the flex/kink performance of the Zilver PTX stent and delivery system.	Minimum kink radius Stent = 8.5 mm Delivery system = 19 mm	The device met the established acceptance criteria
Crush resistance	Testing was performed to evaluate the resistance of the Zilver PTX stent to crushing	Stent diameter must be within ± 0.3 mm of the nominal diameter for 5-9 mm diameter stents and within ± 0.4 mm of the nominal diameter for 10 mm diameter stents	The device met the established acceptance criteria
Finite Element Analysis	Testing was performed to evaluate the fatigue characteristics of non-overlapped and overlapped Zilver PTX stent models under pulsatile and non-pulsatile loading conditions.	Safety factor > 1	The device met the established acceptance criteria

Test	Description of Test	Specification/ Acceptance Criteria	Test Results
In vitro fatigue	Testing was performed to evaluate fatigue characteristics (equivalent to 10 years) of non-overlapped and overlapped Zilver PTX stents under pulsatile and non-pulsatile loading conditions.	<u>For Pulsatile loading</u> No stent fractures after 100 million cycles and the stent should remain as one connected structure after 400 million cycles <u>For Non-pulsatile loading</u> Endurance limit (i.e. 10 years of non-pulsatile loading with no evidence of stent fractures) for axial, bending or torsional loading conditions must meet or exceed the clinically-relevant loading conditions	The device met the established acceptance criteria
Particulate matter testing	Testing was performed to evaluate the number of particles ≥ 10 µm and ≥ 25 µm in size associated with: • overexpanded (unconstrained) deployment of Zilver PTX stents; • simulated-use tracking and deployment of non-overlapped and overlapped Zilver PTX stents with continuous flow; • non-overlapped and overlapped Zilver PTX stents during pulsatile fatigue with continuous flow; and • non-overlapped and overlapped Zilver PTX stents during axial fatigue with continuous flow.	This testing was performed for characterization only	Characterization of the amount of particulate matter generated under conditions of unconstrained deployment (overexpansion), simulated use, pulsatile fatigue, and axial fatigue was performed for Zilver PTX stents
Delivery system tensile strength	Testing was performed to evaluate the force at break for different bonds between relevant components of the Zilver PTX delivery system	Various acceptance criteria for bonds in delivery system	The device met the established acceptance criteria

B. Animal Studies

A series of animal studies was conducted to evaluate safety, proof of concept, and overall product performance. Non-clinical *in vivo* testing included 413 stents tested in 180 animals to evaluate the safety and performance of the Zilver PTX stent in porcine arteries for up to six months. All the animal studies were conducted in accordance with 21 CFR 58 (Good Laboratory Practices). The animal studies performed and the acceptable study endpoints to support product safety and performance are summarized in Table 6.

Table 6: Zilver PTX stent non-clinical animal studies summary

Test Name	Test Article Size: Dose Density (*clinical dose = 3 µg/mm²*)	Study Endpoints	Met Endpoints?
One-, Three- and Six-month Animal Study of Pivotal Coating Doses in Domestic Swine. GLP: Yes.	10 x 80 mm: 0, 3, 9 µg/mm²	Effects of non-overlapping stents at sub-clinical, clinical, and up to 4X the clinical dose density. • Evaluations for local effects included: o Quantitative angiography o Quantitative histomorphometry o Semi-quantitative and qualitative histopathology • Evaluations for systemic and regional effects included: o Complete necropsy with detailed evaluation of downstream, hind limb tissues o Hematology and serum chemistry • Additional evaluations included: o Animal health o Delivery system performance and stent deployment o Stent integrity	Yes
One-, Three- and Six-month Animal Study of Additional Coating Doses in Domestic Swine. GLP: Yes.	10 x 80 mm: 2, 4, 12 µg/mm²		Yes
One-month Animal Study of Overlapped Stents in Domestic Swine. GLP: Yes.	7 x 30 mm: 0, 3 µg/mm²	Effects of overlapping stents at clinical dose density. • Evaluations for local effects included: o Quantitative angiography o Quantitative histomorphometry o Semi-quantitative and qualitative histopathology • Evaluations for systemic and regional effects included: o Complete necropsy with detailed evaluation of downstream, hind limb tissues o Hematology and serum chemistry • Additional evaluations included: o Animal health o Delivery system performance and stent deployment o Stent integrity	Yes
Three-month Animal Study of Overlapped Stents in Domestic Swine. GLP: Yes.	7 x 30 mm: 0, 3 µg/mm²		Yes
Six-month Animal Study of Overlapped Stents in Miniature Swine. GLP: Yes.	6 x 30 mm: 0, 3 µg/mm²		Yes

Test Name	Test Article Size: Dose Density (*clinical dose = 3 µg/mm²*)	Study Endpoints	Met Endpoints?
One-month Overdose Study of Regional and Systemic Effects of Coated Stents in Domestic Swine. GLP: Yes.	6 x 20 mm: 12 µg/mm² 10 x 40 mm &14 x 40 mm: 9 µg/mm²	Regional and systemic safety evaluation of response to 3X overdose (per animal and per limb) for the maximum number of stents allowed in the clinical trial. • Qualitative angiography • Complete necropsy with detailed evaluation of downstream, hindlimb tissues • Hematology and serum chemistry • Animal health • Delivery system performance and stent deployment	Yes
Twenty-four Hour Pharmacokinetic Study of Coated Stents in Domestic Swine. GLP: Yes.	6 x 20 mm: 3 µg/mm²	Acute pharmacokinetic evaluation of stents at clinical dose density. • Systemic paclitaxel levels • Complete necropsy • Hematology and serum chemistry	Yes
Two-month Pharmacokinetic Study of Coated Stents in Domestic Swine. GLP: Yes.	6 x 20 mm: 3 µg/mm²	Long-term pharmacokinetic evaluation of stents at clinical dose density. • Local, regional, and systemic paclitaxel levels • Complete necropsy • Hematology and serum chemistry	Yes
Acute Performance of Long Stents and Delivery Systems in Domestic Swine. GLP: Yes	8 x 140 mm: 0 µg/mm²	Acute performance evaluation of long stent and delivery system. • Delivery system performance and stent deployment • Stent integrity following tracking and deployment • Vessel injury following tracking and deployment	Yes

These comprehensive *in vivo* animal studies, including 413 stents tested in 180 animals and up to 4X the clinical dose density and total dose, showed no safety problems, complete vessel healing without negative sequelae, and no regional (downstream) or systemic effects associated with the Zilver PTX stents. Additionally, pharmacokinetic studies indicated rapid delivery of paclitaxel from the stent to the vessel wall (approximately 95% by 24 hours), persistence of paclitaxel in the vessel wall for approximately 2 months, minimal paclitaxel delivered systemically, and no paclitaxel remaining in the plasma 10 hours after stent implantation. Confirmatory testing of the longest Zilver stents and delivery systems demonstrated that stents and delivery systems were tracked, the stents deployed, and the delivery systems withdrawn without difficulty or incident, and with no damage to the stents or injury to the vessels.

Overall, the animal studies have demonstrated the non-clinical safety of the Zilver PTX stent in the animal model at multiple time points. The Zilver PTX incorporates a drug loading of 3 ug/mm2 and appears to elicit similar biologic responses as the bare metal Zilver stent when implanted in the pig model. Because the animal studies were limited to obtaining sufficient overdose data to support the safety of maximum of two overlapped 80 mm Zilver PTX stents per limb with a maximum stented length of 280 mm per patient, conclusions regarding the non-clinical safety of the Zilver PTX stent could not be drawn for lesion length greater than 140 mm per limb. The stented lengths in the animal studies are consistent with the lesion lengths specified for treatment in the pivotal clinical trial protocol. The results of the animal testing of the Zilver PTX stent thereby support a reasonable assurance of device safety and performance of the stented lengths tested in the randomized trial.

C. Additional Studies

Coating Testing

The coating characterization test methods summarized in Table 7 were developed to set specifications for the Zilver PTX stent.

Table 7: Coating and drug component characterization testing

Test		Description of Test
Chemical analysis (paclitaxel)		Drug substance was tested for identity and to ensure conformity to incoming specifications
In-process testing	Whole-stent paclitaxel content	An assay was conducted to determine the whole-stent paclitaxel content
	Intra-stent coating uniformity	An assay was conducted to characterize the uniformity of coating along the length of the Zilver PTX stent
	Coated stent appearance	A visual inspection was conducted to determine the quality of the stent coating
Finished product testing	Coated stent appearance (after loading, packaging, sterilization, and deployment)	A visual inspection was conducted to determine the quality of the stent coating after loading the stent into the delivery system, packaging, sterilization, and deployment
	Assay (potency)	An assay was conducted to quantitatively determine the total amount of paclitaxel on the Zilver PTX stent
	Identity	An assay was conducted to determine the retention time of the major peak of the paclitaxel in the chromatogram
	Content uniformity	An assay was conducted to verify the content uniformity of the paclitaxel coating from stent to stent
	Impurities/degradants	An assay was conducted to quantitatively determine the type and amount of impurities and degradation products of the Zilver PTX stent
	In vitro release	An assay was developed to measure the *in vitro* release rate of paclitaxel from the Zilver PTX stent

	Particulate matter	Particulate levels were measured for the Zilver PTX stent following tracking and deployment

Chemistry, Manufacturing, and Control (CMC) Testing

As part of the CMC testing, and where applicable, the USP, EP, and International Conference on Harmonization (ICH) Guidelines were referenced during development of the release tests for the Zilver PTX stents. Each batch of finished devices underwent CMC release tests summarized in Table 8.

Table 8: Zilver PTX release tests

Test		Description of Test	Test Results
Finished product testing	Coated stent appearance (after loading, packaging, sterilization, and deployment)	Visual inspection was conducted to verify that the Zilver PTX stent meets finished product coated stent appearance specification	The product met specifications for finished product coated stent appearance
	Assay (potency)	An assay was conducted to quantitatively verify that the total amount of paclitaxel on the Zilver PTX stent meets the finished product assay (potency) specification	The product met specifications for finished product assay (potency)
	Identity	An assay was conducted to verify that the identity of the paclitaxel on the Zilver PTX stent meets the finished product identity specification	The product met specifications for finished product identity
	Content uniformity	Multiple Zilver PTX stents were assayed to verify that the uniformity of the paclitaxel content on individual stents meets the finished product content uniformity specification	The product met specifications for finished product content uniformity
	Impurities/degradants	An assay was conducted to quantitatively verify that the type and the amount of impurities/degradants on the Zilver PTX stents meet the finished product impurity/degradant specification	The product met specifications for finished product impurity/degradant
	In vitro release	The *in vitro* release of paclitaxel from the Zilver PTX stent was measured to verify that the drug release profile meets the finished product *in vitro* release specification	The product met specifications for finished product *in vitro* paclitaxel release
	Particulate matter	Particulate matter levels for the Zilver PTX stent were measured to verify that the level of particulate matter meets the finished product particulate matter specification	The product met specifications for finished product particulate matter

Stability Testing

Coating stability studies were conducted according to USP, EP, and ICH guidelines to establish an expiration date/shelf life for the paclitaxel coating on the Zilver PTX stent. Stability testing evaluation of the coating included assay (potency), impurities/degradants, *in vitro* paclitaxel release, and particulate

matter. Accelerated and thermal cycle stability testing evaluation of the coating included assay (potency) and impurities/degradants. Appropriate engineering tests were also performed on aged product to ensure that the Zilver PTX stent meets the acceptance criteria established for the non-aged devices throughout their shelf 1ife. The data support a 6 month shelf life for the Zilver PTX stent and delivery system.

Sterilization and Packaging

The Zilver PTX stent and delivery system were sterilized by a validated ethylene oxide (EtO) sterilization process to achieve a minimal sterility assurance level (SAL) of 10^{-6}. The EtO and ECH residuals levels were in accordance with ISO 10993-7: 2008, *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 PTX stent and delivery system.

The aged packaging evaluation under the worst case shipping simulation indicated that the packaging would remain acceptable for the shelf life of the Zilver PTX stent and delivery system.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of stenting with the Zilver PTX stent in the United States under IDE # G030251. A single arm clinical study provided additional evidence supporting the safety and effectiveness of the Zilver PTX stent in a broader patient population including more complex lesions. Data from these clinical studies were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between March 21, 2005 and August 25, 2008. The database for this PMA reflected data collected through April 30, 2010 and included 479 patients. There were 55 investigational sites.

The Zilver PTX randomized study is a prospective, controlled, multi-center, multinational study enrolling patients in the United States, Japan, and Germany

with *de novo* or restenotic native lesions of the above-the-knee femoropopliteal artery. Patients were randomized 1:1 to treatment with the Zilver PTX stent (treatment group) or with PTA (control group). Recognizing that balloon angioplasty may not be successful acutely, the trial design mandated provisional stent placement immediately after failure of balloon angioplasty in instances of acute PTA failure. Therefore, patients with suboptimal (failed) PTA underwent a secondary randomization (1:1) to stenting with either Zilver PTX or bare Zilver stents (Figure 4). This secondary randomization allows evaluation of the Zilver PTX stent compared to a bare metal stent.

