Zilver® PTX® Drug-Eluting Stent

Panel Package

Executive Summary

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Table of Contents

1. Executive Summary 1
1.1. Abstract 1
1.2. Background 3
1.3. Proposed Indication for Use 4
1.4. Regulatory and Marketing History 4
1.5. Device Description 5
1.5.1. Stent System 5
1.5.2. Drug Component 6
1.5.3. Principles of Operation 9
1.6. Non-clinical Studies 10
1.6.1. Biocompatibility testing 10
1.6.2. *In Vitro* Bench Testing 10
1.6.3. Chemistry, Manufacturing, and Control (CMC) Testing 12
1.6.4. Non-clinical *In Vivo* Animal Studies 12
1.6.5. Toxicity 16
1.7. Clinical Studies Overview 18
1.8. Zilver PTX Randomized IDE Clinical Study 20
1.8.1. Primary Objective 20
1.8.2. Study Overview 20
1.8.3. Demographics 22
1.8.4. Results 26
1.8.4.1 Safety 28
1.8.4.2 Effectiveness 33
1.8.4.3 Secondary Endpoints 36
1.8.4.4 Substudies 38
1.8.4.5 Stent Integrity 40
1.8.4.6 Results Summary and Conclusions 40
1.8.5. Conclusions 42
1.9. Single Arm Clinical Study 42
1.9.1. Study Overview 42
1.9.2. Demographics 43
1.9.3. Results 43
1.9.3.1 Safety 43
1.9.3.2 Secondary Endpoints 45
1.9.4. Conclusions 47
1.10. Combined Analysis of Randomized and Single Arm Studies 47
1.11. Summary and Conclusions 47
1.12. Proposed Post Approval Study 48
1.12.1. Questions Answered by the Pre-approval Studies 49
1.12.2. Literature Search for Residual Issues 50

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1. Executive Summary

1.1. Abstract

The Zilver® PTX® Drug-Eluting Stent (also referred to as the Zilver PTX stent) is a nitinol stent with a polymer-free paclitaxel coating designed for the treatment of symptomatic lesions in the above-the-knee femoropopliteal arteries and has been evaluated in extensive non-clinical biocompatibility, bench, and animal testing, as well as in a robust clinical trial program.

A thorough panel of biocompatibility, bench, and animal testing was performed on finished and sterilized Zilver PTX stents and delivery systems based on international standards and FDA guidance. The results of the biocompatibility studies showed that the Zilver PTX stent and delivery system are biocompatible and non-pyrogenic, supporting the safety and acceptability for clinical use. The bench studies were performed to verify that the Zilver PTX stent and delivery system perform in accordance with specifications while minimizing the risk of adverse events under anticipated clinical conditions. The results demonstrate device functionality and provide a reasonable assurance of device safety. Animal studies included one-, three-, and six-month pivotal studies to examine local, regional, and systemic effects of Zilver PTX stents, as well as additional studies to evaluate overdose effects and pharmacokinetics.[1] Results of the extensive animal studies demonstrated complete vessel healing, no safety problems, and no regional or systemic effects related to the paclitaxel coating, and support a reasonable assurance of device safety and performance. Additionally, each batch of finished Zilver PTX devices undergoes chemistry, manufacturing, and control (CMC) release testing for appearance, identity, potency, content uniformity, impurities, *in vitro* release, and particulate matter to help assure consistent safety and effectiveness for all Zilver PTX stents.

The clinical trial program included a randomized IDE clinical study and a complementary OUS (outside the United States) single arm clinical study.[2,3] The randomized study is a prospective,

[1] Dake MD, Van Alstine WG, Zhou Q, Ragheb AO. Polymer-free paclitaxel-coated Zilver PTX Stents--evaluation of pharmacokinetics and comparative safety in porcine arteries. J Vasc Interv Radiol. 2011; 22:603-10.
[2] Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: 12-month zilver ptx randomized study results. In Press.
[3] Dake MD, Scheinert D, Tepe G, Tessarek J, Fanelli F, Bosiers M, et al. Nitinol stents with polymer-free paclitaxel coating for lesions in the superficial femoral artery and popliteal artery above the knee: twelve-month safety and effectiveness results from the zilver ptx single-arm clinical study. In Press.

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controlled, multicenter, multinational study that was designed to compare the 12-month safety and effectiveness of the Zilver PTX stent to percutaneous transluminal angioplasty (PTA) and provisional bare metal stenting. The study enrolled 479 patients with *de novo* or restenotic lesions up to 140 mm in length; one lesion per limb could be treated for a maximum total lesion length of 280 mm per patient. Patients were randomly assigned to Zilver PTX or PTA; patients experiencing acute PTA failure underwent secondary randomization to provisional Zilver PTX or bare Zilver. Primary endpoints were the 12-month rates of event-free survival and primary patency.

The Zilver PTX stent met the safety and effectiveness endpoints in the clinical studies, with results from the randomized clinical study demonstrating superior performance of the Zilver PTX stent compared to PTA and compared to the identical bare metal Zilver stent. Specifically, event-free survival (EFS) at 12 months was 90.4% in the Zilver PTX treatment group, non-inferior to the 83.9% EFS rate in the PTA control group ($p < 0.01$). The most common major adverse event was target lesion revascularization (TLR), which occurred significantly more often in the PTA control group (16.3%) compared to the Zilver PTX treatment group (9.6%). Primary patency at 12 months was 82.7% in the Zilver PTX treatment group, superior to the 32.7% primary patency rate in the PTA control group ($p < 0.01$, log rank). Additionally, the provisional Zilver PTX group exhibited superior primary patency (90.2% vs. 72.9%; $p < 0.01$, log rank) compared to the provisional bare Zilver group, demonstrating a significant drug coating effect. Longer-term follow-up has demonstrated that the benefits of the Zilver PTX stent are maintained through 24 months. 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.

The complementary single arm study is a prospective, multicenter, multinational study that enrolled 787 patients from a broader patient population (including long lesions and in-stent restenoses) and allowed up to 4 Zilver PTX stents per patient for treating a single or multiple lesions. This study was part of the overall Zilver PTX clinical plan discussed with FDA that required the safety evaluation of more than 1000 patients treated with the Zilver PTX stent. The results of the single arm clinical study provide additional evidence supporting the safety and effectiveness of the Zilver PTX stent in a large number of patients including more complex lesions. Specifically, the 12-month EFS rate was 89.0%, the 12-month primary patency rate was 83.0%, and 89.3% of lesions remained free from target lesion revascularization (TLR). Stent integrity and the potential for rare adverse events were evaluated in the combined group of more than 1000 patients receiving more than 2000 Zilver PTX stents in the randomized and single arm studies. The results of this analysis demonstrate a low rate of stent fracture and no evidence of

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adverse events related to the paclitaxel coating, further supporting the safety of the Zilver PTX stent.

In conclusion, the results of the Zilver PTX randomized clinical study provide a reasonable assurance of safety and effectiveness for the Zilver PTX stent in the treatment of symptomatic vascular disease of the above-the-knee femoropopliteal arteries, with results from the single arm clinical study providing additional complementary evidence supporting the safety and effectiveness of the Zilver PTX stent in a broader patient population including more complex lesions.

1.2. Background

Endovascular therapy is one option commonly used to treat patients with lifestyle-limiting intermittent claudication or critical limb ischemia due to femoropopliteal peripheral artery disease (PAD). However, percutaneous transluminal balloon angioplasty (PTA) is associated with high one-year restenosis rates (often ≥60%)[4,5,6] that worsen with lesion complexity. Use of some first-generation stents was associated with outcomes similar to PTA.[7,8] More recently, self-expanding nitinol stents have demonstrated improved patency results, yet restenosis remains a limitation, with 12-month restenosis rates between 20% and 37% reported.[6,9,10,11]

[4] Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg. 2007; 45:S5A-S67A.
[5] Rocha-Singh KJ, Jaff MR, Crabtree TR, Bloch DA, Ansel G. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Cath Cardiovasc Interv. 2007; 69:910-919.
[6] Schillinger M, Sabeti S, Loewe C, Dick P, Amighi J, Mlekusch W, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. N Engl J Med. 2006; 354:1879-1888.
[7] Becquemin JP, Favre JP, Marzelle J, Nemoz C, Corsin C, Leizorovicz A. Systematic versus selective stent placement after superficial femoral artery balloon angioplasty: a multicenter prospective randomized study. J Vasc Surg. 2003; 37:487-494.
[8] Grimm J, Muller-Hülsbeck S, Jahnke T, Hilbert C, Brossmann J, Heller M. Randomized study to compare PTA alone versus PTA with Palmaz stent placement for femoropopliteal lesions. J Vasc Interv Radiol. 2001; 12:935-942.
[9] Krankenberg H, Schlüter M, Steinkamp HJ, Bürgelin K, Scheinert D, Schulte KL, et al. Nitinol stent implantation versus percutaneous transluminal angioplasty in superficial femoral artery lesions up to 10 cm in length: the femoral artery stenting trial (FAST). Circulation. 2007;116:285-292.
[10] Bosiers M, Torsello G, Gissler HM, Ruef J, Muller-Hülsbeck S, Jahnke T, et al. Nitinol stent implantation in long superficial femoral artery lesions: 12-month results of DURABILITY I study. J Endovasc Ther. 2009;16:261-269.
[11] Laird JR, Katzen BT, Scheinert D, Lammer J, Carpenter J, Buchbinder M, et al. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery twelve-month results from the RESILIENT randomized trial. Circ Cardiovasc Interv. 2010;3:267-276.

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Success with drug-eluting stents (DES), including paclitaxel coated stents, in coronary artery intervention[12,13,14,15] has led to the investigation of DES in the superficial femoral artery and proximal popliteal artery (SFA/PPA). Paclitaxel has been shown to inhibit neointimal hyperplasia, is highly lipophilic, is avidly protein-bound, and partitions into and is retained by arterial tissue.[16,17,18] Based on the demonstrated clinical success of paclitaxel-coated stents, the Zilver PTX stent was developed for the treatment of symptomatic lesions in the above-the-knee femoropopliteal arteries.

1.3. Proposed Indication for Use

The Zilver PTX Drug-Eluting Stent is indicated for improving luminal diameter for the treatment of *de novo* or restenotic symptomatic lesions in 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. To avoid involvement of the common femoral artery, the most proximal stent end should be placed at least 1 cm below the origin of the superficial femoral artery. To avoid involvement of the below-the-knee popliteal artery, the most distal stent end should be placed above the plane of the femoral epicondyles.

1.4. Regulatory and Marketing History

Working in consultation with FDA, Cook Medical developed the clinical study designs for the Zilver PTX randomized IDE study and the Zilver PTX single arm study. Enrollment in the randomized study began in 2005 and enrollment in the single arm study began in 2006. Both studies completed enrollment in 2008 and the final module of a modular PMA was submitted to FDA in 2010. The Zilver PTX stent was CE Marked in 2009 and as of July 2011 is

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[12] Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al. One-year clinical results with slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. Circulation. 2004;109:1942-1947.
[13] Fajadet J, Morice MC, Bode C, Barragan P, Serruys P, Wijns W, et al. Maintenance of long-term clinical benefit with sirolimus-eluting coronary stents: three-year results of the RAVEL trial. Circulation. 2005;111:1040-1044.
[14] Gershlick A, Scheerder ID, Chevalier B, Stephens-Lloyd A, Camenzind E, Vrints C, et al. Inhibition of restenosis with a paclitaxel-eluting, polymer-free coronary stent: the European evaluation of paclitaxel eluting (ELUTES) trial. Circulation. 2004; 109:487-493.
[15] Park SJ, Shim WH, Ho DS, Raizner AE, Park SW, Hong MK, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. N Engl J Med. 2003;348:1537-1545.
[16] Axel DI, Kunert W, Göggelmann C, Oberhoff M, Herdeg C, Küttner A, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration *in vitro* and *in vivo* using local drug delivery. Circulation. 1997;96:636-645.
[17] Creel CJ, Lovich MA, Edelman ER. Arterial paclitaxel distribution and deposition. Circ Res. 2000;86:879-884.
[18] Levin AD, Vukmirovic N, Hwang CW, Edelman ER. Specific binding to intracellular proteins determines arterial transport properties for rapamycin and paclitaxel. Proc Natl Acad Sci USA. 2004;101:9463-9467.

