Attachment 1 – Zilver PTX Post-Approval Study Investigational Plan

1. Purpose

The purpose of the post-approval study is to evaluate the long-term safety of the Zilver PTX stent for the treatment of symptomatic vascular disease of the above-the-knee femoropopliteal artery.

2. Name and Intended Use of the Device

The Zilver® PTX® Drug-Eluting Peripheral Stent (Zilver PTX stent) is indicated 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.

3. Device Description

The Zilver PTX stent is a self-expanding nitinol stent coated on its outer surface with the drug paclitaxel (without any polymer, binder, or excipient) at a dose density of 3 $\mu g/mm^2$. Upon deployment, the Zilver PTX stent is designed to establish and maintain patency in the stented region. To facilitate fluoroscopic visualization of the stent, 4 radiopaque gold markers are positioned on each end of the device.

4. Regulatory History

The Zilver PTX stent was CE marked on July 24, 2009, and as of April 2011 is under regulatory review in the United States and Japan.

5. Duration of the Post-Approval Study

The post-approval study will consist of continued follow-up through 5 years for patients enrolled in the randomized IDE clinical study (G030251). Patients will be evaluated at yearly intervals through 5 years (see section 10.1 for additional details on patient follow-up).

6. Background

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 have been

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collected from a large global single arm study (Zilver PTX global registry) 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-approval studies, and proposed target endpoints for a post-approval study to answer these questions.

6.1 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 6-month EFS rate of 97.4% for the Zilver PTX stent was shown to be non-inferior to the prospectively defined objective performance criterion of 75% ($p < 0.01$).[1-6] Additionally, the 12-month EFS rate of 89.0% in the single arm study is concordant with the EFS rate in the Zilver PTX treatment group in the randomized study, 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 ($p < 0.01$; intent-to-treat). 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 that received a Zilver PTX stent ($p < 0.01$, log-rank).

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

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nearly 1000 patients and more than 1800 stents, the Zilver PTX stent has a 98.6% rate of integrity at 12 months.

The randomized study demonstrated a significant improvement in clinical outcomes (ABI, Rutherford classification, walking speed and distance, and quality of life). The mean ABI in the Zilver PTX treatment group (intent-to-treat) of the randomized study increased from 0.67 ± 0.19 at baseline to 0.91 ± 0.23 at 12 months. A clinical improvement of at least 1 Rutherford classification level was observed in 76.2% of the patients in the treatment group. Patient-perceived walking speed, distance, and climbing scores also improved significantly from baseline to 12 months. The baseline walking speed, distance, and climbing scores were 27.5 ± 27.1%, 25.1 ± 27.6%, and 35.9 ± 32.2% respectively, at baseline and these scores improved to 55.7 ± 37.1%, 57.8% ± 37.9% and 55.6 ± 37.3%, respectively, at 12 months ($p < 0.01$). Significant improvements from pre-procedure to 12-month follow-up were also noted for general pain and discomfort, mobility, usual activity level, and anxiety and depression in the treatment group ($p < 0.05$); nearly all patients noted no problems with self care at both pre-procedure and 12 months.

The single arm study also demonstrated a significant improvement in clinical outcomes (ABI, Rutherford classification, walking speed and distance, and quality of life). A significant ABI improvement from 0.64 ± 0.26 to 0.90 ± 0.24 ($p < 0.01$) and a clinical improvement of at least 1 Rutherford classification in 84.1% (551/655) was demonstrated at 12 months in the patients participating in the single arm study. Patient-perceived walking speed and distance scores also improved significantly from baseline to 12 months. The baseline walking speed and distance scores were 34.7 ± 27.8% and 31.0 ± 26.2% respectively, and these scores improved to 66.3 ± 31.1% and 71.2 ± 32.2%, respectively at 12 months ($p < 0.01$). Similarly, the patient's perceived quality of life (anxiety and depression, mobility, pain and discomfort, self care, and usual activities) also improved significantly from pre-procedure to the 12-month follow-up ($p < 0.01$).

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.

6.2 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 C and D class lesions. This

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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 (see Table 1).[7-10] 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.

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Table 1: Literature comparisons

	Literature			12-month Rates of Inclusion Criteria Matched Zilver PTX Single Arm Study Cohort	Reduction in Rates with Zilver PTX Stent
Comparison Study: Stent	**Inclusion Criteria**	**Event Type**	**12-month Rates of Comparison Stent**		
Resilient[7]: LifeStent	• No in-stent restenosis • Lesion length < 15 cm • Rutherford 1-3	TLR	13% (n = 134)	4% (n = 434)	69%
	• PSVR* < 2.5 patent	Restenosis	19% (n = 134)	13% (n = 429)	32%
FAST[8]: Luminexx Stent	• *De novo* lesions • Length 1-10 cm • Multiple lesions < 10 cm total • ≥ 70% DS	TLR	15% (n = 127)	5% (n = 260)	67%
	• PSVR* < 2.4 patent	Restenosis	32% (n = 101)	13% (n = 258)	59%
Durability[9]: Protégé EverFlex Stent	• No in-stent restenosis • Lesion length ≤ 14 cm • Rutherford 2-4	TLR	21% (n = 134)	4% (n = 442)	81%
	• PSVR* < 2.5 patent	Restenosis	28% (n = 133)	10% (n = 436)	64%
STRIDES[10]: Dynalink-E Everolimus-eluting stent	• Single SFA lesion • No in-stent restenosis • Lesion length 3-17 cm • Rutherford 2-5	TLR	20% (n = 104)	5% (n = 309)	75%
	• PSVR* < 2.4 patent	Restenosis	32% (n = 104)	12% (n = 320)	63%

*PSVR: peak systolic velocity ratio.