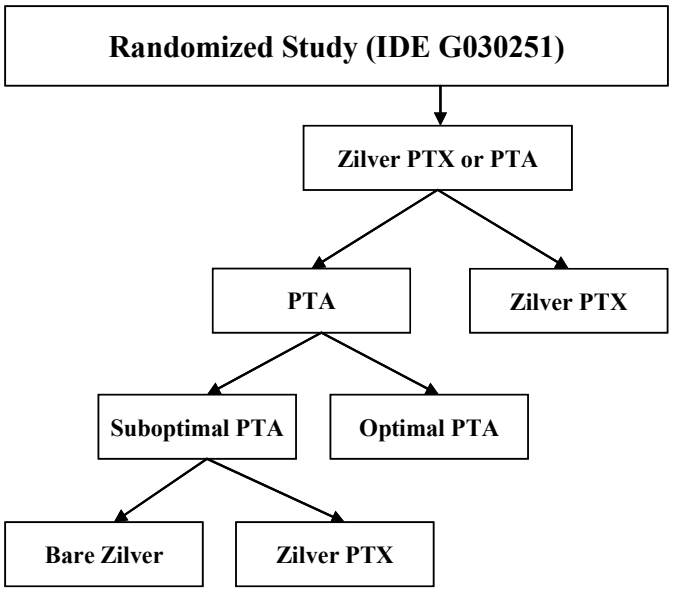


Figure 4: Patient enrollment

The study was overseen by an independent data safety monitoring board (DSMB) comprised of physicians and a biostatistician. An independent CEC adjudicated major adverse events, including all patient deaths, and independent core laboratories provided uniformly defined imaging analysis.

1. Clinical Inclusion and Exclusion Criteria

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

   - Patient has up to 2 documented stenotic or occluded atherosclerotic lesions (≤ 14 cm long, or ≤ 7 cm for the first 60 subjects enrolled) of the above-

the-knee femoropopliteal artery, up to one in each limb, that meet all of the inclusion criteria and none of the exclusion criteria.

- 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 Category 2 or greater.
- Patient has a resting ABI < 0.9 or an abnormal exercise ABI if resting ABI is normal. Patient with incompressible arteries (ABI > 1.2) must have a TBI < 0.8.

Patients were <u>not</u> permitted to enroll in the Zilver PTX study if they met any of the following exclusion criteria:

- 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 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 planned procedure involving arterial interventional treatment of the study leg(s) within the 12-month follow-up period.
- Patient has had previous stenting of the target vessel.
- Patient lacks at least one patent vessel of runoff with < 50% stenosis throughout its course.
- Patient has untreated angiographically-evident thrombus in the target lesion.
- Patient has a bypass graft with an anastomosis in the target vessel.
- Patient has lesions requiring atherectomy (or ablative devices), cutting balloons, cryoplasty balloons, or any other advanced device to facilitate stent delivery.

Subjects eligible to be enrolled in the study had single or bilateral stenotic or occluded atherosclerotic lesions (≤ 14 cm long) of the above-the-knee femoropopliteal artery with a reference vessel diameter of 4 mm to 9 mm. Of the 479 patients enrolled, 238 were in the PTA control group and 241 were in the Zilver PTX treatment group. Five patients in the Zilver PTX group were enrolled as live cases (i.e., with no randomization) and are included in analyses of the as treated population but not the intent to treat or per protocol populations. Acute PTA failure was common, occurring in 120 patients in the control group, and these patients underwent a second randomization to provisional stenting with either Zilver PTX stents or bare Zilver stents.

2. Follow-up Schedule

   All patients were scheduled to return for follow-up clinical assessment and ultrasound imaging prior to discharge, at 6 and 12 months, and annually thereafter. Additionally, x-rays were required prior to discharge and at 1, 3, and 5 years to assess stent integrity. Telephone contact was scheduled for 1, 3, 9, and 18 months. Patient subsets were assigned to a pharmacokinetic substudy and to an IVUS/angiography substudy.

   Tables 10 – 13 detail the preoperative evaluations and postoperative objective parameters measured during the study. Adverse events and complications were recorded at all visits.

Table 10: Control group/PTA only follow-up

Procedure	Up to 7 Days Before Procedure	During Procedure (including baseline and final)	After the Procedure before Hospital Discharge	1 and 3 Months after the Procedure	6 Months after the Procedure	9 Months after the Procedure	12 Months after the Procedure	18 Months after the Procedure	Years 2-5 after the Procedure
Clinical Assessment, including ABI and Rutherford	√		√[1]		√		√		√
Walking and QOL Questionnaires	√				√		√		√
Blood Test	√		√						
Angiography		√					√[2]		
Ultrasound			√		√		√		√[3]
X-ray of the Stent									
IVUS									
Telephone Update				√		√		√	

[1] Rutherford not required after the procedure.
[2] For patients randomized to the angiographic/IVUS substudy only.
[3] For patients randomized to the ultrasound substudy only.

Table 11: Acute PTA failure/bare Zilver stent follow-up

Procedure	Up to 7 Days Before Procedure	During Procedure (including baseline and final)	After the Procedure before Hospital Discharge	1 and 3 Months after the Procedure	6 Months after the Procedure	9 Months after the Procedure	12 Months after the Procedure	18 Months after the Procedure	Years 2-5 after the Procedure
Clinical Assessment, including ABI and Rutherford	√		√[1]		√		√		√
Walking and QOL Questionnaires	√				√		√		√
Blood Test	√		√						
Angiography		√			*[3]				
Ultrasound			√		√		√		√
X-ray of the Stent			√		*[3]		√		√[2]
IVUS					*[3]				
Telephone Update				√		√		√	

[1] Rutherford not required after the procedure.
[2] X-ray at 3 and 5 years only; not required for the first 60 patients enrolled.
[3] Additional requirements for the first 60 patients enrolled.

Table 12: Acute PTA failure/Zilver PTX stent follow-up

Procedure	Up to 7 Days Before Procedure	During Procedure (including baseline and final)	After the Procedure before Hospital Discharge	1 and 3 Months after the Procedure	6 Months after the Procedure	9 Months after the Procedure	12 Months after the Procedure	18 Months after the Procedure	Years 2-5 after the Procedure
Clinical Assessment, including ABI and Rutherford	√		√[1]		√		√		√
Walking and QOL Questionnaires	√				√		√		√
Blood Test	√		√		√		√		√[2]
Angiography		√			*[3]				
Ultrasound			√		√		√		√
X-ray of the Stent			√		*[3]		√		√[4]
IVUS		*[3]			*[3]				
Telephone Update				√		√		√	

[1] Rutherford not required after the procedure.
[2] Blood tests required at 2-year follow-up only.
[3] Additional requirements for the first 60 patients enrolled.
[4] X-ray at 3 and 5 years only; not required for the first 60 patients enrolled.

Table 13: Treatment group/Zilver PTX stent follow-up

Procedure	Up to 7 Days Before Procedure	During Procedure (including baseline and final)	After the Procedure before Hospital Discharge	1 and 3 Months after the Procedure	6 Months after the Procedure	9 Months after the Procedure	12 Months after the Procedure	18 Months after the Procedure	Years 2-5 after the Procedure
Clinical Assessment, including ABI and Rutherford	√		√[1]		√		√		√
Walking and QOL Questionnaires	√				√		√		√
Blood Test	√		√[3]		√		√		√[2]
Angiography		√			√[4,6]		√[4]		
Ultrasound			√		√		√		√
X-ray of the Stent			√		*[5]		√		√[5]
IVUS		√[4,6]			*[5]		√[4]		
Telephone Update				√		√		√	

[1] Rutherford not required after the procedure.
[2] Blood tests required at 2-year follow-up only.
[3] There will be an additional 3 blood draws for patients randomized to the PK substudy.
[4] For patients randomized to the angiographic and IVUS substudy only.
[5] X-ray at 3 and 5 years only; not required for the first 60 patients enrolled.
[6] Additional requirements for the first 60 patients enrolled.

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

3. Clinical Endpoints

With regards to safety, the primary hypothesis was non-inferior (i.e., equivalent or superior) event-free survival (defined as freedom from the clinical events committee (CEC) adjudicated major adverse events of death, target lesion revascularization, target limb ischemia requiring surgical intervention or surgical repair of the target vessel, and freedom from worsening of the Rutherford classification by 2 classes or to class 5 or 6) at 12 months.

With regards to effectiveness, the primary hypothesis was superior primary patency at 12 months for the Zilver PTX treatment group compared to the PTA control group. Secondary analyses included evaluation of the effectiveness of the Zilver PTX stent compared to a bare metal stent.

With regards to success/failure criteria, the primary objective of the Zilver PTX randomized study was to demonstrate non-inferior (equivalent or superior) safety and superior effectiveness of the Zilver PTX stent compared to percutaneous balloon angioplasty (PTA) for the treatment of *de novo* or

restenotic lesions of the above-the-knee femoropopliteal artery. The patients in the PTA control group included those with optimal PTA and suboptimal (failed) PTA that underwent a secondary randomization to stenting with either Zilver PTX or bare Zilver stents.

B. Accountability of PMA Cohort

At the time of database lock, of 479 patients enrolled in PMA study, *97% of* patients were available for analysis at the completion of the study, the 1-year post-operative visit.

Patient availability for study follow-up is summarized in Table 14.

Table 14: Clinical and imaging follow-up data

Follow-up	Eligible for Follow-up[1]	Percent of Data Available			Events Occurring Before Next Visit				Not Due for Next Visit (n)
		Clinical Follow-up[2]	Core Laboratory X-ray Follow-up	Core Laboratory Ultrasound Follow-up[3]	Death	Withdrawn	Lost to Follow-up	Other Endpoint[4]	
Control Group									
Procedure	238	100.0% (238/238)	97.5% (117/120)[5]	86.6% (206/238)	2	3	0	1	0
6-month	232	94.0% (218/232)	76.5% (13/17)[5,6]	80.6% (187/232)	2	4	2	2	0
12-month	222	97.3% (216/222)	76.0% (114/150)[5]	83.3% (185/222)	4	5	0	3	0
2-year	210	83.3% (175/210)	n/a[8]	66.7% (84/126)[10]	2	4	2	0	154
3-year	48	91.7% (44/48)	n/a[5,9]	66.7% (14/21)[10]	1	1	0	0	22
4-year	24	75.0% (18/24)	n/a[8]	66.7% (10/15)[10]	0	0	0	0	24
Treatment Group									
Procedure	236[7]	100.0% (236/236)	96.2% (227/236)	89.4% (211/236)	0	1	1	0	0
6-month	234	94.0% (220/234)	86.2% (25/29)[6]	80.3% (188/234)	9	4	4	0	0
12-month	217	97.7% (212/217)	84.3% (183/217)	87.1% (189/217)	9	4	3	3	0
2-year	198	83.8% (166/198)	n/a[8]	51.0% (101/198)	3	5	0	0	160
3-year	30	86.7% (26/30)	n/a[9]	46.7% (14/30)	0	0	1	0	13
4-year	16	56.3% (9/16)	n/a[8]	43.8% (7/16)	0	0	0	0	16

[1] Eligible for follow-up = previous eligibility for follow-up – (previous death + withdrawn + LTF).
[2] Includes cases with at least one of any of the following submitted: clinical form, death form, withdrawn form, or lost to follow-up form.
[3] Includes only ultrasound studies considered diagnostic by the core lab.
[4] Patients who reached an "other endpoint" include 5 patients whose site closed and therefore will not complete clinical follow-up, 2 patients who received a non-study stent during reintervention, 1 patient whose study lesion was bypassed, and 1 patient who moved but has not formally withdrawn from the trial.
[5] Only patients implanted with stents (i.e., acute PTA failure) were required to have X-ray follow-up.
[6] Only first 60 patients enrolled were required to have 6-month X-ray follow-up.
[7] Five patients treated as live cases not included.
[8] Patients were not required to have 2- and 4-year X-ray follow-up.
[9] Three-year X-ray follow-up not required for first 60 patients enrolled.
[10] Only patients implanted with stents or in the Duplex Ultrasound substudy were required to have 2-, 3-, or 4-year duplex ultrasound follow-up.

In summary, nearly all eligible patients were seen for their 12-month follow-up visit and more than 80% have been seen for their 2-year clinical follow-up visit.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a peripheral arterial disease study performed in the US. Baseline patient characteristics were similar between the PTA control group and Zilver PTX treatment group. Demographics (Table 10) and medical history (Table 11) were similar for the two groups, with the only significant difference being a more frequent history of hypertension in the Zilver PTX group ($p = 0.02$). Similarly, baseline angiographic data, lesion location, and lesion characteristics indicated that the two groups were well matched, though lesions in the Zilver PTX treatment group had more severe calcification and inflow tract stenosis documented by core lab analysis (Tables 15 – 19).

Table 15: Demographics

Demographic	Control Group	Treatment Group	Diff. (95% CI)[1]	*P*-value[2]
Age (years)	67.7 ± 10.6 (238)	67.9 ± 9.6 (236)	-0.1 (-2.0, 1.7)	0.88
Gender				
Male	63.9% (152/238)	65.7% (155/236)	-1.8 (-10.4, 6.8)	0.70
Female	36.1% (86/238)	34.3% (81/236)	1.8 (-6.8, 10.4)	
Ethnicity				
Asian	14.1% (29/206)	11.9% (25/210)	2.2 (-4.3, 8.6)	
Black/African American	11.2% (23/206)	11.9% (25/210)	-0.7 (-6.9, 5.4)	0.81
Hispanic/Latino	5.3% (11/206)	7.1% (15/210)	-1.8 (-6.5, 2.8)	
White/Caucasian	69.4% (143/206)	69.0% (145/210)	0.4 (-8.5, 9.2)	
Height (in)	66.4 ± 4.4 (238)	66.7 ± 3.6 (236)	-0.2 (-1.0, 0.5)	0.55
Weight (lbs)	178.5 ± 44.3 (238)	180.4 ± 40.0 (236)	-1.9 (-9.5, 5.8)	0.62
Body mass index	28.2 ± 5.6 (238)	28.4 ± 5.3 (236)	-0.2 (-1.2, 0.8)	0.71

[1] Confidence interval is the difference in means for continuous variables and difference in percentages for categorical variables.
[2] *P* values are based on *t*-test for continuous variables and Fisher's exact test for categorical variables.