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commercially available in lengths up to 120 mm and diameters from 5 mm to 10 mm outside the US, including Asia, Europe, Middle East/Africa, and South America, for use in the treatment of symptomatic vascular disease of the above-the knee femoropopliteal arteries having reference vessel diameter from 4 mm to 9 mm. No products have been withdrawn from the market in any country for any reason.

1.5. Device Description

The Zilver® PTX® Drug-Eluting Stent (Zilver PTX stent) is a combination product comprised of two components: a device (stent system) providing the primary mode of action and an ancillary drug coating (paclitaxel). The stent is coated on its outer surface with the drug paclitaxel (with no polymer, binder or excipient) at a dose density of 3 $\mu g/mm^2$. This results in total paclitaxel amounts ranging from approximately 175 µg for the smallest (5 x 20 mm) stent, up to 760 µg for the largest (10 x 80 mm) stent, which are approximately 300-1300 times less than the paclitaxel amount in a single dose of the chemotherapeutic drug Taxol.

1.5.1. Stent System

The Zilver PTX stent uses the nitinol self-expanding Zilver® Flex™ stent platform, which was chosen because it is a flexible stent designed to provide durability in the mechanically-challenging SFA/PPA environment.

The Zilver PTX stent is preloaded in a 6 Fr delivery system. Upon deployment, the 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 1.5.1-1).

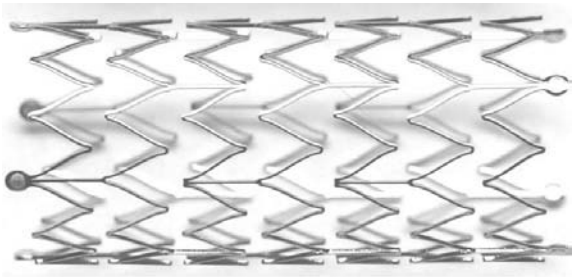

Figure 1.5.1-1: Photograph of the Zilver stent

The delivery system is available in 80 cm and 125 cm lengths and is compatible with a 0.035 inch wire guide (Figure 1.5.1-2). The delivery system is identical to that used with the

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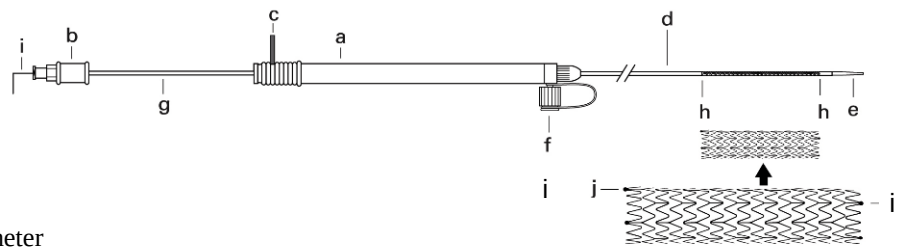
FDA approved and proven Zilver Vascular Stent indicated for the treatment of symptomatic vascular disease of the iliac arteries.



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. Gold radiopaque markers on the stent

Figure 1.5.1-2: Schematic drawing of the Zilver PTX stent and delivery system

The current Zilver PTX application includes stent diameters from 5 mm to 10 mm and stent lengths from 20 to 80 mm (Table 1.5.1-1).

Table 1.5.1-1: Sizes of Zilver PTX stents

Stent Outer Diameter (mm)	Stent Length (mm)				
	20	30	40	60	80
5	✓	✓	✓	✓	✓
6	✓	✓	✓	✓	✓
7	✓	✓	✓	✓	✓
8	✓	✓	✓	✓	✓
9	✓	✓	✓	✓	✓
10	✓	✓	✓	✓	✓

1.5.2. Drug Component

The Zilver PTX stent is coated on its outer surface with the drug paclitaxel (without any polymer, binder, or excipient) at a dose density of 3 $\mu g/mm^2$. The polymer-free paclitaxel coating on the Zilver PTX stent is designed to inhibit neointimal hyperplasia and reduce restenosis. The ASPECT and ELUTES clinical studies of paclitaxel-coated coronary stents manufactured by Cook have demonstrated the benefit of this coating technology (polymer-free

paclitaxel coating) and dose density for reducing restenosis with coronary stents.[19,20] Paclitaxel is the same active pharmaceutical ingredient (API) as used in the FDA approved TAXUS® Express2® Paclitaxel-Eluting Coronary Stent System, TAXUS® Liberté® Paclitaxel-Eluting Coronary Stent System, and ION™ Paclitaxel-Eluting Platinum Chromium Coronary Stent System. Paclitaxel is also the same API in Taxol® (Bristol-Myers Squibb), used for the treatment of certain cancers; the amount of paclitaxel on a Zilver PTX stent is approximately 300-1300 times less than the amount used for a single chemotherapeutic dose in treatment with Taxol.

The properties of paclitaxel make it particularly well suited to polymer-free local delivery, avoiding the potential inflammatory and thrombotic reactions that may occur with polymers. Paclitaxel is highly hydrophobic (i.e., not water soluble), lipophilic, and protein bound. As a result, paclitaxel is readily absorbed into arterial tissue, binding to lipids and proteins within cells and the interstitium. Animal studies have shown that paclitaxel in the arterial wall reaches a peak level immediately following Zilver PTX stent implantation, is sustained near 20% of the peak level through 14 days, and remains present through 56 days.

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 using a proprietary process. No excipients, polymers, carriers, binding agents, other materials, or other device modifications are involved. The chemical description of paclitaxel is provided in Figure 1.5.2-1.

[19] Gershlick A, Scheerder ID, Chevalier B, Stephens-Lloyd A, Camenzind E, Vrints C, et al. Inhibition of restenosis with a paclitaxel-eluting, polymer-free coronary stent: the European evaluation of paclitaxel eluting (ELUTES) trial. Circulation. 2004;109:487-493.
[20] Park SJ, Shim WH, Ho DS, Raizner AE, Park SW, Hong MK, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. N Engl J Med. 2003;348:1537-1545.

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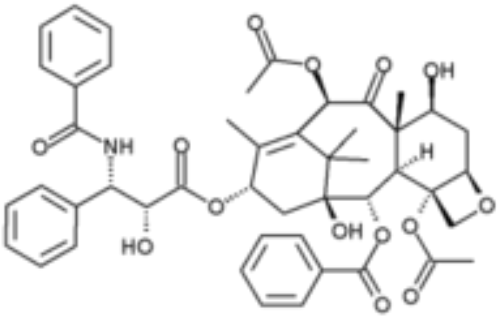
Paclitaxel
• Synonyms: Taxol, Taxol A, Hunxol I, Paclitaxelum • IUPAC systematic name: *β-(benzoylamino)-α-hydroxy-,6,12b-bis(acetyloxy)-12-(benzoyloxy) 2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca(3,4)benz(1,2-b)oxet-9-yl ester,(2aR-(2a-α,4-β,4a-β,6-β,9-α(α-R*,β-S*),11-α,12-α,12a-α,2b-α))-ben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

Figure 1.5.2-1: Chemical description of paclitaxel

The mechanism by which a Zilver PTX stent affects neointimal production has not been fully 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.[21,22] Clinical studies of the Boston Scientific TAXUS® stent and the Cook V-Flex Plus™ Paclitaxel Coated Stent[23] have demonstrated that paclitaxel reduces restenosis in coronary vasculature.

Table 1.5.2-1 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.

[21] Sollott SJ, Cheng L, Pauly RR, Jenkins GM, Monticone RE, Kuzuya M, et al. Taxol inhibits neointimal smooth muscle cell accumulation after angioplasty in the rat. J Clin Invest. 1995;95(4):1869-76.
[22] Axel DI, Kunert W, Göggelmann C et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. Circulation. 1997;96(2):636-45.
[23] The Cook V-Flex Plus™ Paclitaxel Coated Stent is a polymer-free paclitaxel coated coronary stent manufactured by Cook that was CE marked and commercialized in Europe, but is no longer marketed for business reasons.

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Table 1.5.2-1: Paclitaxel total quantity by stent size (for dose density of 3 µg/mm^2)

Stent Size (diameter x length, mm)	Total Paclitaxel (µg/stent)
5 x 20	174
6 x 20	174
7 x 20	174
8 x 20	180
9 x 20	195
10 x 20	216
5 x 30	261
6 x 30	261
7 x 30	261
8 x 30	270
9 x 30	294
10 x 30	270
5 x 40	390
6 x 40	390
7 x 40	390
8 x 40	360
9 x 40	390
10 x 40	378
5 x 60	564
6 x 60	564
7 x 60	564
8 x 60	540
9 x 60	537
10 x 60	540
5 x 80	738
6 x 80	738
7 x 80	738
8 x 80	762
9 x 80	732
10 x 80	759

1.5.3. Principles of Operation

The Zilver PTX stent is mounted on the inner catheter of the delivery system and constrained within an outer sheath. The delivery system is used to deliver the stent to the appropriate location in the vasculature. The stent is deployed by retracting the outer sheath via the handle while holding the inner catheter stationary via the central metal cannula. Full deployment of the stent occurs when the distal end of the sheath has been retracted past the proximal end of the stent.

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1.6. Non-clinical Studies

1.6.1. Biocompatibility testing

The materials used in the Zilver PTX stent platform and delivery system have a long history of clinical use with no reported concerns of toxicity. The paclitaxel active pharmaceutical ingredient (API) is the same API successfully used in the FDA approved TAXUS® Express2® Paclitaxel-Eluting Coronary Stent System, TAXUS® Liberté® Paclitaxel-Eluting Coronary Stent System, and ION™ Paclitaxel-Eluting Platinum Chromium Coronary Stent System. In addition to the history of clinical use of the materials, a thorough panel of biocompatibility testing was performed on finished, sterilized Zilver PTX stents and delivery systems in accordance with international standard ISO 10993 and 21 CFR 58 Good Laboratory Practice (GLP) requirements to demonstrate that the components are non-toxic. Additional details on biocompatibility testing are provided in Section IX of the draft Summary of Safety and Effectiveness Data (SSED). The results of the biocompatibility studies showed that the Zilver PTX stent and delivery system was biocompatible and non-pyrogenic, supporting the safety and acceptability for clinical use.

1.6.2. *In Vitro* Bench Testing

Non-clinical *in vitro* bench testing studies were conducted in accordance with GLP requirements or were performed according to ASTM standards under pre-determined protocols and controlled conditions. Table 1.6.2-1 lists the standards used to formulate the bench testing plan for the Zilver PTX stent.

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Table 1.6.2-1. International standards and guidances used to formulate the Zilver PTX stent bench testing plan

Standard	Title
ASTM F2063	Wrought Nickel-Titanium Shape Memory Alloys for Medical Devices and Surgical Implants
ASTM F2129	Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices
ASTM F2052	Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment
ASTM F2213	Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment
ASTM F2182	Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging
ASTM F2119	Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants
ASTM F2081	Standard Guide for Characterization and Presentation of the Dimensional Attributes of Vascular Stents
ASTM F2514	Standard Guide for Finite Element Analysis (FEA) of Metallic Vascular Stents Subjected to Uniform Radial Loading
ASTM F2477	Standard Test Methods for *in vitro* Pulsatile Durability Testing of Vascular Stents
ASTM F2096	Standard Test Method for Detecting Gross Leaks in Medical Packaging by Internal Pressurization (Bubble Test)
ASTM F1980	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices

The *in vitro* bench testing plan was also developed in accordance with the FDA *Guidance for Industry and FDA Staff: Non-clinical tests and recommended labeling for intravascular stents and associated delivery systems*, January 2005. The express intent of bench testing was to verify that the Zilver PTX stent and delivery system performed in accordance with its specifications while minimizing the risk of adverse events under anticipated clinical conditions. *In vitro* bench testing performed on the Zilver PTX stent included:

- Corrosion testing
- MRI compatibility testing
- Percent vessel surface area covered
- Tensile strength testing of stent bars
- Deployment and dimensional analysis
- Radial force testing
- Flex/kink evaluation
- Crush resistance testing
- Finite element analysis (FEA)
- *In vitro* fatigue testing
- Particulate matter testing
- Structural integrity testing of the delivery system

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Results obtained from *in vitro* bench testing are summarized in Section IX of the SSED. These results demonstrate device functionality and provide a reasonable assurance of device safety and performance.