Table 16: Medical history

Condition	Control Group	Treatment Group	Diff. (95% CI)[1]	*P*-value[2]
Diabetes	42.0% (100/238)	49.6% (117/236)	-7.6 (-16.5, 1.4)	0.11
Diabetes type				
Type I	13.0% (13/100)	16.2% (19/117)	-3.2 (-12.6, 6.2)	0.56
Type II	87.0% (87/100)	83.8% (98/117)	3.2 (-6.2, 12.6)	
Hypercholesterolemia	69.7% (166/238)	76.3% (180/236)	-6.5 (-14.5, 1.5)	0.12
Hypertension	81.5% (194/238)	89.0% (210/236)	-7.5 (-13.8, -1.1)	0.02*
Carotid disease	20.2% (48/238)	18.2% (43/236)	2.0 (-5.1, 9.0)	0.64
Renal disease	10.5% (25/238)	10.2% (24/236)	0.3 (-5.2, 5.8)	> 0.99
Pulmonary disease	16.0% (38/238)	19.1% (45/236)	-3.1 (-9.9, 3.7)	0.39
Congestive heart failure	10.5% (25/238)	11.9% (28/236)	-1.4 (-7.0, 4.3)	0.66
Previous cardiac arrhythmia	13.0% (31/238)	10.6% (25/236)	2.4 (-3.4, 8.2)	0.47
Previous MI	17.2% (41/238)	21.2% (50/236)	-4.0 (-11.0, 3.1)	0.29
Smoking status				0.70
Never smoked	15.5% (37/238)	13.6% (32/236)	2.0 (-4.4, 8.3)	
Quit	51.7% (123/238)	55.5% (131/236)	-3.8 (-12.8, 5.1)	

Condition	Control Group	Treatment Group	Diff. (95% CI)[1]	*P*-value[2]
Still smokes	32.4% (77/238)	30.9% (73/236)	1.4 (-7.0, 9.8)	
Unknown	0.4% (1/238)	0.0% (0/236)	0.4 (N/A)	
Existing tissue loss[3]	8.4% (20/238)	9.4% (22/235)	-1.0 (-6.1, 4.2)	0.74
Currently taking medications	99.2% (236/238)	99.6% (235/236)	-0.4 (-1.8, 1.0)	> 0.99

[1] Confidence interval is the difference in means for continuous variables and difference in percentages for categorical variables.
[2] *P* values are based on *t*-test for continuous variables and Fisher's exact test for categorical variables.
[3] Tissue loss includes amputations, gangrene, and ischemic ulcers.
***** Statistically significant.

Table 17: Baseline angiographic data (core lab reported)

Baseline Angiographic Data	Control Group	Treatment Group	Diff. (95% CI)[1]	P-value[2]
Stenosed lesion length (mm)[3]	53.2 ± 40.3 (248)	54.6 ± 40.7 (242)	-1.3 (-8.5, 5.9)	0.71
Normal-to-normal Lesion length (mm)[4]	63.2 ± 40.5 (251)	66.4 ± 38.9 (246)	-3.2 (-10.2, 3.8)	0.36
Proximal RVD (mm)	5.0 ± 1.0 (249)	5.1 ± 0.9 (242)	-0.05 (-0.2, 0.1)	0.58
Distal RVD (mm)	5.0 ± 1.0 (249)	5.0 ± 1.0 (242)	-0.01 (-0.2, 0.2)	0.95
MLD in lesion (mm)	1.1 ± 0.9 (249)	1.0 ± 0.9 (242)	0.1 (-0.1, 0.2)	0.38
Percent diameter stenosis (%)	78.4 ± 17.1 (249)	79.8 ± 17.0 (242)	-1.3 (-4.4, 1.7)	0.38

[1] Confidence interval is the difference in means for continuous variables and difference in percentages for categorical variables.
[2] P values are based on t-test for continuous variables and Fisher's exact test for categorical variables.
[3] Region with > 20% diameter stenosis
[4] Site reported

Table 18: Lesion location

Vessel	Control Group	Treatment Group	Diff. (95% CI)[1]	*P*-value[2]
Left proximal SFA	10.8% (27/251)	8.9% (22/247)	2.9 (-4.3, 10.1)	0.63
Right proximal SFA	12.0% (30/251)	10.9% (27/247)		
Left proximal SFA/distal SFA	3.6% (9/251)	5.7% (14/247)	-2.1 (-6.7, 2.5)	
Right proximal SFA/distal SFA	2.8% (7/251)	2.8% (7/247)		
Left distal SFA	34.7% (87/251)	30.4% (75/247)	-1.0 (-9.5, 7.4)	
Right distal SFA	28.7% (72/251)	34.0% (84/247)		
Left distal SFA/popliteal artery	0.4% (1/251)	0.8% (2/247)	-1.3 (-4.3, 1.8)	
Right distal SFA/popliteal artery	2.0% (5/251)	2.8% (7/247)		
Left popliteal artery	2.0% (5/251)	0.8% (2/247)	1.5 (-2.1, 5.1)	
Right popliteal artery	3.2% (8/251)	2.8% (7/247)		

[1] Confidence interval is the difference in means for continuous variables and difference in percentages for categorical variables.
[2] *P* values are based on *t*-test for continuous variables and Fisher's exact test for categorical variables.

Table 19: Lesion characteristics

Characteristics		Control Group	Treatment Group	Diff. (95% CI)[2]	*P*-value[3]
Lesion class (TASC)[1]	A	36.0% (86/239)	29.4% (69/235)	6.6 (-1.8, 15.04)	0.07
	B	25.9% (62/239)	22.6% (53/235)	3.4 (-4.3, 11.1)	
	C	31.0% (74/239)	42.6% (100/235)	-11.6 (-20.2, -3.0)	
	D	7.1% (17/239)	5.5% (13/235)	1.6 (-2.8, 6.0)	
Accessibility	Readily accessible	100% (215/215)	100% (215/215)	0 (0, 0)	N/A
	Moderate tortuosity	0.0% (0/215)	0.0% (0/215)	N/A	
	Excessive tortuosity	0.0% (0/215)	0.0% (0/215)	N/A	
Lesion angulation	Non-angulated	95.2% (237/249)	95.4% (228/241)	-0.3 (-4.0, 3.5)	> 0.99
	Moderate	4.8% (12/249)	4.6% (11/241)	0.3 (-3.5, 4.0)	
Calcification	None	4.8% (12/249)	1.7% (4/241)	3.2 (0.05, 6.3)	< 0.01*
	Little	38.2% (95/249)	25.7% (62/241)	12.4 (4.3, 20.6)	
	Moderate	22.1% (55/249)	35.3% (85/241)	-13.2 (-21.1, -5.3)	
	Severe	34.9% (87/249)	37.3% (90/241)	-2.4 (-10.9, 6.1)	
Other stenosis in artery	None	51.4% (111/216)	51.7% (107/207)	-0.3 (-9.8, 9.2)	0.71
	≤ 50%	34.3% (74/216)	31.4% (65/207)	2.9 (-6.1, 11.8)	
	> 50%	14.4% (31/216)	16.9% (35/207)	-2.6 (-9.5, 4.4)	
Inflow tract stenosis	None	41.6% (96/231)	37.1% (76/205)	4.5 (-4.7, 13.7)	0.03*
	≤ 50%	45.5% (105/231)	40.5% (83/205)	5.0 (-4.3, 14.3)	
	> 50%	13.0% (30/231)	22.4% (46/205)	-9.5 (-16.6, -2.3)	
Patent runoff vessels	0	17.3% (26/150)	14.8% (22/149)	2.6 (-5.8, 10.9)	0.47
	1	52.7% (79/150)	47.7% (71/149)	5.0 (-6.3, 16.3)	
	2	21.3% (32/150)	22.8% (34/149)	-1.5 (-10.9, 7.9)	
	3	8.0% (12/150)	14.1% (21/149)	-6.1 (-13.2, 1.0)	
Ulceration		19.0% (47/248)	16.7% (40/240)	2.3 (-4.5, 9.1)	0.55

[1] TASC lesion class was determined by the site and was not evaluated by the core lab.
[2] Confidence interval is the difference in means for continuous variables and difference in percentages for categorical variables.
[3] *P* values are based on *t*-test for continuous variables and Fisher's exact test for categorical variables.
* Statistically significant.

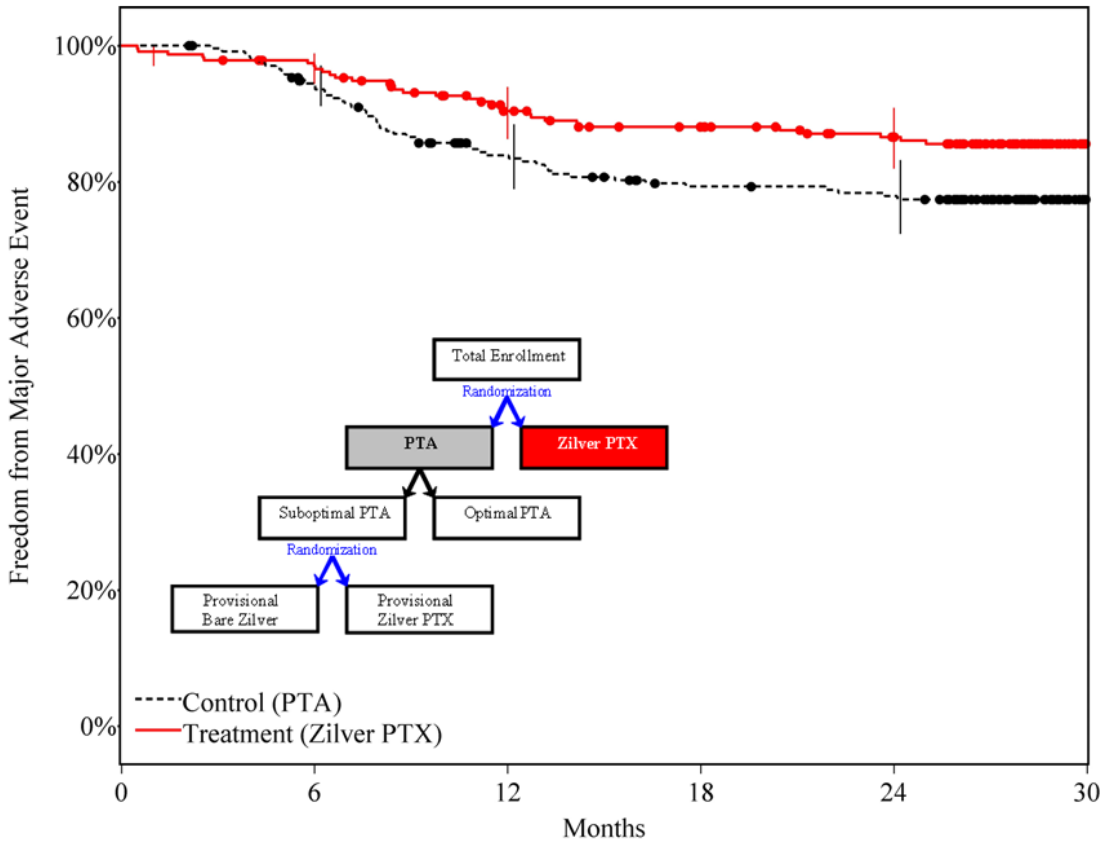
In summary, lesions were similar between the PTA control group and Zilver PTX treatment group in nearly all parameters. The core lab data demonstrated significant differences in lesion calcification and inflow tract stenosis, with lesions in the Zilver PTX treatment group having more severe calcification and higher inflow tract stenosis. While statistically significant, these differences likely do not represent a clinically significant difference between lesions in the treatment and control groups. Moreover, these data indicate that if a difference in lesion characteristics exists, the Zilver PTX treatment group contains potentially more severe lesions and patients with more severe overall peripheral arterial disease—characteristics which would be expected to have an adverse (if any) effect on safety and effectiveness outcomes in the Zilver PTX treatment group.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the treatment (Zilver PTX) group of 223 patients available for the 12 month evaluation. The key safety outcomes for this study are presented below in Table 16. Adverse effects are reported in Tables 17 and 18.

The primary safety endpoint of non-inferior (i.e., equivalent or superior) safety for the Zilver PTX stent compared to PTA was met with a superior event-free survival rate at 12 months of 90.4% for the Zilver PTX treatment group compared to 83.9% for the PTA control group ($p = 0.01$[1]), as illustrated in Figure 5 and Table 16. The most common major adverse event was TLR (Table 17), which occurred approximately twice as often in the PTA group relative to the Zilver PTX group (16.1% vs. 9.5%, respectively; $p = 0.04$). No patient deaths were adjudicated by the CEC as related to the device or procedure. The benefit of the Zilver PTX stent was maintained through 24 months.



[1] Adjusted for multiplicity

Figure 5: Kaplan-Meier curves for event-free survival

Table 20: Kaplan-Meier estimates for event-free survival

Months Post-procedure	Event-free Survival Estimate		Standard Error		Cumulative Failed		Cumulative Censored		Number Remaining	
	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)
0	100.0%	100.0%	0.0%	0.0%	0	0	0	0	236	235
1	100.0%	99.1%	0.0%	0.6%	0	2	0	0	236	233
6	94.4%	97.0%	1.5%	1.1%	13	7	6	3	217	225
12	83.9%	90.4%	2.4%	1.9%	37	22	15	16	184	197
24	77.9%	86.6%	2.8%	2.3%	50	30	22	33	164	172

Adverse effects that occurred in the PMA clinical study:

Table 21: Rates of individual major adverse events at 12 months

Major Adverse Event	Control (PTA)[1]	Treatment (Zilver PTX)[1]	*P*-value	Diff. (95% CI)[3]
Clinically-driven TLR	16.1% (36/223)[2]	9.5% (21/220)	0.04	(0.4, 12.79)
Worsening of Rutherford classification by 2 classes or to a class 5 or 6	0.9% (2/223)[2]	0.0% (0/220)	0.49	-
Amputation	0.0% (0/223)	0.5% (1/220)	0.49	-

[1] Denominator is the number of patients remaining free from MAE at 12 months plus the number that have experienced a MAE or died prior to 12 months.
[2] One patient experienced a worsening Rutherford and a TLR and is included in both categories in this table.
[3] Confidence interval is the difference in percentages.

Table 18 provides a summary of other adverse events through 24 months, not including major adverse events, occurring in the control and treatment groups. No patient deaths were adjudicated by the CEC as related to the study device or procedure.

Table 22: Adverse events

Event Type	Control		Treatment	
	% (n/N)	Events	% (n/N)	Events
Occurring within 12 months of the study procedure				
Death	1.7% (4/236)	4	3.4% (8/236)	8
Major Adverse Events				
Clinically-driven TLR	15.3% (36/236)	36	8.9% (21/235)	21
Worsening of Rutherford classification by 2 classes or to a class 5 or 6	0.8% (2/236)	2	0.0% (0/235)	0
Amputation	0.0% (0/236)	0	0.4% (1/235)	1
Cardiovascular Events				
Cardiac ischemia requiring intervention	3.0% (7/236)	7	3.8% (9/235)	13
Non-Q-Wave MI	0.4% (1/236)	1	0.9% (2/235)	2
Congestive heart failure	0.8% (2/236)	2	3.0% (7/235)	7
Refractory hypertension	0.4% (1/236)	1	0.0% (0/235)	0

	Control		Treatment	
Arrhythmia requiring intervention or new treatment	1.7% (4/236)	5	3.4% (8/235)	9
Other cardiovascular events	12.3% (29/236)	41	7.7% (18/235)	20
Pulmonary Events				
Pulmonary edema requiring treatment	0.0% (0/236)	0	0.4% (1/235)	1
Ventilation greater than 24 hours in duration	0.4% (1/236)	1	1.3% (3/235)	3
Pneumonia requiring antibiotics	2.1% (5/236)	6	5.1% (12/235)	14
Supplemental oxygen at time of discharge (exclude if for high altitude)	0.0% (0/236)	0	0.4% (1/235)	1
Re-intubation	0.0% (0/236)	0	0.4% (1/235)	1
COPD	1.7% (4/236)	5	0.9% (2/235)	4
Other pulmonary events	3.0% (7/236)	11	8.5% (20/235)	28
Renal Events				
UTI requiring antibiotic treatment	0.8% (2/236)	3	2.6% (6/235)	7
Serum creatinine rise greater than 30% above baseline resulting in persistent value greater than 2 mg/dl	0.8% (2/236)	2	0.0% (0/235)	0
Other renal events	2.5% (6/236)	8	4.3% (10/235)	12
Gastrointestinal Events				
Other gastrointestinal events	3.8% (9/236)	12	10.2% (24/235)	30
Wound Events				
Wound infection/abscess formation	1.3% (3/236)	3	1.7% (4/235)	5
Tissue necrosis requiring debridement	1.3% (3/236)	3	0.4% (1/235)	1
Wound complication requiring return to operating room	1.7% (4/236)	5	0.9% (2/235)	3
Other wound events	2.5% (6/236)	6	0.9% (2/235)	2
Vascular Events				
Post-procedure percutaneous intervention (e.g., PTA and/or stent) to the study vessel	8.1% (19/236)	22	5.5% (13/235)	14
Post-procedure percutaneous intervention (e.g., PTA and/or stent) to another vessel	16.9% (40/236)	52	21.3% (50/235)	62
Ischemia requiring surgical intervention (i.e., bypass or amputation) of another vessel	2.5% (6/236)	6	1.7% (4/235)	4
Embolism distal to treated study vessel	0.4% (1/236)	1	0.9% (2/235)	2
Embolism within another vessel	0.0% (0/236)	0	1.3% (3/235)	3
Thrombosis of the study lesion	0.8% (2/236)	2	2.6% (6/235)	6
Thrombosis other than study lesion	0.0% (0/236)	0	0.9% (2/235)	2
Blue toe syndrome	0.0% (0/236)	0	0.4% (1/235)	1
Aneurysm (other)	0.0% (0/236)	0	0.9% (2/235)	2
Deep vein thrombosis	0.4% (1/236)	1	0.9% (2/235)	2
Hematoma requiring intervention at access site	0.4% (1/236)	1	0.4% (1/235)	1
Pulmonary embolism	0.4% (1/236)	1	0.0% (0/235)	0
Pseudoaneurysm or AV fistula of the study vessel	0.8% (2/236)	2	0.4% (1/235)	1
Pseudoaneurysm or AV fistula of another vessel	0.4% (1/236)	1	0.4% (1/235)	2
Study vessel spasm	0.0% (0/236)	0	0.4% (1/235)	1
Worsened claudication/rest pain	6.8% (16/236)	21	4.3% (10/235)	12
Stroke	0.8% (2/236)	2	0.4% (1/235)	1
Vascular/surgical repair of injury to another vessel (other than amputation or bypass)	0.4% (1/236)	1	0.9% (2/235)	3
Post-procedure transfusion	4.2% (10/236)	15	5.5% (13/235)	13
Other vascular events	16.5% (39/236)	47	9.8% (23/235)	29
Miscellaneous Events				
Drug reaction (including contrast reaction)	2.1% (5/236)	5	3.8% (9/235)	10
Hypersensitivity/allergic reaction	2.1% (5/236)	5	2.1% (5/235)	6
Other miscellaneous events	26.7% (63/236)	120	28.1% (66/235)	115
Occurring between 12 and 24 months following the study procedure				

	Control		Treatment	
Death	3.0% (7/236)	7	5.5% (13/235)	13
Major Adverse Events				
Clinically-driven TLR	4.7% (11/236)	11	3.4% (8/235)	8
Worsening of Rutherford classification by 2 classes or to a class 5 or 6	1.7% (4/236)	4	0.0% (0/235)	0
Cardiovascular Events				
Cardiac ischemia requiring intervention	3.0% (7/236)	7	3.4% (8/235)	8
Non-Q-Wave MI	0.8% (2/236)	2	0.4% (1/235)	1
Congestive heart failure	1.3% (3/236)	4	1.3% (3/235)	6
Refractory hypertension	0.4% (1/236)	1	0.0% (0/235)	0
Arrhythmia requiring intervention or new treatment	0.8% (2/236)	2	1.7% (4/235)	5
Other cardiovascular events	7.6% (18/236)	30	3.8% (9/235)	10
Pulmonary Events				
Pulmonary edema requiring treatment	0.0% (0/236)	0	0.4% (1/235)	1
Pneumonia requiring antibiotics	1.3% (3/236)	3	1.7% (4/235)	4
Supplemental oxygen at time of discharge (exclude if for high altitude)	0.0% (0/236)	0	0.4% (1/235)	1
COPD	0.8% (2/236)	2	0.0% (0/235)	0
Pleural effusion requiring treatment	0.0% (0/236)	0	0.4% (1/235)	2
Other pulmonary events	3.0% (7/236)	7	3.4% (8/235)	10
Renal Events				
UTI requiring antibiotic treatment	0.8% (2/236)	2	0.4% (1/235)	1
Serum creatinine rise greater than 30% above baseline resulting in persistent value greater than 2 mg/dl	0.8% (2/236)	2	0.0% (0/235)	0
Other renal events	1.7% (4/236)	8	2.1% (5/235)	5
Gastrointestinal Events				
Other gastrointestinal events	3.4% (8/236)	9	2.6% (6/235)	6
Wound Events				
Wound infection/abscess formation	0.4% (1/236)	2	1.3% (3/235)	3
Wound complication requiring return to operating room	0.4% (1/236)	1	0.0% (0/235)	0
Other wound events	0.0% (0/236)	0	1.3% (3/235)	3
Vascular Events				
Post-procedure percutaneous intervention (e.g., PTA and/or stent) to the study vessel	5.1% (12/236)	14	3.8% (9/235)	9
Post-procedure percutaneous intervention (e.g., PTA and/or stent) to another vessel	5.9% (14/236)	16	6.0% (14/235)	16
Ischemia requiring surgical intervention (i.e., bypass or amputation) of another vessel	0.8% (2/236)	2	1.7% (4/235)	4
Embolism distal to treated study vessel	0.0% (0/236)	0	0.4% (1/235)	1
Embolism within another vessel	0.4% (1/236)	1	0.0% (0/235)	0
Thrombosis of the study lesion	0.0% (0/236)	0	0.4% (1/235)	1
Blue toe syndrome	0.0% (0/236)	0	0.4% (1/235)	1
Deep vein thrombosis requiring surgical or lytic therapy	0.0% (0/236)	0	0.4% (1/235)	1
Worsened claudication/rest pain	2.5% (6/236)	6	3.4% (8/235)	9
Stroke	1.7% (4/236)	4	1.3% (3/235)	3
Vascular/surgical repair of injury to the study vessel (other than amputation or bypass)	0.0% (0/236)	0	0.4% (1/235)	2
Vascular/surgical repair of injury to another vessel (other than amputation or bypass)	0.4% (1/236)	1	0.0% (0/235)	0
Post-procedure transfusion	0.0% (0/236)	0	1.7% (4/235)	5
Other vascular events	4.7% (11/236)	12	3.4% (8/235)	10
Miscellaneous Events				

	Control		Treatment	
Hypersensitivity/allergic reaction	0.0% (0/236)	0	0.4% (1/235)	1
Other miscellaneous events	14.0% (33/236)	44	15.7% (37/235)	55

In summary, event-free survival at 12 months was 90.4% in the Zilver PTX treatment group and 83.9% in the PTA control group ($p < 0.01$), with the most common major adverse event being TLR, which occurred significantly more often in the PTA group (16.1%) compared to the Zilver PTX group (9.5%). In conclusion, the primary safety hypothesis of the study was met, indicating that treatment with the Zilver PTX stent is as safe as or safer than treatment with PTA—even when including provisional stenting (bare and PTX coated) in the PTA group.

2. Effectiveness Results

The analysis of effectiveness was based on the 471 evaluable lesions at the 12-month time point. Key effectiveness outcomes are presented in Tables 19 to 21.

The primary effectiveness endpoint of superior primary patency (conservatively defined as a PSV ratio < 2.0) for the Zilver PTX stent compared to PTA was met ($p < 0.01$[2]) with a primary patency rate at 12 months of 82.7% for the Zilver PTX treatment group and 32.7% for the PTA control group, as illustrated in Figure 6 and Table 19. The benefit of the Zilver PTX stent was maintained through 24 months.

[2] Adjusted for multiplicity.

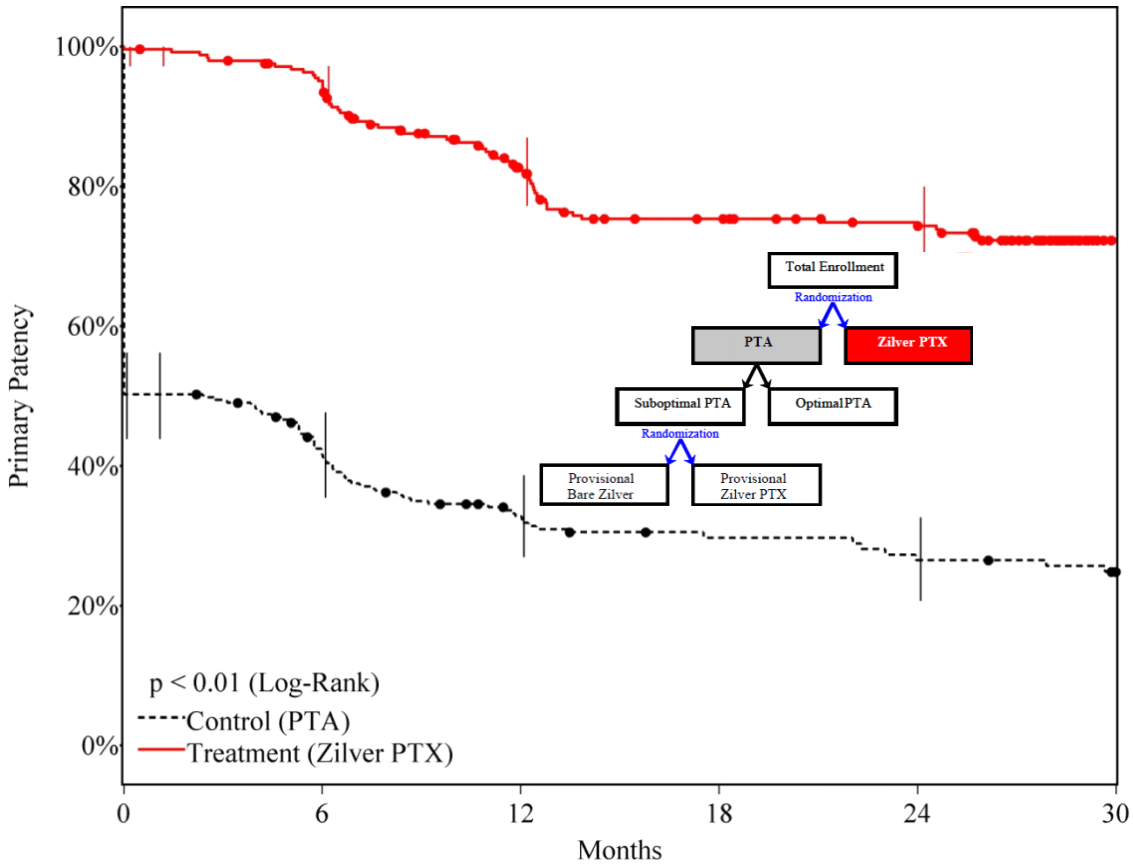


Figure 6: Kaplan-Meier curves for primary patency

Table 23: Kaplan-Meier estimates for primary patency

Months Post-procedure	Primary Patency Estimate		Standard Error		Cumulative Failed		Cumulative Censored		Number Remaining	
	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)	Control (PTA)	Treatment (Zilver PTX)
0	50.2%	99.6%	3.2%	0.4%	125	1	0	0	126	245
1	50.2%	99.6%	3.2%	0.4%	125	1	0	1	126	244
6	41.6%	95.1%	3.1%	1.4%	146	12	5	4	100	230
12	32.7%	82.7%	3.0%	2.5%	167	41	11	23	73	182
24	26.5%	74.8%	3.1%	2.9%	177	58	41	39	33	149

Comparison of the results for patients treated with the Zilver PTX Drug-Eluting Stent to those treated with the bare metal Zilver stent when used in a similar patient population (i.e., those patients who had acute failure of PTA) provides an evaluation of the paclitaxel drug effect. Both patient populations were selected in the same way (and randomized), and both stents have the identical stent platform; therefore, this comparison provides a direct measurement of the effectiveness of the Cook PTX® drug coating on the Zilver PTX stent. As illustrated in Figure 7

and Table 20, there was a significant difference in patency outcomes between the groups ($p < 0.01$[3]), with the Zilver PTX group exhibiting a higher primary patency rate at 12 months of 90.2% compared to 72.9% for the bare Zilver group. The benefit of the Zilver PTX stent was maintained through 24 months with a 24-month patency rate of 83.4% for the Zilver PTX group compared to 64.1% for the bare Zilver group. Therefore, stenting with the paclitaxel-coated Zilver PTX stent is significantly more effective in maintaining primary patency through 24 months than stenting with a bare (uncoated) stent—indicating that the PTX® coating has a significant effect, and further supporting the effectiveness of the Zilver PTX stent.