1.6.3. 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 1.6.3-1.

Table 1.6.3-1: Zilver PTX stent release tests

Test	Description of Test
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
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
Identity	An assay was conducted to verify that the identity of the paclitaxel on the Zilver PTX stent meets the finished product identity specification
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
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
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
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

These release tests help assure consistent safety and effectiveness for all Zilver PTX stents. Each batch of Zilver PTX stents manufactured for distribution in the United States will be tested according to these release tests and must meet the final product specifications prior to distribution.

1.6.4. Non-clinical *In Vivo* Animal Studies

Numerous non-clinical *in vivo* animal studies were conducted to evaluate safety and overall product performance of the Zilver PTX stent in porcine arteries for up to six months. All the animal studies were conducted in accordance with GLP requirements. The animal studies performed and the acceptable study endpoints to support product safety and performance are summarized in Table 1.6.4-1 and in text following the table.

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Table 1.6.4-1: Zilver PTX stent non-clinical animal studies summary

Test	Test Article Size: Paclitaxel Amount	Study Endpoints	Number of Stents Assessed	Met Acceptance Criteria?
One-, Three- and Six-month Animal Study of Clinical and 3X Coating Doses in Swine	10 x 80 mm: 0, 3 µg/mm^2 (clinical dose density), 9 µg/mm^2 (3X clinical dose density)	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, hindlimb tissues o Hematology and serum chemistry • Additional evaluations included: o Animal health o Delivery system performance and stent deployment o Stent integrity	83 stents in 62 animals	Yes
One-, Three- and Six-month Animal Study of Additional Coating Doses in Swine	10 x 80 mm: 2, 4, 12 µg/mm^2 (up to 4X clinical dose density)		84 stents in 63 animals	Yes
One-, Three-, and Six-month Animal Study of Overlapped Stents in Swine	One month 7 x 30 mm: 0, 3 µg/mm^2	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, hindlimb tissues o Hematology and serum chemistry • Additional evaluations included: o Animal health o Delivery system performance and stent deployment • Stent integrity	20 stent pairs in 10 animals	Yes
	Three months 7 x 30 mm: 0, 3 µg/mm^2		20 stent pairs in 10 animals	Yes
	Six months 6 x 30 mm: 0, 3 µg/mm^2		18 stent pairs in 9 animals	Yes

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Test	Test Article Size: Paclitaxel Amount	Study Endpoints	Number of Stents Assessed	Met Acceptance Criteria?
One-month Overdose Study of Regional and Systemic Effects of Coated Stents in Swine	Multiple sizes: 10,500 µg total	Regional and systemic safety evaluation of response to 3X overdose of total paclitaxel quantity per animal from a total stent length of 320 mm. • Qualitative angiography • Complete necropsy with detailed evaluation of downstream, hindlimb tissues • Hematology and serum chemistry • Animal health • Delivery system performance and stent deployment	54 stents in 6 animals	Yes
Two-month Pharmacokinetic Study of Coated Stents in Swine	Mutiple sizes: 3 µg/mm^2	Long-term pharmacokinetic evaluation stents at clinical dose density • Local, regional and systemic paclitaxel levels • Complete necropsy • Hematology and serum chemistry	64 stents in 16 animals	Yes
Twenty-four Hour Pharmacokinetic Study of Coated Stents in Swine	Multiple sizes: 3 µg/mm^2	Acute pharmacokinetic evaluation of stents at clinical dose density • Systemic paclitaxel levels • Complete necropsy • Hematology and serum chemistry	8 stents in 2 animals	Yes

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One-, three-, and six-month animal studies were conducted in swine to examine the local, regional, and systemic effects of non-overlapped stents coated with a paclitaxel dose density of either 0, 3 (clinical dose), or 9 µg/mm^2 (3X clinical dose). An additional study evaluated coating doses up to 12 µg/mm^2 (4X clinical dose). The testing of paclitaxel dose densities up to 9 and 12 µg/mm^2 (i.e., up to 3X and 4X the nominal clinical dose density) helps establish a drug safety margin, particularly with respect to local effects. To further establish a drug safety margin with respect to regional and systemic effects, a one-month overdose study evaluated the regional and systemic effects of a total paclitaxel amount of 10,500 µg, which is approximately 3 times the amount that a patient would receive when implanted with the maximum number of stents necessary to treat two 140 mm lesions (one per limb).

The safety of overlapping stents was evaluated in one-, three-, and six-month studies of overlapped stents coated with paclitaxel at the clinical dose density of 3 µg/mm^2.

Pharmacokinetic studies were conducted to evaluate paclitaxel release from the Zilver PTX stent and the distribution of paclitaxel from the stent to the surrounding arterial tissue, limb tissue and plasma. Specifically, a long-term (two-month) pharmacokinetic study evaluated local, regional, and systemic paclitaxel levels, and an acute (twenty-four hour) pharmacokinetic study evaluated systemic paclitaxel levels at additional time points to further define the timing of the peak plasma paclitaxel level.

Results from the comprehensive *in vivo* animal studies, which included 409 stents tested in 178 animals at up to 4X the clinical dose density and up to 3X the total paclitaxel quantity, showed no safety problems; complete vessel healing without negative sequelae; no thromboses; no vessel ruptures, aneurysms, or pseudoaneurysms; no drug-related medial thinning; no evidence of variable paclitaxel effect along the stented length; and no regional (downstream) or systemic effects associated with the Zilver PTX stents. Detailed pathological evaluation found no regional (downstream) or systemic effects related to the paclitaxel coating and supports a substantial safety factor with respect to any potential risks from the coating. Additionally, the *in vivo* pharmacokinetic data demonstrated rapid and reproducible delivery of paclitaxel from the stent to the vessel wall, with approximately 95% of the drug delivered to the vessel wall during the first 24 hours post-stenting. Paclitaxel levels remained detectable in the vessel wall for approximately two months following deployment of the stent. Minimal paclitaxel was detected in the systemic circulation post-stenting (C_{max} < 10 ng/mL); no paclitaxel was

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detectable in the plasma 10 hours after stent implantation. The results from the extensive animal testing of the Zilver PTX stent thereby support a reasonable assurance of device safety and performance.

1.6.5. Toxicity

The toxicity of the Zilver PTX stent has been investigated in exhaustive *in vivo* animal studies that included evaluation of dose densities and total paclitaxel amounts that are 3X-4X what a patient would receive when implanted with the maximum number of Zilver PTX stents necessary to treat two 140 mm lesions (one per limb). The studies involved characterization of the local tolerance and healing response following implantation of the Zilver PTX stent, along with evaluation of the regional or systemic effects associated with the paclitaxel coating. As described in the previous section, detailed data were gathered on the local tissue responses (evaluating injury, inflammation, hypocellularity, and endothelialization) that would detect toxicity-related concern with the Zilver PTX stent. These included one-, three-, and six-month animal studies that examined the local, regional, and systemic effects of stents coated with a paclitaxel dose density up to 9 $\mu g/mm^2$ (3X clinical dose density; 2637 µg total paclitaxel quantity) and 12 $\mu g/mm^2$ (4X clinical dose density; 3516 µg total paclitaxel quantity) that helped establish a 3X-4X drug safety margin, particularly with respect to local effects. There were no safety problems, systemic or regional effects, or negative sequelae at any follow-up time point. Observations of local inflammation and necrosis were minimal at one month and absent at three and six months. Importantly, these animal studies also showed no localized injury at any time point or coating dose density as evident by histopathology evaluating potential damage to the internal elastic lamina (IEL), media, and external elastic lamina (EEL) of the stented vessels. The vessel healing, although progressing at a slower rate for 9 and 12 $\mu g/mm^2$ dose densities (3X and 4X overdoses) at the one- and three-month time points, was adequate with complete endothelialization observed at six-month follow-up. Additionally, quantitative angiographic and histomorphometric measurements demonstrated no evidence of drug-related aneurysm, pseudo-aneurysm or medial thinning.

In the Zilver PTX randomized clinical study (IDE G030251), the rates of adverse events which could potentially be related to localized toxicity from Zilver PTX stents (i.e., aneurysm, pseudoaneurysm, thrombosis, and stent malapposition) were low, and were not increased for patients receiving a Zilver PTX stent compared to an uncoated stent. Specifically, there was no aneurysm or stent malapposition detected at the 6-month or 12-

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month follow-ups and the rates of aneurysm and stent malapposition were low immediately post-stenting (2.4%, 2/85 aneurysm, 2/84 malapposition assessed in the IVUS substudy) and were not associated with clinical sequelae. Both aneurysm and stent malapposition were detected in two patients immediately post-stenting and, in both patients, were associated with a pre-existing aneurysm visible on the angiogram prior to stent implantation. Additionally, consistent with published literature on femoropopliteal stenting, stent thrombosis through 24 months was reported for 2.3% (7/305) of patients receiving the Zilver PTX stent. These data further confirm that the polymer-free paclitaxel drug coating on the Zilver PTX stent does not increase the risk of localized toxicity in the stented arterial tissue.

Regarding the potential for systemic toxicity, an overdose animal study (described in the previous section) included the implantation of multiple Zilver PTX stents with a total paclitaxel amount of 10,500 µg, which is approximately 3 times the amount that a patient would receive when implanted with the maximum number of stents necessary to treat two 140 mm lesions (one per limb). Follow-up procedures conducted up to one month after stent implantation included angiograms of the stented arteries (orthogonal views) and hematology assessment of blood samples including serum chemistry. After follow-up, the animals were euthanized and complete necropsies were performed on all animals by an independent board-certified veterinary pathologist. The necropsy included gross examination of the integumentary, musculoskeletal, respiratory, cardiovascular, digestive, genitourinary, lymphatic, endocrine, and nervous systems, and histopathologic examination of hind limb muscles and tissue specimens, including but not limited to, liver, spleen, thymus, kidneys, heart, lungs, brain, spinal cord, regional lymph nodes, sciatic nerve, and sternal and femoral bone marrow. The results of this study showed no safety problems, no evidence of regional or systemic effects, and the stented vessels remained widely patent with no evidence of aneurysm or pseudo-aneurysm. Hematology and serum chemistry results of blood samples collected at implant, 7 days post-implant and one-month follow-up procedures did not indicate regional (downstream) or systemic safety concerns. Also, the necropsy results showed no regional (downstream) or systemic safety concerns, no paclitaxel effects, and no particulate or embolic effects associated with the Zilver PTX stents. Additionally, pharmacokinetic data indicated minimal paclitaxel delivered systemically, with no paclitaxel remaining in the plasma 10 hours after stent implantation in the animal studies and less than 1 ng/mL (1 part per billion) remaining in the plasma at the 8- and 12-hour time points in the clinical study.

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In summary, the results from extensive animal studies and clinical data provide a reasonable assurance of no device-related toxicity due to the paclitaxel drug coating or the drug release profile, thereby supporting the safety of the Zilver PTX stent.

1.7. Clinical Studies Overview

The overall clinical trial program for the Zilver PTX stent (Figure 1.7-1) has included both a multicenter randomized clinical study (IDE #G030251) and a complementary multicenter single arm clinical study. The randomized study enrolled 479 patients with *de novo* or restenotic lesions up to 140 mm in length; one lesion per limb could be treated for a maximum total lesion length of 280 mm per patient. The 12-month results from the randomized study provide pivotal clinical evidence for evaluating the safety and effectiveness of the Zilver PTX stent. The complementary single arm study was performed as part of the overall clinical plan to evaluate safety in more than 1000 patients treated with the Zilver PTX stent. Accordingly, the single arm study enrolled 787 patients from a broader patient population (including long lesions and in-stent restenoses) and allowed up to 4 Zilver PTX stents per patient for treating a single or multiple lesions. The 12-month results from the single arm study, the combined analysis using pooled results from the randomized and single arm studies, and longer-term follow-up from both the randomized and single arm studies provide important supportive evidence regarding safety and effectiveness. The following sections provide a summary of the available clinical evidence from each of these sources. Additional details on the clinical studies are provided in Appendix A.

As further described below, the results from the randomized study support the safety and effectiveness of the Zilver PTX stent. Specifically, the event-free survival rate for the Zilver PTX treatment group was non-inferior (i.e., equivalent or superior) to that for the PTA control group. Moreover, the rate of event-free survival in the Zilver PTX group was significantly higher than in the PTA group, suggesting that primary stenting[24] with the Zilver PTX stent is associated with a lower major adverse event (MAE) rate than the current standard care of PTA with provisional stenting performed in cases of acute PTA

[24] As specified in the study protocol, for those patients randomized to Zilver PTX the target lesion was treated with a stent, regardless of the outcome of any preceding PTA.

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failure. The primary patency rate 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, in a randomized comparison of lesions with acute PTA failure, provisional stenting with the Zilver PTX stent demonstrated superior effectiveness to provisional stenting with the bare Zilver stent. As also further described below, the results from the single arm clinical study provide additional important evidence supporting the safety and effectiveness of the Zilver PTX stent in a broader patient population including more complex lesions.

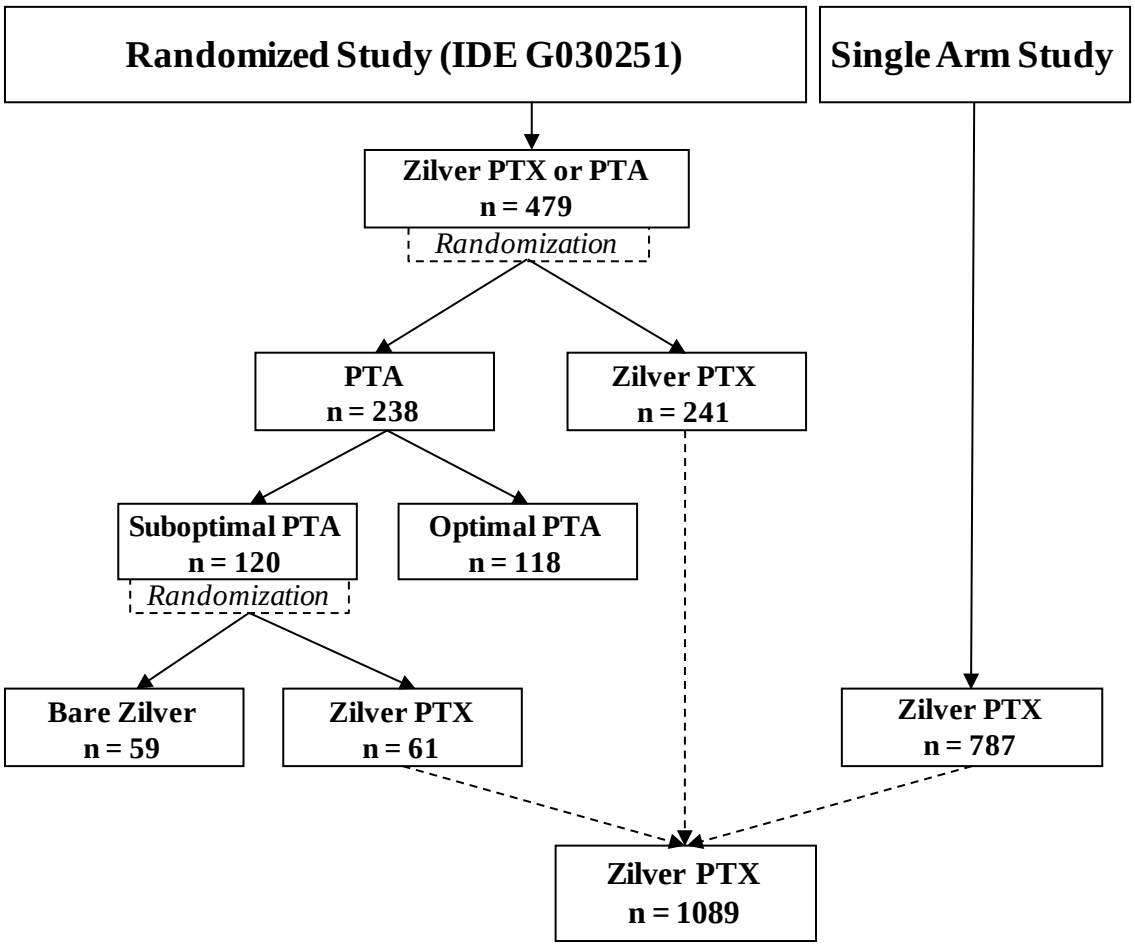

Figure 1.7-1: Patient enrollment

1.8. Zilver PTX Randomized IDE Clinical Study

1.8.1. Primary Objective

The primary objective of the Zilver PTX randomized study was to demonstrate the safety and 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.

1.8.2. Study Overview

The Zilver PTX randomized study is a prospective, controlled, multicenter, multinational study enrolling patients in the United States, Japan, and Germany with *de novo* or restenotic lesions of the above-the-knee femoropopliteal artery. The design of this study was developed based on experience with similar devices, guidance from a physician steering committee consisting of key opinion leaders in the treatment of peripheral vascular disease, and interactions with FDA in the United States and PMDA in Japan to incorporate the best science, medicine, and ethics possible. Patients were randomized to treatment with the Zilver PTX stent (treatment group) or with balloon angioplasty (PTA; control group). The control group was carefully chosen to balance a number of factors:

- At the time of the study design (2002-2003) no appropriate stents were approved by the FDA in the United States or the PMDA in Japan, and comparison to an approved therapy was considered mandatory.
- Historically, patients with less than 30% residual stenosis following PTA (i.e., optimal PTA) are considered to have good acute results and to do well in the long term; comparison of PTA to stenting was therefore considered clinically relevant.
- Patients with residual stenosis of > 30% following PTA (i.e., suboptimal/failed PTA) historically have done poorly in the long term. Therefore, acute PTA failure was considered unacceptable and these patients were treated with a stent.
- Patients with suboptimal (failed) PTA underwent a secondary randomization to stenting with either Zilver PTX or bare Zilver stents, allowing comparison of results for the Zilver PTX stent to those for the bare metal Zilver stent in well matched patient groups.

The overall randomized study design is illustrated in Figure 1.8.2-1.

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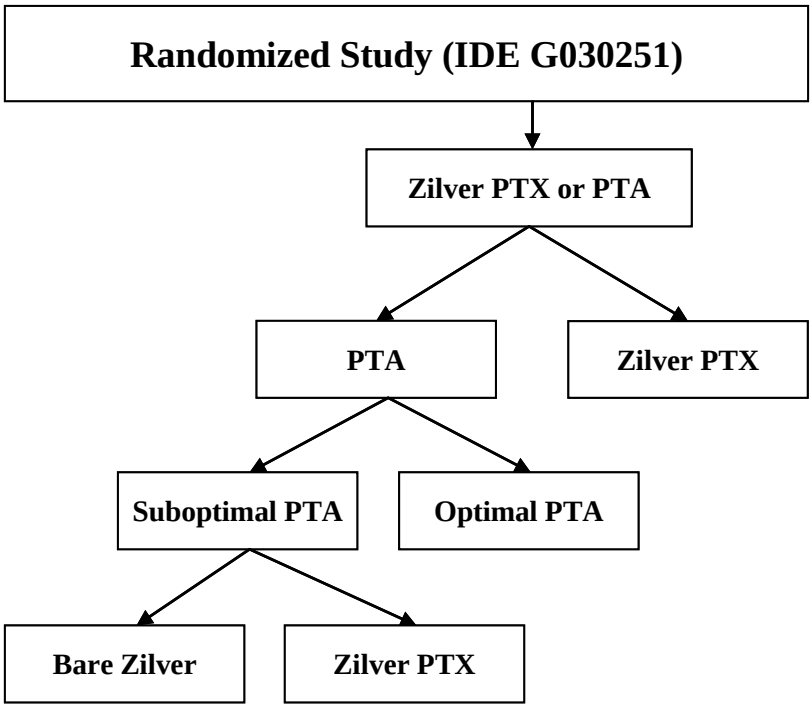

Figure 1.8.2-1: Patient enrollment

The study was designed to assess primary safety and effectiveness hypotheses regarding the Zilver PTX treatment group compared to the PTA control group. Specifically, the primary safety hypothesis was non-inferior 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. The primary effectiveness hypothesis was superior primary patency at 12 months for the Zilver PTX treatment group compared to the PTA control group. Safety (event-free survival) was evaluated on a per-patient basis, and effectiveness (primary patency) was evaluated on a per-lesion basis. Secondary analyses included evaluation of the effectiveness of the Zilver PTX stent compared to a bare metal stent.

Subjects eligible to be enrolled in the study had up to two 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. Fifty-five (55) institutions enrolled 479 patients, including 238 in the PTA control group and 241 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 (AT) population but not the

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intent-to-treat (ITT) or per-protocol (PP) populations[25]. 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. Stent sizes available during the study enrollment period included diameters from 6 to 10 mm and lengths from 20 to 80 mm.

Follow-up included 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. Patients in both the control and treatment groups were to remain on clopidogrel or ticlopidine for 60 days following the study procedure and aspirin indefinitely.

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.

1.8.3. Demographics

Baseline patient characteristics were similar between the PTA control group and Zilver PTX treatment group (analyses in this section include the 474 patients in the ITT population; the 5 live case patients are not included). Demographics (Table 1.8.3-1) and medical history (Table 1.8.3-2) 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 ($p < 0.01$) and inflow tract stenosis (p = 0.03) documented by core lab analysis (Tables 1.8.3-3 - 1.8.3-5).

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[25] Intent-to-treat (ITT) - treatment group assignments are as originally randomized regardless of the actual treatment received.
Per-protocol (PP) - identical to the intent-to-treat population with the following exception: any patient not treated with the original randomized treatment assignment is excluded.
As-treated (AT) - each patient is included in the treatment group for the actual treatment received, regardless of the original randomization assignment.

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Table 1.8.3-1: 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 1.8.3-2: 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				
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)	0.70
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.

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Table 1.8.3-3: Baseline angiographic data (core laboratory reported)

Baseline Angiographic Data	Control Group	Treatment Group	Diff. (95% CI)[1]	*P*-value[2]
Lesion length (mm)	53.2 ± 40.3 (248)	54.6 ± 40.7 (242)	-1.3 (-8.5, 5.9)	0.71
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.

Table 1.8.3-4: Lesion location

Vessel	Control Group	Treatment Group	*P*-value[2]
Left proximal SFA	10.8% (27/251)	8.9% (22/247)	0.79
Right proximal SFA	12.0% (30/251)	10.9% (27/247)	
Left proximal SFA/distal SFA	3.6% (9/251)	5.7% (14/247)	
Right proximal SFA/distal SFA	2.8% (7/251)	2.8% (7/247)	
Left distal SFA	34.7% (87/251)	30.4% (75/247)	
Right distal SFA	28.7% (72/251)	34.0% (84/247)	
Left distal SFA/popliteal artery	0.4% (1/251)	0.8% (2/247)	
Right distal SFA/popliteal artery	2.0% (5/251)	2.8% (7/247)	
Left popliteal artery	2.0% (5/251)	0.8% (2/247)	
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.