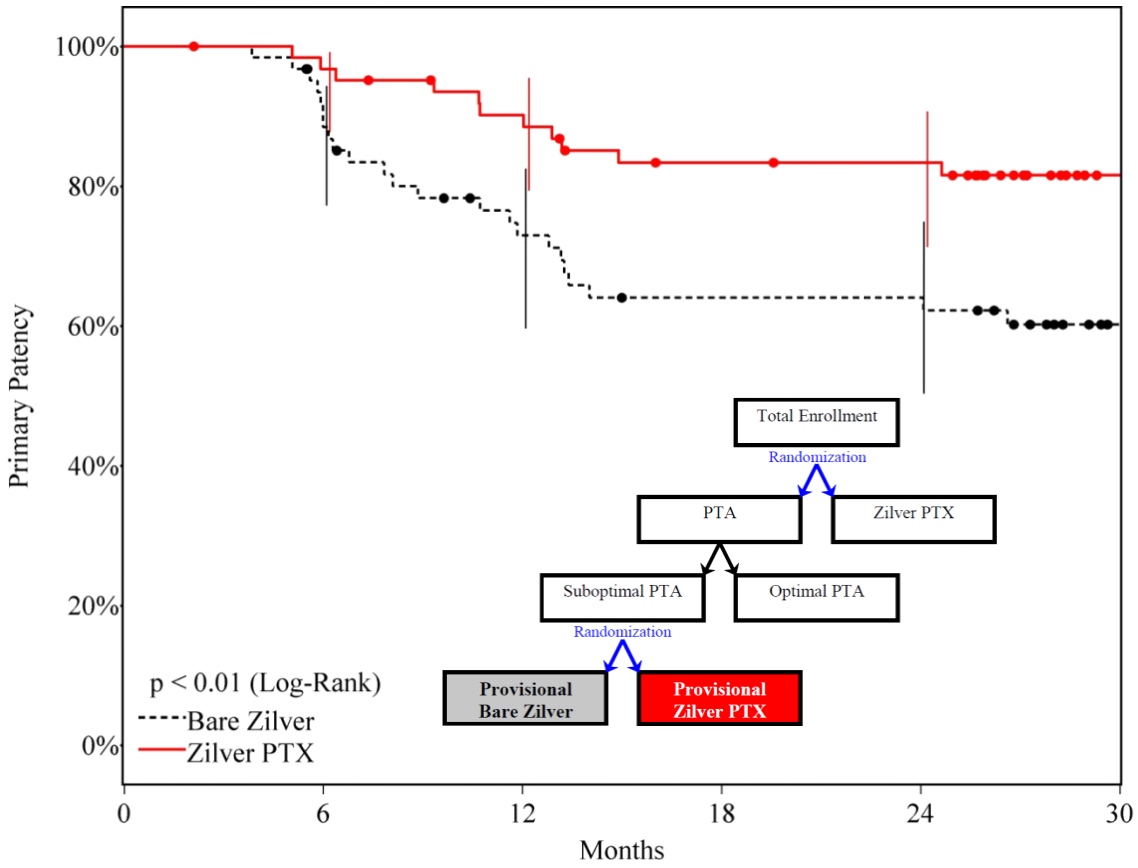


Figure 7: Kaplan-Meier curves for primary patency for provisional bare Zilver vs. provisional Zilver PTX

Table 24: Kaplan-Meier estimates for bare Zilver vs. Zilver PTX

Months Post-procedure	Primary Patency Estimate		Standard Error		Cumulative Failed		Cumulative Censored		Number Remaining	
	Bare Zilver	Zilver PTX	Bare Zilver	Zilver PTX	Bare Zilver	Zilver PTX	Bare Zilver	Zilver PTX	Bare Zilver	Zilver PTX

[3] Adjusted for multiplicity

0	100.0%	100.0%	0.0%	0.0%	0	0	0	0	62	63
1	100.0%	100.0%	0.0%	0.0%	0	0	0	0	62	63
6	88.4%	96.8%	4.1%	2.2%	7	2	2	1	53	60
12	72.9%	90.2%	5.8%	3.8%	16	6	5	3	41	54
24	64.1%	83.4%	6.3%	4.8%	21	10	6	7	35	46

In summary, the primary patency rate at 12 months was 82.7% in the Zilver PTX treatment group and 32.7% in the PTA control group. The effect of covariates, including diabetes, lesion length, and occluded/stenosed lesions, was not significantly different between the Zilver PTX and PTA groups. As defined in the study protocol, acute PTA failure is an endpoint for primary patency. Results for patients randomized after acute PTA failure to treatment with either the Zilver PTX stent or the bare metal Zilver stent were compared to provide an evaluation of the paclitaxel drug effect. The primary patency rate at 12 months was 90.2% for the Zilver PTX stent compared to 72.9% for the bare Zilver stent, demonstrating a significant drug effect in reducing restenosis with the Zilver PTX stent as compared to the bare Zilver stent. The benefit of the Zilver PTX stent was maintained through 24 months.

In conclusion, the primary effectiveness hypothesis of the study was met, indicating that treatment with the Zilver PTX stent is significantly more effective than treatment with PTA. Additionally, results from patient groups within the secondary randomization demonstrated that stenting with the paclitaxel-coated Zilver PTX stent is significantly more effective in maintaining primary patency than stenting with the same bare (uncoated) stent, indicating that the PTX® coating has a significant effect and further supporting the effectiveness of the Zilver PTX stent.

Secondary Endpoints

Secondary endpoint analyses include procedural success, the patient-centered measure of freedom from symptoms of ischemia (i.e., clinical benefit), clinical status (i.e., clinical improvement defined as improvement by 1 Rutherford class and clinical success defined as improvement by 2 Rutherford classes), and functional status (measured by ABI and Walking Impairment Questionnaire).

Table 25: Secondary endpoint estimates and 95% confidence intervals

	PTA Control Group	**Zilver PTX Treatment Group**
Procedural success	57.3% (50.8%, 63.5%)	95.0% (91.5%, 97.4%)
12-month clinical success	57.8% (50.7%, 64.6%)	54.9% (47.8%, 61.8)

12-month clinical improvement	77.7% (71.4%, 83.2%)	76.2% (69.8%, 81.9%)
12-month secondary patency	98.5% (95.5%, 99.5%)	98.2% (95.2%, 99.3%)
12-month restenosis rate[1]	33.5% (26.9%, 39.1%)	23.5% (18.6%, 29.5%)
12-month thrombosis rate	n/a	2.0% (0.7%, 3.9%)[2]
ABI[3]	0.21 (0.18, 0.25)	0.24 (0.20, 0.28)
Speed score[3]	28.6 (22.1, 35.0)	28.2 (21.9, 34.5)
Distance score[3]	31.4 (25.1, 37.7)	32.8 (26.5, 39.1)
Climb score[3]	22.8 (16.0, 29.6)	19.8 (12.8, 26.8)

[1] Estimated based on GEE model for primary patency; the 12-month restenosis rate is the converse of the 12-month primary patency rate when acute PTA failure is not considered a loss of primary patency and lesions are further treated with stenting (bare Zilver or Zilver PTX).
[2] Estimate reported for all Zilver PTX subjects (i.e., including provisional Zilver PTX in PTA control group).
[3] Estimates reported for the change in value from pre-procedure to 12 months.

Procedural success (< 30% residual stenosis) was significantly higher ($p < 0.01$) in the Zilver PTX treatment group (95.0%; 229/241) compared to the PTA control group (57.3%; 142/248), demonstrating that the Zilver PTX stent is effective in establishing acute patency.

Clinical benefit was evaluated in terms of freedom from the patient-centered measures of worsening claudication, worsening Rutherford class, tissue loss, and other symptoms indicating the need for reintervention (e.g., rest pain, ulcer, persistent claudication), and was considered to provide a clinically-based evaluation of patient benefit in this study, without the inclusion of surrogate endpoints. In this evaluation, patients in the Zilver PTX treatment group achieved a significantly higher ($p < 0.01$) freedom from symptoms of ischemia (i.e., clinical benefit) compared to patients in the PTA control group (86.9% vs. 75.4% at 12 months). Similarly, in subgroups within the PTA control group, patients receiving provisional Zilver PTX stents achieved a significantly higher freedom from symptoms of ischemia (i.e., clinical benefit) compared to patients receiving optimal PTA (87.3% vs. 69.4% at 12 months; $p < 0.01$ by log rank) or provisional bare Zilver stents (87.3% vs. 72.3% at 12 months; $p < 0.01$ by log rank). These results demonstrate that the Zilver PTX stent delivers superior effectiveness and clinical benefit for the patient and support the conclusion that the Zilver PTX stent is safe and effective.

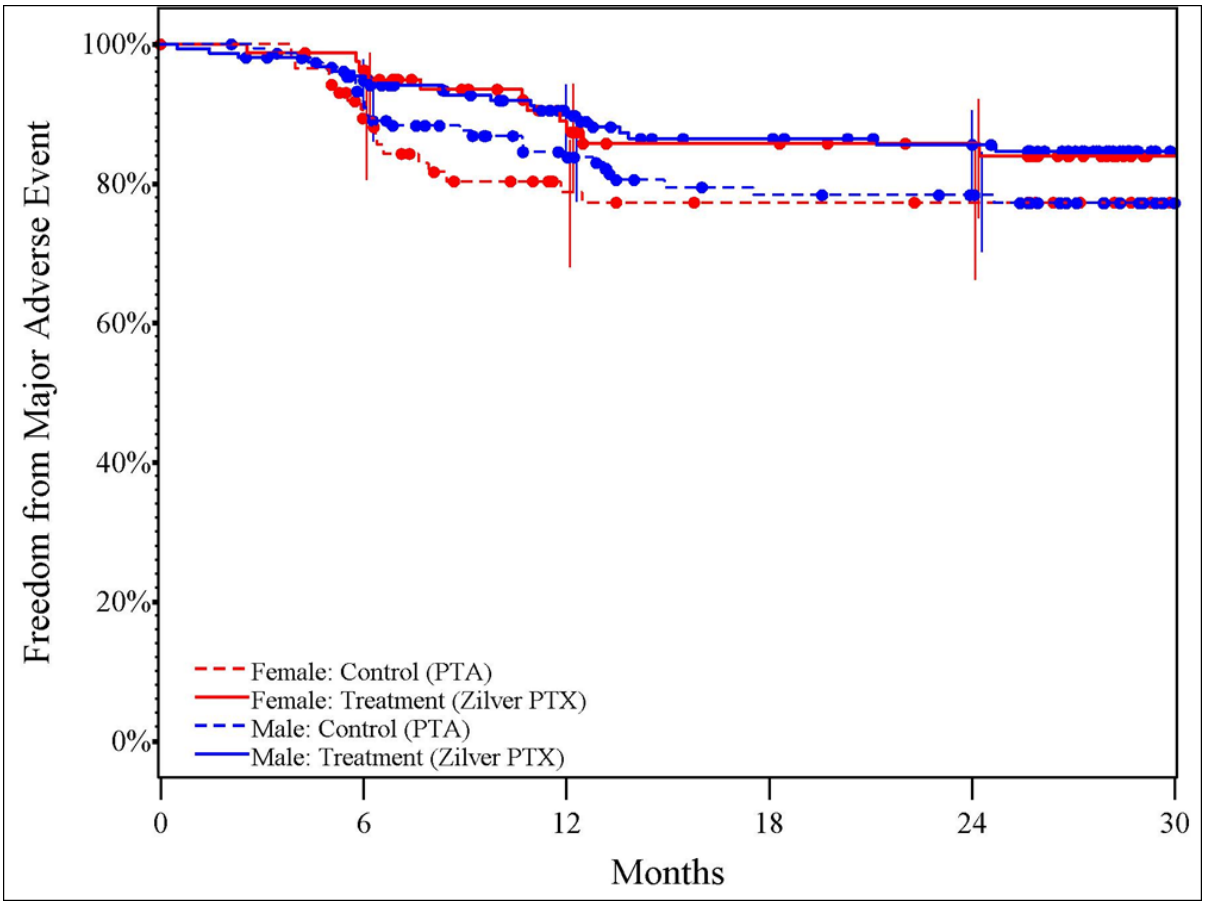
3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes:

Sex/Gender Analysis

The effect of sex/gender on the performance of the Zilver PTX stent was analyzed post-hoc by comparing the primary safety and effectiveness outcomes for the 167/474 (35%) female subjects and 307/474 (65%) male subjects. The event-free survival rates for female were 88.9% and 78.8% for the treatment and control arms, respectively. The rates for male were 90.5% and 84.5% for the treatment and control arms. The difference in outcome as a function of sex/gender for the primary safety endpoint was not statistically significant, suggesting that the event-free survival rate is comparable among male and female subjects within both the control and treatment arms (Figure 11).