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Table 1.8.3-5: 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 (Dormandy J, Rutherford R. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). J Vasc Surg. 2000;31(1 Pt 2):S1-S296.) 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, demographics, patient history, and lesions were similar between the PTA control group and Zilver PTX treatment group in nearly all parameters. Although statistically significant, the differences in hypertension, lesion calcification, and inflow tract stenosis likely do not represent a clinically significant difference between patients or lesions in the treatment and control groups. Moreover, these data indicate that if a difference 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.

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Nearly all patients were discharged taking aspirin and clopidogrel or ticlopidine, and approximately 90% of patients continued to take aspirin from 1 month through 2 years. Usage of clopidogrel or ticlopidine was lower, with approximately 85% of patients remaining on this medication at 1 month, 70% at 3 months, and 60% through 2 years. The use of these medications was comparable between the PTA control group and the Zilver PTX treatment group at all time points.

1.8.4. Results

Patient availability for study follow-up for the 238 patients randomized to the control group and 236 patients randomized to the treatment group (the 5 live case patients are not included) is summarized in Table 1.8.4-1.

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Table 1.8.4-1: 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 – (patients not yet due for visit) – (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. Patients remain in active follow-up with clinical visits scheduled through 5 years.

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1.8.4.1 Safety

The primary safety endpoint of non-inferior safety for the Zilver PTX stent compared to PTA was met, with an event-free survival rate at 12 months of 90.4% for patients in the Zilver PTX treatment group and 83.9% for patients in the PTA control group ($p < 0.01$[26]), as illustrated in Figure 1.8.4.1-1 and Table 1.8.4.1-1. Additionally, the observed data support that the event-free survival rate of the Zilver PTX treatment group is superior to that of the PTA control group ($p = 0.01$). Event-free survival was defined as freedom from the CEC adjudicated major adverse events of death, target lesion revascularization (a reintervention performed for ≥ 50% diameter stenosis within ± 5 mm proximal and/or distal to the target lesion after documentation of recurrent clinical symptoms of PAD following the initial procedure), target limb ischemia requiring surgical intervention (bypass or amputation of toe, foot, or leg) 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. The most common major adverse event was TLR (Table 1.8.4.1-2), which occurred approximately 70% more often in the PTA group relative to the Zilver PTX group (16.3% vs. 9.6%, respectively; $p = 0.04$). No patient deaths were adjudicated by the CEC as related to the device or procedure. The safety benefit of the Zilver PTX stent was maintained through 24 months.

[26] Adjusted for multiplicity

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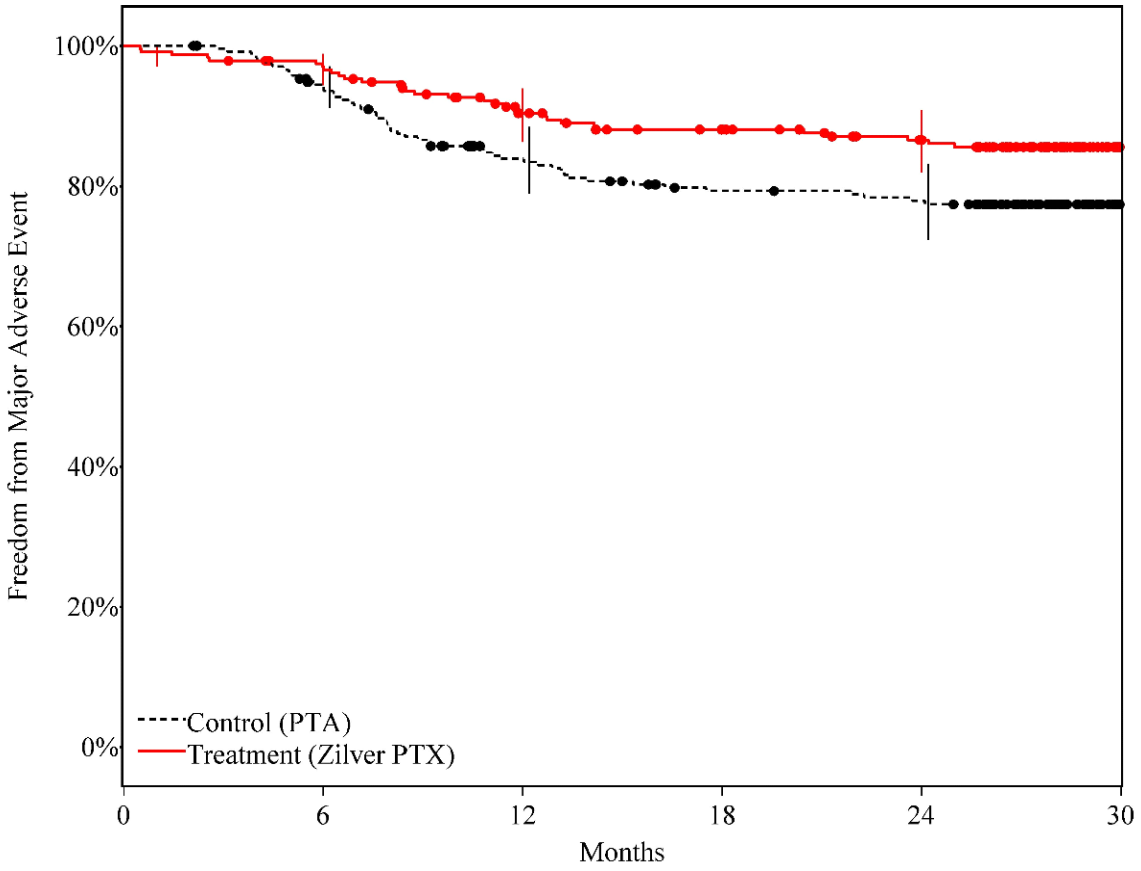

Figure 1.8.4.1-1: Kaplan-Meier curve for event-free survival

Table 1.8.4.1-1: Kaplan-Meier estimates for event-free survival at 0, 1, 6, 12, and 24 months

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

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Table 1.8.4.1-2: Rates of individual major adverse events at 12 months

Major Adverse Event	Control (PTA)[1]	Treatment (Zilver PTX)[1]	*P*-value	Difference (95% CI)[3]
Clinically-driven TLR	16.3% (36/221)[2]	9.6% (21/219)	0.04	(0.5, 12.9)
Worsening of Rutherford classification by 2 classes or to a class 5 or 6	0.9% (2/221)[2]	0.0% (0/219)	0.49	-
Amputation	0.0% (0/221)	0.5% (1/219)	0.49	-

[1] Denominator in this table is the number of patients remaining free from MAE at 12 months plus the number who have experienced a MAE 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.

Tables 1.8.4.1-3 and 1.8.4.1-4 provide a summary of other adverse events, in addition to major adverse events, occurring in the control and treatment groups through 12 and 24 months, respectively. No patient deaths were adjudicated by the CEC as related to the study device or procedure.

Table 1.8.4.1-3: Adverse events occurring within 12 months of the study procedure

Event Type	Control		Treatment	
	% (n) N = 236 patients	Events	% (n) N = 235 patients	Events
Death	1.7% (4)	4	3.4% (8)	8
Major Adverse Events				
Clinically-driven TLR	15.3% (36)	36	8.9% (21)	21
Worsening of Rutherford classification by 2 classes or to a class 5 or 6	0.8% (2)	2	0.0% (0)	0
Amputation	0.0% (0)	0	0.4% (1)	1
Cardiovascular Events				
Cardiac ischemia requiring intervention	3.0% (7)	7	3.8% (9)	13
Non-Q-Wave MI	0.4% (1)	1	0.9% (2)	2
Congestive heart failure	0.8% (2)	2	3.0% (7)	7
Refractory hypertension	0.4% (1)	1	0.0% (0)	0
Arrhythmia requiring intervention or new treatment	1.7% (4)	5	3.4% (8)	9
Other cardiovascular events	12.3% (29)	41	7.7% (18)	20
Pulmonary Events				
Pulmonary edema requiring treatment	0.0% (0)	0	0.4% (1)	1
Ventilation greater than 24 hours in duration	0.4% (1)	1	1.3% (3)	3
Pneumonia requiring antibiotics	2.1% (5)	6	5.1% (12)	14
Supplemental oxygen at time of discharge (exclude if for high altitude)	0.0% (0)	0	0.4% (1)	1
Re-intubation	0.0% (0)	0	0.4% (1)	1
COPD	1.7% (4)	5	0.9% (2)	4
Other pulmonary events	3.0% (7)	11	8.5% (20)	28
Renal Events				
UTI requiring antibiotic treatment	0.8% (2)	3	2.6% (6)	7
Serum creatinine rise greater than 30% above baseline resulting in persistent value greater than 2 mg/dl	0.8% (2)	2	0.0% (0)	0
Other renal events	2.5% (6)	8	4.3% (10)	12
Gastrointestinal Events				
Other gastrointestinal events	3.8% (9)	12	10.2% (24)	30

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Wound Events				
Wound infection/abscess formation	1.3% (3)	3	1.7% (4)	5
Tissue necrosis requiring debridement	1.3% (3)	3	0.4% (1)	1
Wound complication requiring return to operating room	1.7% (4)	5	0.9% (2)	3
Other wound events	2.5% (6)	6	0.9% (2)	2
Vascular Events				
Post-procedure percutaneous intervention (e.g., PTA and/or stent) to the study vessel	8.1% (19)	22	5.5% (13)	14
Post-procedure percutaneous intervention (e.g., PTA and/or stent) to another vessel	16.9% (40)	52	21.3% (50)	62
Ischemia requiring surgical intervention (i.e., bypass or amputation) of another vessel	2.5% (6)	6	1.7% (4)	4
Embolism distal to treated study vessel	0.4% (1)	1	0.9% (2)	2
Embolism within another vessel	0.0% (0)	0	1.3% (3)	3
Thrombosis of the study lesion	0.8% (2)	2	2.6% (6)	6
Thrombosis other than study lesion	0.0% (0)	0	0.9% (2)	2
Blue toe syndrome	0.0% (0)	0	0.4% (1)	1
Aneurysm (other)	0.0% (0)	0	0.9% (2)	2
Deep vein thrombosis	0.4% (1)	1	0.9% (2)	2
Hematoma requiring intervention at access site	0.4% (1)	1	0.4% (1)	1
Pulmonary embolism	0.4% (1)	1	0.0% (0)	0
Pseudoaneurysm or AV fistula of the study vessel	0.8% (2)	2	0.4% (1)	1
Pseudoaneurysm or AV fistula of another vessel	0.4% (1)	1	0.4% (1)	2
Study vessel spasm	0.0% (0)	0	0.4% (1)	1
Worsened claudication/rest pain	6.8% (16)	21	4.3% (10)	12
Stroke	0.8% (2)	2	0.4% (1)	1
Vascular/surgical repair of injury to another vessel (other than amputation or bypass)	0.4% (1)	1	0.9% (2)	3
Post-procedure transfusion	4.2% (10)	15	5.5% (13)	13
Other vascular events	16.5% (39)	47	9.8% (23)	29
Miscellaneous Events				
Drug reaction (including contrast reaction)	2.1% (5)	5	3.8% (9)	10
Hypersensitivity/allergic reaction	2.1% (5)	5	2.1% (5)	6
Other miscellaneous events	26.7% (63)	120	28.1% (66)	115

Table 1.8.4.1-4: Adverse events occurring between 12 and 24 months following the study procedure

Event Type	Control		Treatment	
	% (n) N = 236 patients	Events	% (n) N = 235 patients	Events
Death	1.7% (4)	4	4.3% (10)	10
Major Adverse Events				
Clinically-driven TLR	4.7% (11)	11	3.4% (8)	8
Worsening of Rutherford classification by 2 classes or to a class 5 or 6	1.7% (4)	4	0.0% (0)	0
Cardiovascular Events				
Cardiac ischemia requiring intervention	3.0% (7)	7	3.4% (8)	8
Non-Q-Wave MI	0.8% (2)	2	0.4% (1)	1
Congestive heart failure	1.3% (3)	4	1.3% (3)	6
Refractory hypertension	0.4% (1)	1	0.0% (0)	0
Arrhythmia requiring intervention or new treatment	0.8% (2)	2	1.7% (4)	5
Other cardiovascular events	7.6% (18)	30	3.8% (9)	10
Pulmonary Events				

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Pulmonary edema requiring treatment	0.0% (0)	0	0.4% (1)	1
Pneumonia requiring antibiotics	1.3% (3)	3	1.7% (4)	4
Supplemental oxygen at time of discharge (exclude if for high altitude)	0.0% (0)	0	0.4% (1)	1
COPD	0.8% (2)	2	0.0% (0)	0
Pleural effusion requiring treatment	0.0% (0)	0	0.4% (1)	2
Other pulmonary events	3.0% (7)	7	3.4% (8)	10
Renal Events				
UTI requiring antibiotic treatment	0.8% (2)	2	0.4% (1)	1
Serum creatinine rise greater than 30% above baseline resulting in persistent value greater than 2 mg/dl	0.8% (2)	2	0.0% (0)	0
Other renal events	1.7% (4)	8	2.1% (5)	5
Gastrointestinal Events				
Other gastrointestinal events	3.4% (8)	9	2.6% (6)	6
Wound Events				
Wound infection/abscess formation	0.4% (1)	2	1.3% (3)	3
Wound complication requiring return to operating room	0.4% (1)	1	0.0% (0)	0
Other wound events	0.0% (0)	0	1.3% (3)	3
Vascular Events				
Post-procedure percutaneous intervention (e.g., PTA and/or stent) to the study vessel	5.1% (12)	14	3.8% (9)	9
Post-procedure percutaneous intervention (e.g., PTA and/or stent) to another vessel	5.9% (14)	16	6.0% (14)	16
Ischemia requiring surgical intervention (i.e., bypass or amputation) of another vessel	0.8% (2)	2	1.7% (4)	4
Embolism distal to treated study vessel	0.0% (0)	0	0.4% (1)	1
Embolism within another vessel	0.4% (1)	1	0.0% (0)	0
Thrombosis of the study lesion	0.0% (0)	0	0.4% (1)	1
Blue toe syndrome	0.0% (0)	0	0.4% (1)	1
Deep vein thrombosis requiring surgical or lytic therapy	0.0% (0)	0	0.4% (1)	1
Worsened claudication/rest pain	2.5% (6)	6	3.4% (8)	9
Stroke	1.7% (4)	4	1.3% (3)	3
Vascular/surgical repair of injury to the study vessel (other than amputation or bypass)	0.0% (0)	0	0.4% (1)	2
Vascular/surgical repair of injury to another vessel (other than amputation or bypass)	0.4% (1)	1	0.0% (0)	0
Post-procedure transfusion	0.0% (0)	0	1.7% (4)	5
Other vascular events	4.7% (11)	12	3.4% (8)	10
Miscellaneous Events				
Hypersensitivity/allergic reaction	0.0% (0)	0	0.4% (1)	1
Other miscellaneous events	14.0% (33)	44	15.7% (37)	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 ($p < 0.01$), and this benefit was maintained through 24 months. The most common major adverse event was TLR, which occurred significantly more often in the PTA group (16.3%) compared to the Zilver PTX group (9.6%). In conclusion, the primary safety hypothesis of the study was met, indicating that

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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.

1.8.4.2 Effectiveness

The primary effectiveness endpoint of superior primary patency (conservatively defined as a peak systolic velocity (PSV) ratio < 2.0) for the Zilver PTX stent compared to PTA was met ($p < 0.01$[27]), with a primary patency rate (Kaplan-Meier estimate) at 12 months of 82.7% for lesions in the Zilver PTX treatment group and 32.7% for lesions in the PTA control group, as illustrated in Figure 1.8.4.2-1 and Table 1.8.4.2-1. Clinically important covariates, including diabetes, *de novo*/restenotic lesions, and occluded/stenosed lesions were evaluated for their potential contribution to the treatment effect and overall event rates. The effect of these covariates on primary patency did not alter the significant difference between the treatment and control groups. The benefit of the Zilver PTX stent was maintained through 24 months.

[27] Adjusted for multiplicity

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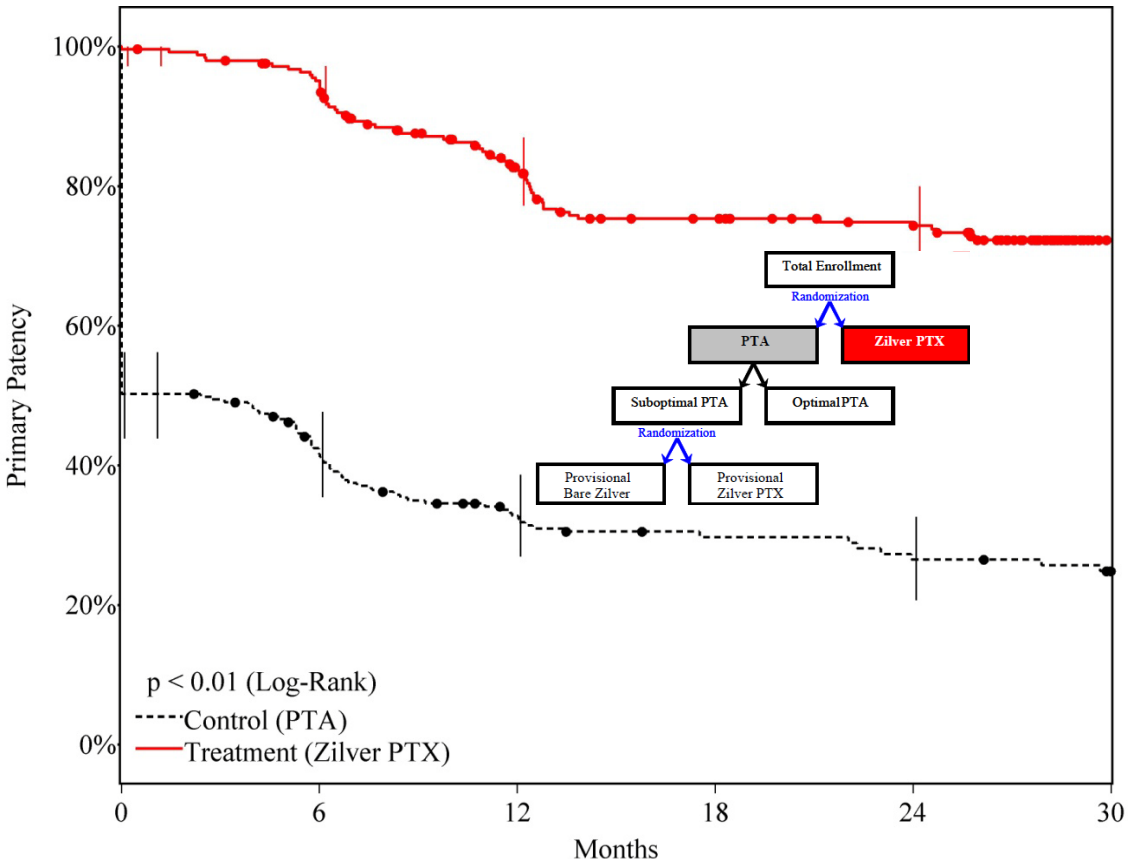

Figure 1.8.4.2-1: Kaplan-Meier curve for primary patency

Table 1.8.4.2-1: Kaplan-Meier estimates for primary patency at 0, 1, 6, 12, and 24 months

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 stent to those treated with the bare metal Zilver stent following acute PTA failure 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 1.8.4.2-2 and Table 1.8.4.2-2, there was a significant difference in patency outcomes between the groups,

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($p < 0.01$[28]), with the Zilver PTX group exhibiting a higher primary patency rate at 12 months of 90.2% of lesions compared to 72.9% of lesions 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.

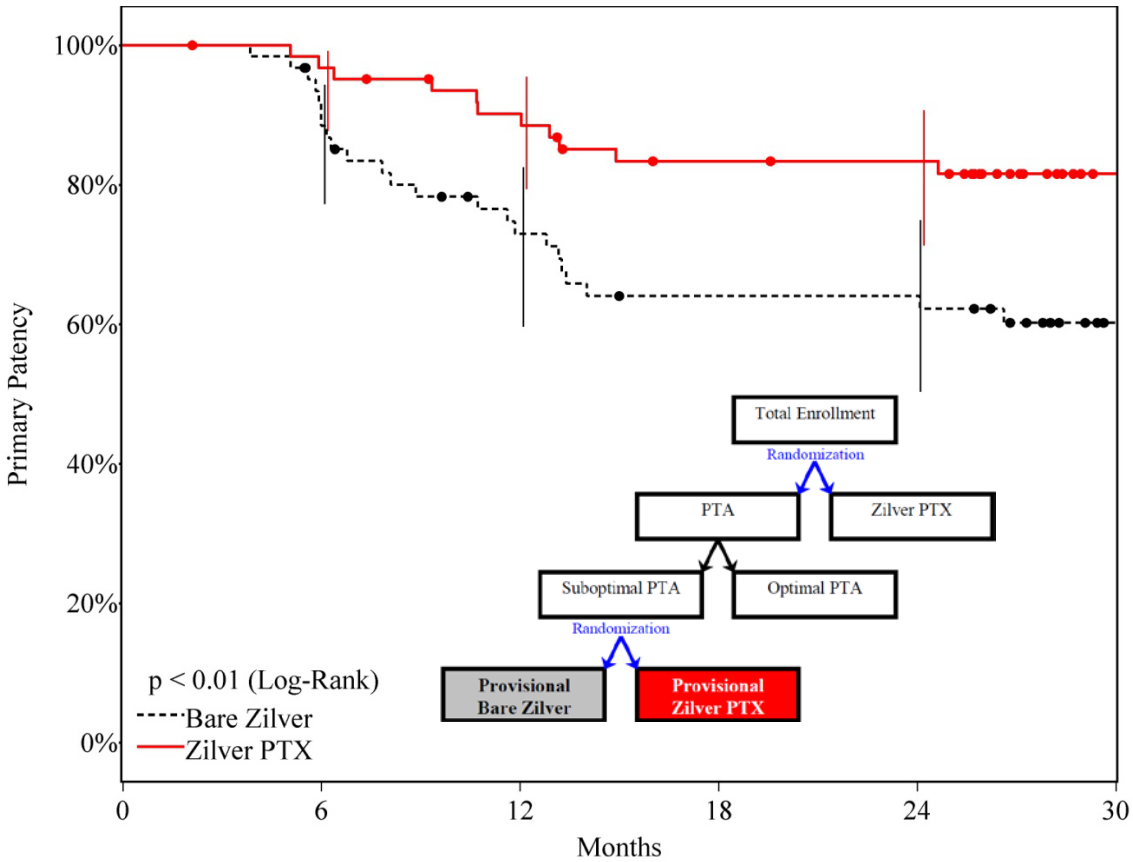

Figure 1.8.4.2-2: Kaplan-Meier curves for primary patency for provisional bare Zilver vs. provisional Zilver PTX (ITT)

[28] Adjusted for multiplicity

Table 1.8.4.2-2: Kaplan-Meier estimates for primary patency 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
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 clinically important covariates, including diabetes, *de novo*/restenotic lesions, and occluded/stenosed lesions, did not alter the significant difference 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.

1.8.4.3 Secondary Endpoints

Secondary endpoint analyses included procedural success, the patient-centered measure of freedom from worsening symptoms of ischemia (i.e., sustained 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).

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Procedural success (< 30% residual stenosis determined angiographically immediately after the procedure) 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 patency. Approximately three-quarters of the patients had an improvement by at least one Rutherford class, and more than half had an improvement of at least two Rutherford classes at 12 months. Additionally, ABI and walking distance, speed, and climbing scores were significantly improved at 12 months.

Sustained clinical benefit (i.e., freedom from worsening symptoms of ischemia) 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 ($p < 0.01$) sustained 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 sustained 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. Furthermore, based on the clinical benefits of the Zilver PTX stent compared to PTA seen in this study, the Zilver PTX stent is reasonable and necessary for patients suffering from peripheral arterial disease.