A covariate analysis utilizing a logistic regression model was performed on the primary safety endpoint. The model included the treatment effect, gender and gender/treatment interaction, and other demographic and clinical covariates. Neither the treatment/gender interaction nor the gender main effect were significant (p = 0.74 and 0.58, respectively).

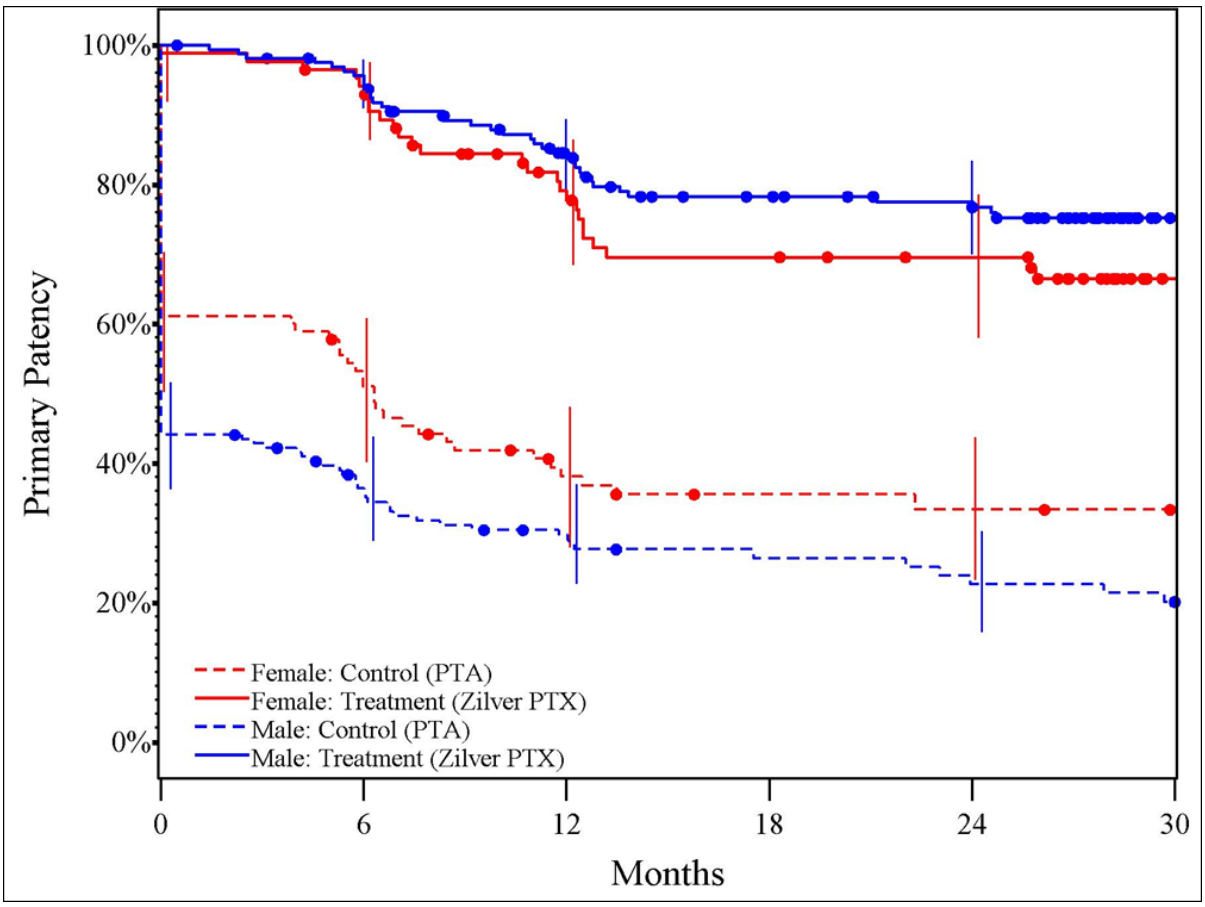


Months Post-procedure	Event-free Survival Estimate		Standard Error		Cumulative Failed		Cumulative Censored		Number Remaining	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Treatment (Zilver PTX)										
0	100%	100%	0%	0%	0	0	0	0	80	154
1	100%	99.4%	0%	0.6%	0	1	0	0	80	153
6	96.2%	95.4%	2.1%	1.7%	3	7	1	3	76	144
12	88.9%	90.5%	3.7%	2.4%	8	14	15	23	57	117
24	85.7%	85.6%	4.2%	3.0%	10	20	23	37	47	97
Control (PTA)										
0	100%	100%	0%	0%	0	0	0	0	86	152
1	100%	100%	0%	0%	0	0	0	0	86	152
6	89.4%	91.8%	3.4%	2.3%	9	12	6	9	71	131
12	78.8%	84.5%	4.6%	3.0%	17	22	17	21	52	109
24	77.3%	78.3%	4.8%	3.6%	18	29	36	54	32	69

Figure 8: Kaplan-Meier estimates for event-free survival for female and male subjects

For the primary effectiveness endpoint, a covariate analysis utilizing the GEE model was performed. The treatment effect was significant ($p < 0.01$) after adjusting for gender, hypercholesterolemia, smoking status, total occlusion, lesion length, and treatment/gender interaction. The p-value for the treatment-gender interaction was 0.052. This borderline significant interaction suggests that the magnitude of the treatment benefit may potentially be greater for males than for females.

Despite the potentially significant interaction, a pronounced treatment effect can be observed for both genders. For females, the primary patency rates were 79.1% and 38.1% for the treatment and control arms, respectively. For males, the rates were 84.5% and 29.7% for the treatment and control.



Months Post-procedure	Primary Patency Estimate		Standard Error		Cumulative Failed		Cumulative Censored		Number Remaining	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Treatment (Zilver PTX)										
0	98.8%	100%	1.2%	0.0%	1	0	0	0	84	161
1	98.8%	100%	1.2%	0.0%	1	0	0	1	84	160
6	94.1%	95.6%	2.6%	1.6%	5	7	1	3	79	151
12	79.1%	84.5%	4.5%	2.9%	17	24	9	14	59	123
24	69.6%	77.5%	5.2%	3.4%	24	34	14	25	47	102
Control (PTA)										
0	61.1%	44.1%	5.1%	3.9%	35	90	0	0	55	71
1	61.1%	44.1%	5.1%	3.9%	35	90	0	0	55	71
6	51.0%	36.4%	5.3%	3.8%	44	102	1	4	45	55
12	38.1%	29.7%	5.2%	3.6%	55	112	5	6	30	43
24	33.3%	22.6%	5.3%	3.7%	58	119	17	24	15	18

Figure 9: Kaplan-Meier estimates for primary patency for female and male subjects

Pharmacokinetic Substudy

A subgroup of 60 patients from the Zilver PTX treatment group was included in the pharmacokinetic (PK) substudy. Each patient was assigned 3 of a possible 11 time points, which included post-procedure (time 0), 20 min, 40 min, and 1, 1.5, 2, 3, 4, 6, 8, and 12 hours. Patients were divided into two groups based on the

number of stents with which they were implanted. The number of patients and total quantity of paclitaxel for each group are shown in Table 21.

Table 26: Pharmacokinetic substudy groups

# of Stents	# of Patients[1]	# of Samples	Paclitaxel Dose Range (µg)
1	42	125	312 - 864 (mean ± SD = 694 ± 200)
2	16	48	1083 - 1728 (mean ± SD = 1398 ± 228)

[1] Two patients were not included in the analysis; samples from one patient were assayed beyond the known stability timeframe; one patient received three Zilver PTX stents.

A parametric curve was fit to the data and the maximum observed plasma paclitaxel concentration (C_{max}), time to maximum concentration (T_{max}), area under the plasma concentration-time curve (AUC), half-life ($t_{1/2}$), and paclitaxel total clearance (CL_{plasma}) were estimated, along with 95% confidence intervals (Table 22). Additionally, a curve was fit to previously reported pharmacokinetic results obtained for animals implanted with Zilver PTX stents with a total of 876 µg paclitaxel coating per animal, and C_{max}, T_{max}, AUC, $t_{1/2}$, and CL_{plasma} were estimated.

Table 27: Pharmacokinetic parameters (with 95% confidence intervals)

Parameter	One Stent (n = 42)	Two Stents (n = 16)	Animal PK Study (n = 2)[1]
T_{max} (min)	20	22	20
C_{max} (ng/mL)	4.4 (4.2 - 4.6)	6.6 (6.3 - 6.9)	7.1
$AUC_{0\text{-last}}$[2] (ng·h/mL)	6.5 (4.7 - 8.5)	14.0 (10.7 - 17.2)	12.8
$AUC_{0\text{-inf}}$[3] (ng·h/mL)	6.5 (4.7 - 8.5)	14.9 (11.2 - 18.7)	12.8
$t_{1/2}$ (h)	2.4 (1.8 - 3.3)	7.0 (5.2 - 10.8)	1.6
CL_{plasma} (L/h)	107 (81.4 – 147.3)	93.3 (74.6 – 124.7)	68.5

[1] Confidence intervals were not calculated for this group because of the sample size of 2.
[2] AUC from time zero to time of last measured concentration.
[3] AUC from time zero to infinity.

The results show that pharmacokinetics of paclitaxel in humans were similar to previously reported results in animals. Minimal paclitaxel was delivered systemically (C_{max} < 10 ng/mL), and less than 1 ng/mL remained in the plasma at the 8- and 12-hour time points. The very low concentration and short duration of paclitaxel in the blood support the safety of the Zilver PTX stent.

Angiographic/IVUS Substudy

A subset of 80 patients, 40 from each study group, was assigned to an IVUS/angiographic substudy. The lesions in the Zilver PTX treatment group were evaluated with IVUS post-stenting and at the 12-month follow-up, and the patients in both the Zilver PTX treatment group and the PTA control group were evaluated with angiography at the 12-month follow-up (in the event of acute or long-term PTA failure and subsequent stent placement the patient was removed from the substudy).

The angiographic analysis includes all patients with both angiography and duplex ultrasound obtained at the 12-month follow-up and analyzed by the core laboratory. The agreement of angiography and duplex ultrasound for assessing lesion patency was evaluated. At 12-month follow-up, approximately 89% of lesions assessed by both angiography and duplex ultrasound were determined to be either patent or not patent by both measures (Table 23).

Table 28: Correlation of angiography and duplex ultrasound for assessing patency

		Patent by Ultrasound	
		Yes	**No**
Patent by Angiography	**Yes**	74.5% (41/55)	7.2% (4/55)
	No	3.6% (2/55)	14.5% (8/55)

In summary, as expected, the high correlation between angiography and ultrasound confirms the validity of duplex ultrasound for assessing patency in the absence of angiography.

IVUS results include all patients with available IVUS imaging (i.e., IVUS substudy and IVUS from the first 60 patients enrolled). There was no aneurysm or stent malapposition detected at the 6-month or 12-month follow-ups and the rate of aneurysm and stent malapposition was low immediately after stenting (2.4%, see Table 24) and was not associated with clinical sequelae. Both events of aneurysm and stent malapposition detected immediately post-stenting were associated with a pre-existing aneurysm visible on the angiogram prior to stent implantation.

Table 29: IVUS core laboratory findings

Period	Aneurysm Observed	Malapposition Observed
Post-stent	2.4% (2/85)[1]	2.4% (2/84)[1]
6 months[2]	0% (0/28)	0% (0/28)
12 months	0% (0/36)	0% (0/36)

[1] In both cases, aneurysm was also present immediately prior to stent implantation, and the stent malapposition was observed in the location of the pre-existing aneurysm.
[2] Six-month IVUS was required for the first 60 patients in the study who received study stents, but was not required as part of the IVUS substudy.

In summary, the pharmacokinetic substudy demonstrated that minimal paclitaxel was delivered systemically (C_{max} < 10 ng/mL), and less than 1 ng/mL remained in the plasma at the 8- and 12-hour time points. Additionally, the clinical results were in close agreement with previously reported results from animal studies. The angiographic substudy indicated a high correlation of angiography and ultrasound for assessing lesion patency, confirming the validity of duplex ultrasound for assessing patency in the absence of angiography. The IVUS substudy found no aneurysm or stent malapposition at the 6-month or 12-month follow-ups and a low rate of aneurysm and stent malapposition immediately post-stenting (2.4%), which was associated with pre-existing aneurysms prior to stent implantation and was not associated with clinical sequelae. In conclusion, the results from these substudies support the safety and effectiveness of the Zilver PTX stent.

Stent Integrity

Zilver stent integrity (including both the Zilver PTX stent and the bare metal Zilver stent used in bailout stenting procedures) was evaluated prior to discharge and at 12 months by high resolution stent x-rays intended to provide visualization of the individual stent struts. As shown in Table 25, no stent fractures were detected upon procedure completion (0/528) and only four stent fractures (4/457) were detected at 12 months, for a 12-month stent fracture rate of 0.9%. Each of the fractures was located in the distal SFA, with two Type I (single strut fracture) and two Type III (multiple strut fractures resulting in complete transection of the stent, without displacement of the stent segments) fractures. Both of the stents with a Type III fracture were found to have been elongated during the implant procedure. This is a known predisposition to stent fracture. As indicated above, one of the Type I fractures occurred at the location of a pre-existing arterial aneurysm. All four of the patients with a stent fracture maintained primary patency and remained free from TLR through 12-month follow-up, indicating that

the stent fractures did not adversely affect patient safety or the effectiveness of the Zilver PTX stent.