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1.8.4.4 Substudies

Pharmacokinetic Substudy

A subgroup of 60 patients from the Zilver PTX treatment group was included in the pharmacokinetic (PK) substudy to evaluate systemic paclitaxel delivery. Each patient was assigned to have blood drawn for assay of paclitaxel at 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 1.8.4.4-1.

Table 1.8.4.4-1: Pharmacokinetic substudy groups

# of Stents	# of Patients[1]	# of Samples	Range of Total Paclitaxel Quantity (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 1.8.4.4-2). Additionally, a curve was fit to previous non-clinical 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 1.8.4.4-2: 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.

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The results show that pharmacokinetics of paclitaxel in humans were similar to results found in previous animal studies that demonstrated an acceptable safety profile of the Zilver PTX stent. Minimal paclitaxel was delivered systemically (C_{max} < 10 ng/mL), and less than 1 ng/mL (1 part per billion) 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

IVUS was intended to confirm the lack of aneurysm or stent malapposition related to the Zilver PTX stent, consistent with previous results from animal studies, and angiography was intended to confirm the concordance of angiography and duplex ultrasound for assessing vessel patency at follow-up. For the first 60 patients enrolled in the study, IVUS was required post-stenting and at 6 months for those patients receiving stents. An additional eighty (80) patients, 40 each from the control and treatment groups, were assigned to an angiographic/IVUS substudy. All substudy patients were required to have angiography at the 12-month follow-up and substudy patients in the Zilver PTX treatment group were also required to have IVUS post-stenting and at the 12-month follow-up.

The angiographic analysis includes all patients with both angiography and duplex ultrasound obtained at the 12-month follow-up and analyzed by the core laboratories. The agreement of angiography and duplex ultrasound for assessing lesion patency was evaluated. At the 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; this excellent concordance between angiography and ultrasound confirms the validity of duplex ultrasound for assessing patency in the absence of angiography.

IVUS results demonstrated that no aneurysm or stent malapposition were detected at the 6-month or 12-month follow-ups, and the rates of aneurysm and stent malapposition were low immediately after stenting (2.4%, 2/85 aneurysm, 2/84 malapposition) and were not associated with clinical sequelae. Both aneurysm and stent malapposition were detected in two patients immediately post-stenting and, in both patients, were associated with a pre-existing aneurysm visible on the angiogram prior to stent implantation.

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 reasonable

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agreement with previously reported results from animal studies. The angiographic substudy indicated a high correlation between angiography and duplex 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%). Furthermore, the events of aneurysm and stent malapposition were evident as pre-existing aneurysms prior to stent implantation and were not associated with clinical sequelae. In conclusion, the results from these substudies support the safety and effectiveness of the Zilver PTX stent.

1.8.4.5 Stent Integrity

Zilver stent integrity 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 1.8.4.5-1, 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%. 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 1.8.4.5-1: Stent integrity prior to discharge and at 12 months

Time Point	Stents Visualized by X-ray	Stents with Fracture	Stent Fracture Rate
Prior to discharge	528	0	0.0%
12 months	457	4	0.9%

In summary, the stent fracture rate at 12 months 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.

1.8.4.6 Results Summary and Conclusions

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 (16.3%) compared to the Zilver PTX treatment group (9.6%). 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

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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 ($p < 0.01$). Furthermore, longer-term follow-up has demonstrated that the benefits of the Zilver PTX stent are maintained through 24 months. 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 sustained clinical benefit compared to patients in the PTA control group. Similarly, patients receiving Zilver PTX stents achieved a significantly higher rate of sustained 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, 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 reasonable agreement with results from previous animal studies. The angiographic substudy indicated a high correlation between angiography and duplex 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%). Furthermore, the events of aneurysm

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and stent malapposition were associated with pre-existing aneurysms prior to stent implantation and were 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 at 12 months was low (0.9%, 4/457) 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.

1.8.5. Conclusions

In conclusion, the results of the Zilver PTX randomized clinical study provide a reasonable assurance of safety and effectiveness for the Zilver PTX stent in the treatment of symptomatic vascular disease of the above-the-knee femoropopliteal arteries, and furthermore, based on the clinical benefits of the Zilver PTX stent compared to PTA seen in this study, the Zilver PTX stent is reasonable and necessary for patients suffering from peripheral arterial disease.

1.9. Single Arm Clinical Study

The Zilver PTX single arm study is a prospective, non-randomized, open-label, multicenter single arm 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. This study was part of the overall Zilver PTX clinical plan discussed with FDA that required the safety evaluation of more than 1000 patients treated with the Zilver PTX stent. The single arm study had broad inclusion/exclusion criteria to allow enrollment of a broader patient population, including long lesions up to approximately 300 mm.

1.9.1. Study Overview

The study was designed to quantify the safety and performance of the Zilver PTX stent. The primary hypothesis was that the event-free survival rate at 6 months for patients receiving the Zilver PTX stent was comparable to that seen in recent studies in similar patient populations. Furthermore, this study was designed to contribute to a multi-study pool of more than 1000 Zilver PTX patients to provide broad clinical data and to establish the rate of potentially rare (device- or drug-related) adverse events with reasonable precision.

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Adverse events, including all patient deaths, were adjudicated by an independent clinical events committee. A data safety monitoring board comprised of independent physicians and a biostatistician monitored the safety of the study.

Between April 7, 2006 and June 18, 2008, 787 patients were enrolled at 30 sites. The study entry criteria were similar to the randomized study with the exceptions that there was no limitation on lesion length or the number of lesions treated per patient (up to 4 Zilver PTX stents [up to 80 mm stent lengths] 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 was available for 740 patients at 12 months and 500 patients at 24 months at the time of data analysis.

1.9.2. Demographics

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.

1.9.3. Results

1.9.3.1 Safety

The 6-month event-free survival (EFS) rate for patients with a Zilver PTX stent was 97.4% (Figure 1.9.3.1-1 and Table 1.9.3.1-1), 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 1.9.3.1-2 and Table 1.9.3.1-2).

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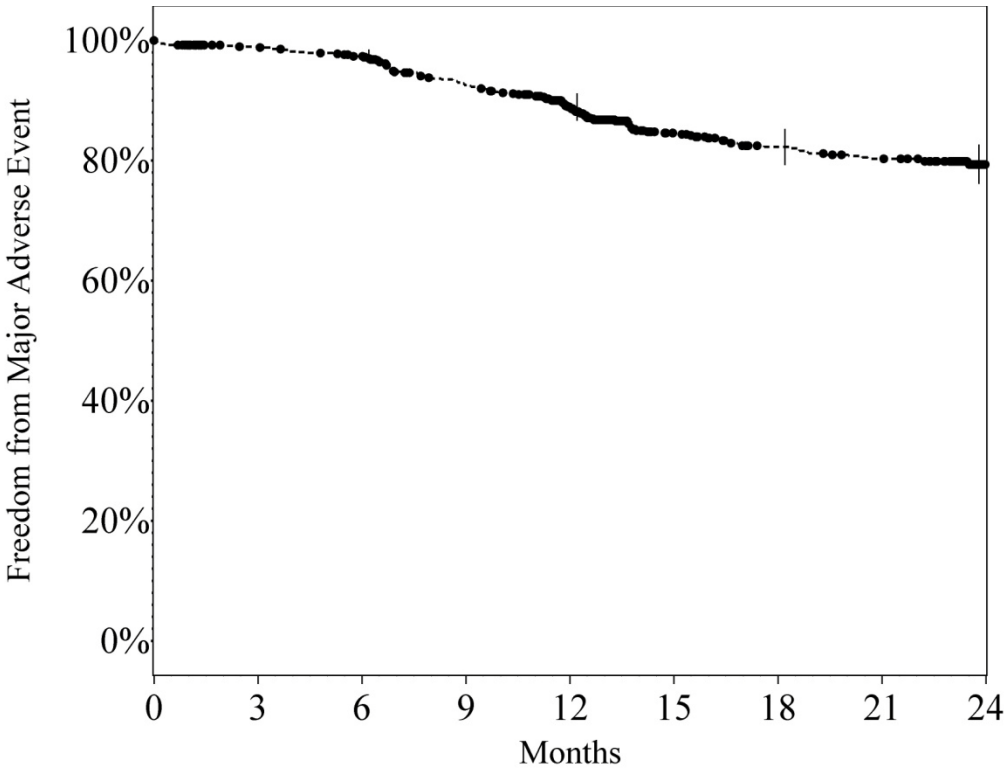

Figure 1.9.3.1-1: Kaplan-Meier curve for event-free survival

Table 1.9.3.1-1: 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	6	781
1	99.2%	0.3%	6	13	768
6	97.4%	0.6%	20	42	725
12	89.0%	1.2%	80	143	564
18	82.3%	1.5%	115	292	380
24	79.3%	1.7%	128	419	240

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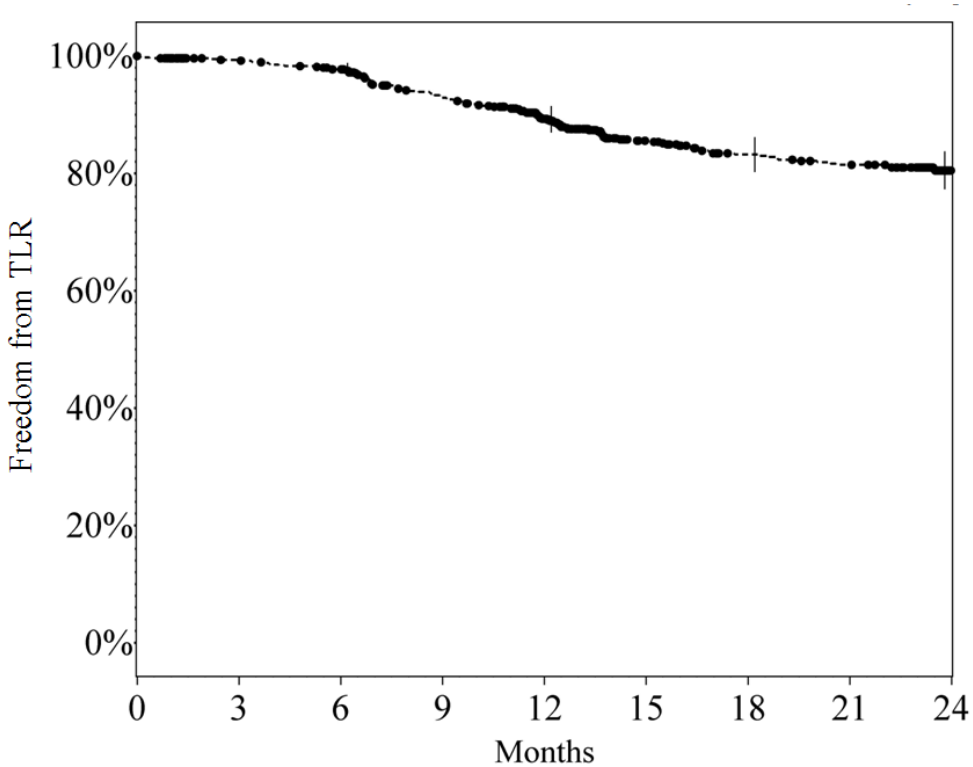

Figure 1.9.3.1-2: Kaplan-Meier curve for freedom from TLR

Table 1.9.3.1-2: 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	6	778
1	99.6%	0.2%	3	13	768
6	97.7%	0.5%	17	42	725
12	89.3%	1.2%	77	144	563
18	83.2%	1.5%	108	296	380
24	80.5%	1.7%	120	423	241

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, including lesions up to 300 mm in length.

1.9.3.2 Secondary Endpoints

Secondary outcomes were also favorable. Specifically, primary patency was 83.0% at 12 months (Figure 1.9.3.2-1 and Table 1.9.3.2-1).