Table 30: Stent integrity prior to discharge and at 12 months

Timepoint	Stents visualized by x-ray	Stents with fracture	Stent fracture rate
Prior to discharge	528	0	0%
12 months	457	4	0.9%

In summary, the stent fracture rate was low (0.9%) and the safety and effectiveness outcomes for patients with a stent fracture indicate that the stent fractures did not adversely affect patient safety or the effectiveness of the Zilver PTX stent. These results further support the safety of the Zilver PTX stent.

Results Summary

Event-free survival at 12 months was 90.4% in the Zilver PTX treatment group and 83.9% in the PTA control group, with the most common major adverse event being TLR, which occurred significantly more often in the PTA control group (16.1%) compared to the Zilver PTX treatment group (9.5%). Primary patency at 12 months was 82.7% in the Zilver PTX treatment group and 32.7% in the PTA control group. In conclusion, the primary safety and effectiveness hypotheses of the study were both met, indicating that treatment with the Zilver PTX stent is as safe as or safer than treatment with PTA ($p < 0.01$) and that the Zilver PTX stent provides a significantly higher rate of primary patency compared to PTA ($p < 0.01$). These results support the safety and effectiveness of the Zilver PTX stent for the treatment of symptomatic vascular disease of the above-the-knee femoropopliteal arteries.

Additionally, stenting with the paclitaxel-coated Zilver PTX stent is significantly more effective ($p < 0.01$) in maintaining primary patency than stenting with the bare (uncoated) stent, indicating that the PTX® coating has a significant effect and further supporting the effectiveness of the Zilver PTX stent.

Procedural success (< 30% residual stenosis) was significantly higher in the Zilver PTX treatment group (95.0%; 229/241) compared to the PTA control group (57.3%; 142/248) demonstrating that the Zilver PTX stent is effective in establishing patency.

Patients in the Zilver PTX treatment group achieved a significantly higher rate of freedom from symptoms of ischemia (i.e., clinical benefit) compared to patients in the PTA control group. Similarly, patients receiving Zilver PTX stents achieved a significantly higher freedom from symptoms of ischemia (i.e., clinical benefit) compared to patients receiving optimal PTA or provisional bare Zilver stents. These results demonstrate that the Zilver PTX stent delivers superior effectiveness and clinical benefit for the patient and support the conclusion that the Zilver PTX stent is safe and effective. Furthermore, based on the clinical benefits of the Zilver PTX stent compared to PTA seen in this study, primary stenting with the Zilver PTX stent is reasonable and necessary for patients suffering from peripheral arterial disease.

The pharmacokinetic substudy demonstrated that minimal paclitaxel was delivered systemically (C_{max} < 10 ng/mL), and less than 1 ng/mL remained in the plasma at the 8- and 12-hour time points. Additionally, the clinical results were in close agreement with results from previous animal studies. The angiographic substudy indicated a high correlation between angiography and ultrasound for assessing lesion patency, confirming the validity of duplex ultrasound for assessing patency in the absence of angiography. The IVUS substudy found no aneurysm or stent malapposition at the 6-month or 12-month follow-ups and a low rate of aneurysms and stent malapposition immediately post-stenting (2.4%), which was associated with pre-existing aneurysms prior to stent implantation and was not associated with clinical sequelae. In conclusion, the results from these substudies support the safety and effectiveness of the Zilver PTX stent.

The stent fracture rate was low (0.9%) and the safety and effectiveness outcomes for patients with a stent fracture indicate that the stent fractures did not adversely affect patient safety or the effectiveness of the Zilver PTX stent. These results further support the safety of the Zilver PTX stent.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The Zilver PTX single arm study was a prospective, non-randomized, open-label, multi-center study enrolling patients in Europe, Canada, and Korea with *de novo* or restenotic (including in-stent restenosis) lesions of the above-the-knee femoropopliteal artery. All patients enrolled in the study were treated with the Zilver PTX stent.

The study was designed to quantify the safety and performance of the Zilver PTX stent. The study was conducted with the intention that safety data from the registry would be combined with the subject data from the RCT to create a multi-study pool of more than 1000 Zilver PTX subjects and thereby more fully establish the rate of potentially rare device- or drug-related adverse events.

A total of 787 patients were enrolled at 30 sites. The study entry criteria were similar to the randomized study with the exception that there was no limitation on lesion length or the number of lesions treated per patient (up to 4 Zilver PTX stents could be used per patient) and the inclusion of lesions with in-stent restenosis was allowed. The study follow-up schedule included clinical assessment at pre-discharge and at 1, 6, 12, and 24 months, and ultrasound imaging and stent X-rays at pre-discharge and at 6 and 12 months. Telephone contact was scheduled for 3, 9, and 18 months. Clinical follow-up is currently available for 740 patients at 12 months and 500 patients at 24 months.

Patient medical history included a high incidence of diabetes (36%, 285/787), hypercholesterolemia (58%, 458/787), hypertension (80%, 627/787), and past or current smoking (80%, 632/787). A total of 1722 Zilver PTX stents were implanted in 900 lesions during the study procedure, with more than 60% of patients being treated with at least 2 stents. Lesions treated in the study had a mean length of 100 ± 82 mm with 25% of lesions > 14 cm in length (224/900), 38% (345/900) classified as total occlusions and 24% (219/900) having been previously treated, including 130 lesions that had been previously stented. **NOTE**: Lesions > 14 cm in length and previously stented lesions are outside of the approved indication for use.

The 6-month event-free survival (EFS) rate for patients with a Zilver PTX stent was 97.4% (Figure 8 and Table 26), a rate superior to the prospectively defined objective performance criterion of 75% EFS ($p < 0.01$). EFS was 89.0% at 12 months and 79.3% at 24 months. Similarly, freedom from TLR was 89.3% at 12 months and 80.5% at 24 months (Figure 9 and Table 27).

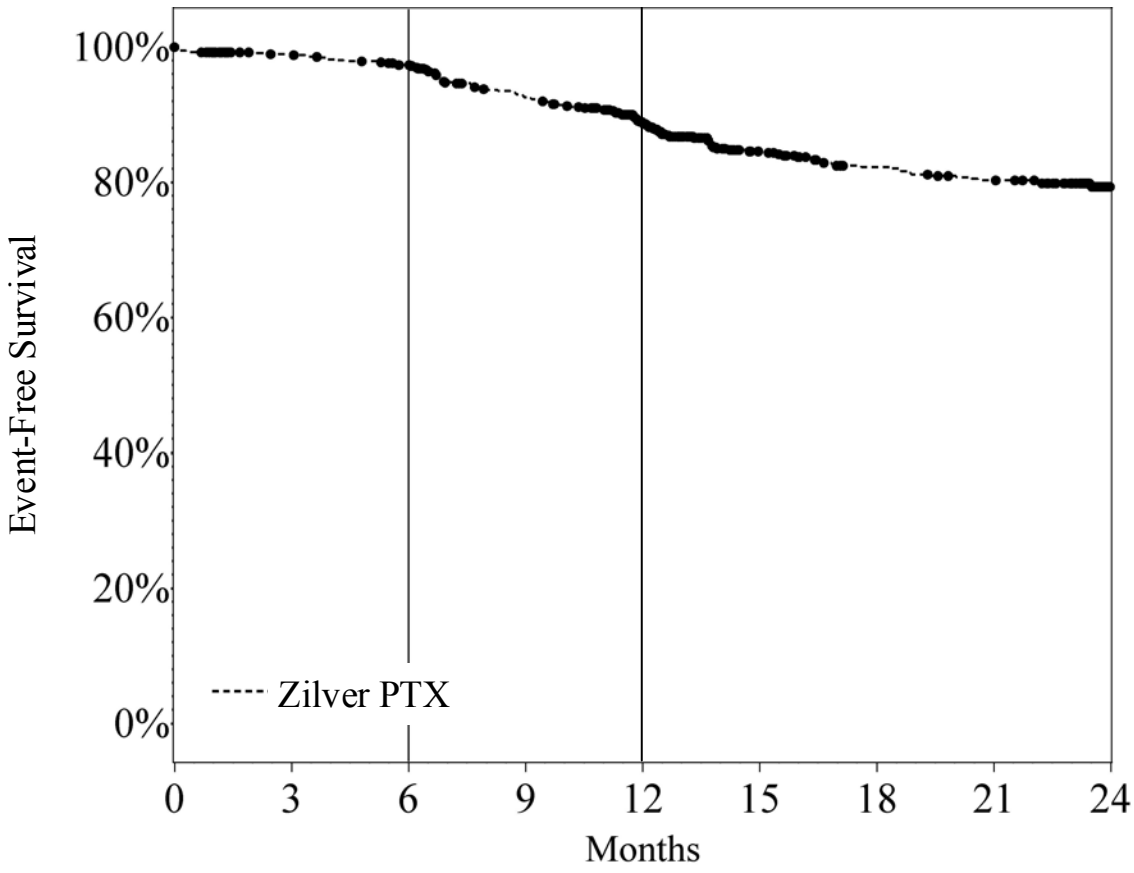


Figure 10: Kaplan-Meier curve for event-free survival

Table 31: Kaplan-Meier estimates for event-free survival

Months post-procedure	Estimate	Standard Error	Cumulative Number Failed	Cumulative Number Censored	Number Remaining
0	100.0%	0%	0	0	780
1	99.2%	0.3%	6	14	767
6	97.4%	0.6%	20	42	725
12	89.0%	1.2%	80	144	563
18	82.2%	1.5%	115	292	380
24	79.3%	1.7%	128	420	239

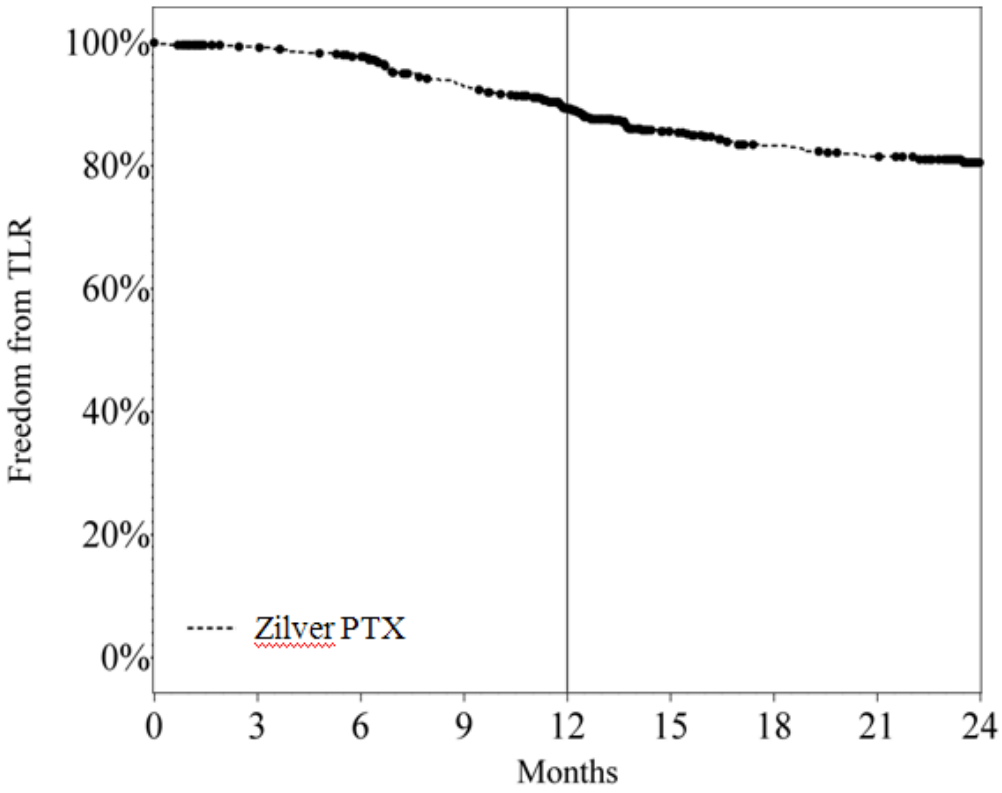


Figure 11: Kaplan-Meier curve for freedom from TLR

Table 32: Kaplan-Meier estimates for freedom from TLR

Months post-procedure	Estimate	Standard Error	Cumulative Number Failed	Cumulative Number Censored	Number Remaining
0	100.0%	0.0%	0	7	778
1	99.6%	0.2%	3	14	768
6	97.7%	0.5%	17	43	725
12	89.3%	1.2%	77	145	563
18	83.2%	1.5%	108	297	380
24	80.5%	1.7%	120	420	245

In summary, the event-free survival rate was 97.4% at 6 months and 89.0% at 12 months and was consistent with the randomized study, which had an EFS rate in the Zilver PTX treatment group of 97.0% at 6 months and 90.4% at 12 months. These results further support a reasonable assurance of safety and effectiveness for the Zilver PTX stent. Secondary outcomes were also favorable. Specifically, primary patency (conservatively defined as a PSV ratio < 2.0) was 83.0% at 12 months (Figure 10 and Table 28).