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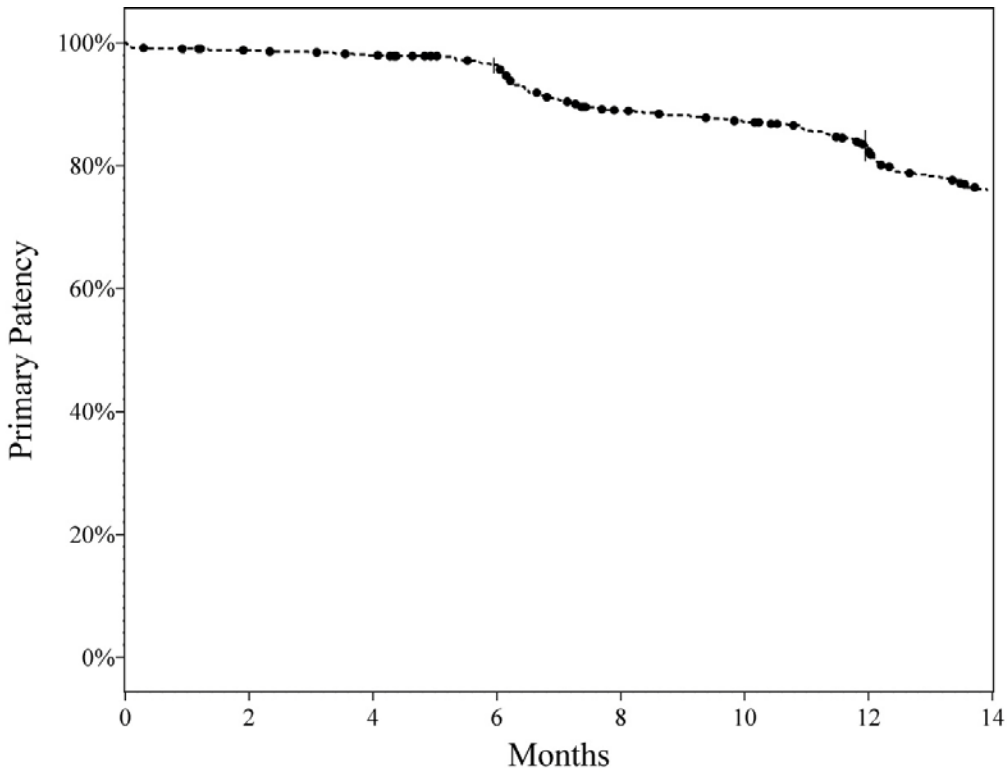

Figure 1.9.3.2-1: Kaplan-Meier curve for primary patency

Table 1.9.3.2-1: 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. These data further demonstrate the durability and clinical benefit of the Zilver PTX stent in a patient population with a substantial incidence of long lesions and pre-existing in-stent restenosis.

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1.9.4. Conclusions

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

1.10. Combined Analysis of Randomized and Single Arm Studies

Stent integrity and the potential for rare adverse events were evaluated in the combined group of more than 1000 patients receiving Zilver PTX stents in the randomized and single arm studies, 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% 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% 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 and effectiveness in a broader patient population.

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 due 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 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 stents, and was not increased for patients receiving a Zilver PTX stent. The low rate of stent thrombosis was not increased for patients receiving a Zilver PTX 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 stents, provide additional evidence supporting the safety of the polymer-free PTX® coating and of the Zilver PTX stent.

1.11. Summary and Conclusions

The safety and effectiveness of the Zilver PTX stent has been demonstrated through extensive biocompatibility testing, *in vitro* bench testing, *in vivo* animal studies, and

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clinical studies. The results of the biocompatibility studies showed that the Zilver PTX stent and delivery system are biocompatible and non-pyrogenic, the bench studies demonstrated device functionality and provide a reasonable assurance of device safety, and animal studies demonstrated complete vessel healing, no safety problems, and no regional or systemic effects related to the paclitaxel coating. These non-clinical tests support a reasonable assurance of device safety and performance. Additionally, each batch of finished Zilver PTX devices undergoes CMC release testing to help assure consistent safety and effectiveness for all Zilver PTX stents.

The Zilver PTX clinical trial program included a multicenter randomized IDE clinical study and a complementary multicenter OUS single arm clinical study. The results from the randomized IDE study provide the pivotal clinical evidence supporting the safety and effectiveness of the Zilver PTX stent. Specifically, the event-free survival rate for the Zilver PTX treatment group was statistically non-inferior to the PTA control group. Moreover, the rate of EFS in the Zilver PTX group was significantly higher than in the PTA group, suggesting 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 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. In conclusion, these results provide a reasonable assurance of safety and effectiveness for the Zilver PTX stent in the treatment of symptomatic vascular disease of the above-the-knee femoropopliteal arteries, with results from the complementary single arm clinical study providing additional evidence supporting the safety and effectiveness of the Zilver PTX stent in a broader patient population.

1.12. Proposed Post Approval Study

The Zilver PTX IDE study is the largest randomized study ever conducted to evaluate SFA stenting. Additional safety and effectiveness data supporting the Zilver PTX stent were collected from the large global single arm study that enrolled a broader patient population with complex disease, including long lesions and in-stent restenosis. To develop a post-approval study plan for the Zilver PTX stent, we first reviewed the scientific questions that the studies supporting approval were designed to answer. We then identified additional questions that were not well covered by the design of the pre-

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approval studies, and proposed target endpoints for a post-approval study to answer these questions.

1.12.1. Questions Answered by the Pre-approval Studies

The randomized study (IDE G030251) to treat lesions of the above-the-knee femoropopliteal artery (SFA) showed that the event-free survival (EFS) rate at 12 months for the Zilver PTX treatment group (90.4%) was superior to the EFS rate for the PTA control group (83.9%, $p = 0.01$). This result is consistent with the Zilver PTX single arm study in which the 12-month EFS rate was 89.0%, increasing confidence in the reliability of this measure of performance.

The randomized study also showed that the Zilver PTX treatment group had a statistically superior primary patency rate at 12-month follow-up compared to that of the PTA control group. The 12-month Kaplan-Meier estimated primary patency rates for Zilver PTX and PTA lesions were 82.7% and 32.7%, respectively ($p < 0.01$). This was consistent with the single arm study that showed a Kaplan-Meier estimated primary patency rate of 83.0% at 12 months for Zilver PTX. Moreover, the randomized study demonstrated that the paclitaxel coating significantly improved the patency rate for lesions treated with the Zilver PTX stent compared to lesions treated with the bare Zilver stent. This conclusion is drawn from an evaluation of patients who failed primary PTA and were immediately re-randomized to receive either a bare Zilver stent or a Zilver PTX stent. In this second randomization, patients who received a bare Zilver stent had a patency rate of 72.9% compared to a patency rate of 90.2% in patients who received a Zilver PTX stent ($p < 0.01$, log rank). The randomized study also demonstrated a significant improvement in clinical outcomes (ABI, Rutherford classification, walking speed and distance, and quality of life), and these improvements were similarly observed in the single arm study.

Furthermore, device integrity was demonstrated to be acceptable at 12-month follow-up in the randomized study with a fracture rate of 0.9% (4/457) and no adverse outcome associated with fractures. The single arm study demonstrated similar device integrity with a fracture rate of 1.5% (22/1432 stents), even in a patient population with a substantial incidence of pre-existing in-stent restenosis at enrollment and long lesions treated with overlapped stents. Collectively, in nearly 1000 patients and more than 1800 stents, the Zilver PTX stent has a 98.6% rate of integrity at 12 months.

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The primary analyses of the pre-approval studies did not address longer term (> 1 year) safety or device integrity. Thus, the post-approval study plan should propose the collection of longer-term safety and device integrity data.

1.12.2. Literature Search for Residual Issues

When designing the single arm study, we considered various common patient cohorts and included patients with in-stent restenosis, long lesions, and TASC (2000) C and D class lesions. This study was intended to identify rare adverse events; thus, we included almost all eligible patients. Therefore, the results from the pre-approval, single arm study were compared to the results of other similar published studies to identify potential remaining issues that should be addressed in a post-approval study.

Subsets of patients were selected from the Zilver PTX single arm study based on matching their baseline characteristics to corresponding enrollment criteria described for the RESILIENT, FAST, Durability, and STRIDES studies.[1-4] Although not rigorously comparable in a statistical sense, the results for these 4 studies were compared with those of the corresponding patient subsets identified from the Zilver PTX single arm study to search for any indication that a particular subset of patients warranted further investigation. The RESILIENT, FAST, and Durability trials included bare metal stents, whereas the STRIDES trial included a drug-eluting (Everolimus) stent. Therefore, the effect of the paclitaxel coating was compared to other bare metal stents as well as another drug-coated stent. From these comparisons, the estimates of the TLR and restenosis rates were lower in the matched subsets of patients from the Zilver PTX single arm study than those reported in any of these published studies. Therefore, this literature review did not identify any additional patient subsets that would warrant further safety investigation.

Endovascular intervention in the SFA is also challenging due to powerful biomechanical forces on the vessel that may affect the durability of stents. Clinical studies have shown fractures in up to 37% of nitinol stents from various manufacturers when implanted in the SFA, and the fractures have been implicated in increased in-stent restenosis and reocclusion.[5] Schlager and colleagues investigated the stent fracture rate for three different stents implanted in long SFA lesions (mean length of 107 ± 71 mm for Wallstents, 139 ± 88 mm for SMART stents, and 125 ± 84 mm for Dynalink/Absolute stents).[6] The observed fracture rates were 19% (15/78), 28% (8/29), and 2% (2/125), respectively, at a mean follow-up of 29 months.[6] Scheinert and collaborators also demonstrated a high fracture rate (37.2%) with SMART, SelfX, and Luminexx stents in

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long SFA lesions (mean length of 15.7 cm).[5] These studies identify device fracture as an important issue.

The Zilver PTX stent demonstrated excellent durability at one year, with an overall fracture rate of 1.4% in the challenging above-the-knee femoropopliteal artery, including complex, long lesions requiring the use of overlapping Zilver PTX stents, and in-stent restenosis. These results are similar to those previously reported by Ferreira, et al., where a fracture rate of 1% (1/96) was observed in the systematic, retrospective medical chart/imaging review of patients treated with the bare metal Zilver Flex stent in the femoropopliteal artery and followed out to 4.8 years.[7] Consistent with other studies, Zilver PTX stents fractured mainly in lesions with stents that overlapped or stents that were inadvertently stretched longitudinally during deployment.[5,6] While these results are encouraging, long-term device integrity (> 1 year) has not been confirmed.

Polymers have been associated with the formation of late stent thromboses (after 1 year), most notably in the use of drug-eluting coronary stents. Polymers have also been shown to lose integrity after deployment, which can increase the risk of thrombosis, microembolism, and late neointimal reactions.[8] Although late thrombosis may arise from multiple causes, delayed healing may be partly responsible for creating a prothrombotic environment in the stented vessel.[9] Autopsy results from a study by Joner et al. indicated slower arterial healing and poorer endothelialization in patients receiving drug-eluting coronary stents than those receiving bare metal stents.[9] Thus, antiplatelet therapy for 6 months or longer has been proposed as standard care for coronary drug eluting stents with polymers. The Zilver PTX stent is a polymer-free nitinol stent. Therefore, as soon as the paclitaxel is released from the stent, only a bare metal stent remains (animal study data indicated that 95% of the entirely paclitaxel coating was delivered after 1 day, 98% delivered after 3 days, and > 99% delivered after 14 days); the Zilver PTX stent should present no increased risk for late thrombosis from residual polymer or retained drug on the stent. At 12 months, Zilver PTX patients in the randomized and single arm studies have a collective rate of 2.8% thrombosis, similar to published results for bare metal stents in the SFA.

Hence, the questions answered by the pre-approval studies and a detailed review of literature suggest that the most appropriate target endpoints for a post-approval study are confirmation of long-term (> 1 year) device safety and integrity and confirmation of the

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lack of late stent thrombosis. A post-approval study protocol reflecting these endpoints is provided in Attachment 1.

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