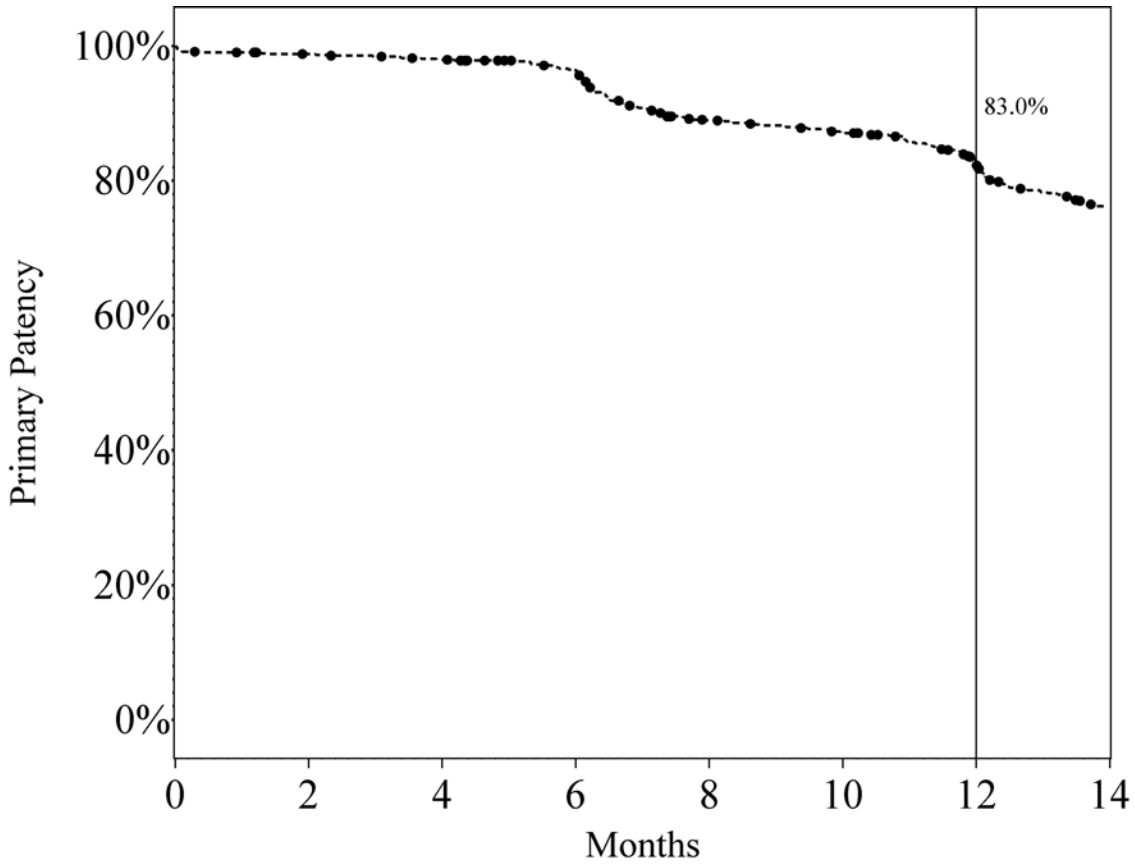


Figure 12: Kaplan-Meier curve for primary patency

Table 33: Kaplan-Meier estimates for primary patency

Months post-procedure	Estimate	Standard Error	Number Failed	Number Censored	Number Remaining
0	99.9%	0.1%	1	0	840
1	99.0%	0.3%	8	2	831
6	96.4%	0.6%	30	18	793
12	83.0%	1.3%	138	50	653

The primary patency rate at 12 months of 83.0% is consistent with the Zilver PTX treatment group in the randomized study, which had a primary patency rate of 82.7% at 12 months, and further supports a reasonable assurance of effectiveness for the Zilver PTX stent, including lesions up to 300 mm in length.

Stent fractures were detected in only 1.5% of stents (22/1432) at 12 months, and clinical and functional status measures (i.e., Rutherford classification, ABI, walking scores, and quality of life scores) improved significantly from pre-procedure to 12 months.

In conclusion, the results from the Zilver PTX single arm study provide supporting evidence confirming the safety of the Zilver PTX Drug-Eluting Stent for the treatment of symptomatic vascular disease of the above-the-knee femoropopliteal arteries.

Combined Analysis of Randomized and Single Arm Studies

The Zilver PTX single arm study was a prospective, non-randomized, open-label, multicenter single arm study enrolling 787 patients in Europe, Canada, and Korea with de novo or restenotic (including in-stent restenosis) lesions of the above-the-knee femoropopliteal artery. The study inclusion/exclusion criteria allowed enrollment of a broad patient population, including long lesions up to approximately 300 mm and enrolment for treatment of in-stent restenosis. All patients enrolled in the study were treated with the Zilver PTX Drug-Eluting Stent. The combined randomized and single arm studies include more than 1000 patients treated with more than 2000 Zilver PTX Drug-Eluting Stents.

Stent integrity and the potential for rare adverse events were evaluated in this combined group of patients receiving Zilver PTX Drug-Eluting Stents, including a substantial number of patients with pre-existing in-stent restenosis at enrollment and long lesions treated with overlapped stents. Event-free survival at 12 months was 90.4% for the primary Zilver PTX group in the randomized study and 89.0% in the single arm study. Primary patency at 12 months was also similar between the two studies at 82.7% for the primary Zilver PTX group in the randomized study and 83.0% in the single arm study. These similar results demonstrate the complementary and supportive nature of the two studies. Whereas the randomized study was the pivotal study supporting safety and effectiveness and enrolled moderate length lesions, the single arm study provides additional clinical evidence supporting safety regarding low frequency adverse events..

Regarding stent integrity, high resolution radiographs demonstrated that 98.6% of stents remained free from stent fracture at 12 months (1863/1889), for a stent fracture rate of 1.4%. Regarding potential rare adverse events, there were no reported drug or hypersensitivity reactions attributed to the paclitaxel drug coating or the nitinol stent, and none of the rare cases of neutropenia were determined to be due to the paclitaxel coating on the Zilver PTX Drug-Eluting Stent or to participation in the study. The incidence of adverse events with a potential to be related to particulate matter (i.e., embolism distal to the study vessel and blue toe syndrome) was low for patients receiving bare Zilver or Zilver PTX Drug-Eluting Stents, and was not increased for

patients receiving a Zilver PTX Drug-Eluting Stent. Among all subjects who received a Zilver PTX (including those assigned to the Zilver PTX arm of the RCT, treated provisionally with the Zilver PTX in the RCT, and enrolled in the global registry), the KM estimates of freedom from thrombosis was 97.2% and 96.5% at 12 and 24 months, respectively. This low rate of stent thrombosis was not increased for patients receiving a Zilver PTX Drug-Eluting Stent compared to patients receiving a bare Zilver stent, and was also consistent with previous femoropopliteal stenting outcomes reported in the literature. These results, including more than 1,000 patients and 2,000 Zilver PTX Drug-Eluting Stents, provide additional evidence supporting the safety of the polymer-free PTX® coating and of the Zilver PTX Drug-Eluting Stent.

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

A. Panel Meeting Recommendation

At an advisory meeting held on October 13, 2011, the Circulatory Systems Devices voted unanimously that there is reasonable assurance the device is safe and that there is reasonable assurance that the device is effective, and that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication.

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM282518.pdf

The Panel made the following recommendations for the labeling:

- The maximum lesion length per limb and per patient specified in the proposed Indications for Use (total lesion lengths up to 140 mm per limb and 280 mm per patient) is appropriate.
- The IFU should be revised to add the word "native" to the vascular disease site.
- A descriptive analysis of the dual anti-platelet therapy used in the RCT should be included in the labeling.
- "Intended use" should be changed to "indications"
- The bleeding disorder clause should be stated not as a contraindication but rather as a precaution that bleeding disorders have not been studied.

- The risk of stent fracture should be listed as a potential complication; as well as the patency problems in longer stents.
- Patients who cannot be on anti-platelet therapy should be listed as a precaution.

The Panel also provided the following recommendations for the post-approval study:

- The post-approval study should be a cohort study to capture stent thrombosis totaling 900 patients captured out to 5 years.
- A majority of the patients in the post-approval study should be enrolled in the United States.
- Other aspects for the post-approval study to capture should include rates of major bleeding, hemorrhage, and GI bleeding, an assessment of gender differences, and an assessment of outcomes in diabetic patients.

B. FDA's Post-Panel Action

FDA implemented all of the Panel's recommendations, with two exceptions. FDA has decided to list the bleeding disorder caluse as a warning instead of a precaution, and to include the anti-platelet clause as a contraindication. FDA made this decision in order to make the Zilver PTX labeling consistent with other approval SFA and coronary DES IFUs. The panel did not have access to these documents to ensure this consistency at the time of the panel meeting.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness data drawn from the Zilver PTX randomized and single arm clinical studies demonstrated a reasonable assurance of effectiveness for the Zilver PTX stent when used in accordance with the inclusion and exclusion criteria for the intended patient population. Primary patency at 12 months was 82.7% in the Zilver PTX treatment group and 32.7% in the PTA control group. In conclusion, the primary effectiveness hypothesis of the study was met, indicating that the Zilver PTX stent provides a significantly higher rate of primary patency compared to PTA ($p < 0.01$). These results support the effectiveness of the Zilver PTX stent for the treatment of symptomatic vascular disease of the above-the-knee femoropopliteal arteries.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in the clinical studies conducted to support PMA approval as described above. The primary safety data drawn from the Zilver PTX randomized and single arm clinical studies demonstrated that event-free survival at 12 months was 90.4% in the Zilver PTX treatment group and 83.9% in the PTA control group, with the most common major adverse event being TLR, which occurred significantly more often in the PTA control group (16.1%) compared to the Zilver PTX treatment group (9.5%). In conclusion, the primary safety hypothesis of the study was met, indicating that treatment with the Zilver PTX stent is as safe as or safer than treatment with PTA ($p < 0.01$). These results support the safety of the Zilver PTX stent for the treatment of symptomatic vascular disease of the above-the-knee femoropopliteal arteries.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefit of the Zilver PTX Drug-Eluting Stent of improving the patient symptoms and quality of life outweigh the probable risks associated with use of the device.

Additional factors to be considered in determining probable risks and benefits for the Zilver PTX Drug-Eluting Stent included:

- Patient follow-up was satisfactory and with limited missing data. The study results are superior to the results of angioplasty alone. Follow-up for the PMA was 24 months, but follow-up will continue for 5 years to evaluate the longer term device performance, such as the duration of the benefit and long term adverse event rates.

- The pivotal study was a multi-center study conducted in the United States, with a registry study which enrolled more "all-comers" type patients, conducted in Europe and Japan. The results already obtained should not differ from the post-market performance.

- Most patients with the disease have symptoms only, but some patients may have more extensive disease involvement. The device treats the hemodynamic consequences of the disease to improve perfusion and function. The disease is

chronic and affects the mobility of the patient and the quality of life. It is treatable but not curable.

- There are alternative treatments available, but this treatment is more durable and more effective than percutaneous transluminal angioplasty. This treatment is highly valued by patients and preferred to the alternatives because it improves their quality of life with lesser need for repeat procedures.

- Patient risk is minimized by limiting use to operators who have the necessary training to use the device safely and effectively and adherence to recommended periprocedural medication regimens.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for using the device 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.

D. Overall Conclusions

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. . Specifically, the event-free survival rate for the Zilver PTX treatment group was superior to the PTA control group, indicating that primary stenting with the Zilver PTX stent is associated with a lower MAE rate than the current standard care of PTA with provisional stenting. The primary patency rate (patency defined as duplex ultrasound measured peak systolic velocity ratio < 2.0 indicating less than 50% diameter stenosis) for the Zilver PTX stent was significantly higher than the primary patency rate for PTA, demonstrating that primary stenting with the Zilver PTX stent is significantly more effective than PTA. Additionally, the Zilver PTX stent demonstrated superior effectiveness to the bare Zilver stent in a randomized comparison in lesions with acute PTA failure. Results from the single arm clinical study provide additional evidence supporting the safety and effectiveness of the Zilver PTX stent in a broader patient population including more complex lesions.

XIV. CDRH DECISION

CDRH issued an approval order on November 14, 2012. The final conditions of approval cited in the approval order are described below.

1. Within 12 months of PMA approval, you should submit a non-clinical post-approval report discussing the results of particulate testing conducted on manufactured lots. If this information indicates that tightening the particulate specification is appropriate, you should submit a PMA supplement requesting such a change.

In addition to the Annual Report requirements, you must provide the following data in post-approval study reports (PAS). Two (2) copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below.

1. *New US Enrollment:* The study will be a prospective, single-arm, multi-center study of newly enrolled subjects implanted with a Zilver PTX stent. A total of 200 *de novo* subjects will be enrolled from a minimum of 10 investigational sites across the United States.

   The primary endpoint is the incidence of target lesion revascularization (TLR) at one year post-procedure. The primary endpoint will be compared to a performance goal of 83.1%, with the study having greater than 80% power to test the primary endpoint.

2. *Zilver PTX Stent PAS*: The study will be a prospective, single-arm, multi-center study of all subjects from the *New US Enrollment* study (detailed above), the Zilver PTX subjects from the pivotal study, the Japanese post-approval study, and if needed additional subjects from the global single-arm pre-market study. A total of 900 subjects will be enrolled and a minimum of 50% will be from the US.

   The objective of this study is to evaluate longer-term stent integrity and any other emerging safety signals. The endpoints are (1) target lesion revascularization (TLR) and stent thrombosis assessed annually through five years post-procedure and (2) stent integrity assessed by X-ray at one, three, and five years post-procedure.

   The incidence of TLR and stent thrombosis will be assessed annually through five years post-implantation in the entire cohort of 900 subjects. This will be reported descriptively for each follow-up interval using 95% confidence intervals.

   Stent integrity, defined as no fractures visible on x-ray imaging, will be assessed in a subset of 600 subjects (all new US enrollment subjects, all Zilver PTX subjects from the pivotal study, and the remainder consisting of the earliest

sequentially enrolled subjects in the Japanese post-approval study). The study will evaluate the five-year stent fracture rate and it is designed to detect a difference of at least 2% change in the rate with 95% confidence and 80% power.

In addition, patency will be assessed annually through five years post-procedure in all new US enrollment subjects and all Zilver PTX subjects from the Pivotal Study, and any remainder consisting of the earliest sequentially enrolled subjects in the Japanese post-approval study. This will be reported descriptively for each follow-up interval using 95% confidence intervals.

Cook will be advised that the results from these studies should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement. Within 30 days of the sponsor's receipt of the approval letter, the sponsor must submit two separate PMA supplements that include the complete protocols of the two post-approval studies. FDA will also remind the sponsor that they are required to submit PAS Progress Reports for each of the studies every six months during the first two years and annually thereafter.

The applicant's manufacturing facility was 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