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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 implanted in the SFA, and the fractures have been implicated in increased in-stent restenosis and reocclusion.[11] 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).[12] The observed fracture rates were 19% (15/78), 28% (8/29), and 2% (2/125), respectively, at a mean follow-up of 29 months.[12] Scheinert and collaborators also demonstrated a high fracture rate (37.2%) with SMART, SelfX, and Luminexx stents in long SFA lesions (mean length of 15.7 cm).[11] 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.[13] Consistent with other studies, Zilver PTX stents fractured mainly in lesions with stents that overlapped or stents that were inadvertently stretched longitudinally during deployment.[11,12] 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.[14] Although late thrombosis may arise from multiple causes, delayed healing may be partly responsible for creating a prothrombotic environment in the stented vessel.[15] 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.[15] 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

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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 lack of late stent thrombosis.

7. Study Objectives

The objectives of the post-approval study include:

1) Evaluation of event-free survival
2) Confirmation of long-term device integrity
3) Confirmation of the lack of late stent thrombosis

8. Study Design

8.1 Hypotheses to be Tested

The primary endpoint of event-free survival at five years will be evaluated according to the hypothesis that patients in the Zilver PTX stent treatment group will have a non-inferior EFS rate compared to patients in the PTA control group, with a non-inferiority margin of $\delta = 10\%$. EFS is defined as freedom from the CEC adjudicated major adverse events of death, target lesion revascularization, target limb ischemia requiring surgical intervention (bypass or amputation of toe, foot, or leg) or surgical repair of the target vessel (e.g., dissection or perforation requiring surgery), and freedom from worsening of the Rutherford classification by 2 classes or to class 5 or 6. EFS will be analyzed per-protocol on a per-patient basis.

The study will be considered a success if the hypothesis that patients in the Zilver PTX stent treatment group will have a non-inferior EFS rate at five years compared to patients in the PTA control group is met.

The secondary endpoints of stent fracture rate and late stent thrombosis rate will be closely monitored and evaluated.

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8.2 Study Design

The study is a controlled, stratified, randomized study intended to compare treatment of *de novo* or restenotic lesions of the above-the-knee femoropopliteal artery using the Zilver PTX stent with Control treatment of percutaneous transluminal angioplasty (PTA). The study enrolled patients with symptomatic stenotic or occlusive atherosclerotic lesions of the above-the-knee femoropopliteal artery.

The study has enrolled 479 patients with symptomatic stenotic or occlusive atherosclerotic lesions (238 in the Control group and 241 in the Zilver PTX group) at 55 investigative sites in the United States, Japan, and Germany. One lesion in each limb (two lesions per patient) could be treated. Lesion length was limited to ≤ 14 cm (placement of up to two Zilver PTX stents).

After a diagnostic angiogram quantitatively documented the need for treatment (> 50% stenosis), patients were randomized to either the Control group or the Zilver PTX group. The study was stratified by lesion length and block randomized at each investigative site. Stratification and randomization ensured that a similar number of patients were enrolled into each of the treatment groups at each site and minimized the potential for site bias

Patients randomized to the Control group who experienced acute PTA failure (≥ 30% diameter stenosis due to residual stenosis, recoil, dissection, or intimal flaps) were re-randomized to treatment with either Zilver PTX stenting or bare (uncoated) Zilver stenting. Prior to stenting as a result of acute PTA failure, a minimum of one repeat and prolonged balloon inflation was recommended to attempt balloon repair.

Patients randomized to the Control group who experienced long-term PTA failure (≥ 50% diameter stenosis of the study lesion within 12 months of the original study procedure) were eligible for treatment with Zilver PTX stenting. Patients randomized to the Control group who experienced PTA failure after 12 months were treated with standard of care for the institution. Patients who experienced restenosis requiring reintervention within a study stent were treated with standard of care for the institution. Patient follow-up is indicated in Table 2.

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Table 2. Schedule of Patient Testing

Time point	Patient Testing
Pre-procedure:	Walking Impairment Questionnaire (WIQ), EQ-5D, resting ABI (exercise ABI if resting ABI is normal), Rutherford, CBC, and blood chemistry.
Intra-procedural:	Angiography (including baseline and final). IVUS for Zilver PTX treatment patients assigned to the angiography/IVUS substudy.
Post-procedural:	Duplex ultrasound (within 3 business days) and bilateral resting ABI. PTA patients: serum creatinine prior to discharge. Zilver PTX treatment patients: CBC and blood chemistry prior to discharge. For patients assigned to the PK substudy, refer to enrollment verification fax for blood draws. X-ray for all stent patients.
1 month:	Telephone contact (assessment of medications, hospitalizations, and medical conditions).
3 month:	Telephone contact (assessment of medications, hospitalizations, and medical conditions).
6 months:	Clinical assessment with WIQ, EQ-5D, bilateral resting ABI (matching baseline protocol), Rutherford, and duplex ultrasound. CBC and blood chemistry for Zilver PTX treatment patients.
9 months:	Telephone contact (assessment of medications, hospitalizations, and medical conditions).
12 months:	Clinical assessment with WIQ, EQ-5D, bilateral resting ABI (matching baseline protocol), Rutherford, and duplex ultrasound. X-ray for all stent patients. CBC and blood chemistry for Zilver PTX treatment patients. IVUS and angiography for all patients in the Zilver PTX treatment group assigned to the angiography/IVUS substudy and for stent patients if the 12-month clinical and x-ray follow-ups indicate that: a) there are stent fractures and the patient is symptomatic, or b) there is a Type IV stent fracture. Angiography for all patients in the control group assigned to the Angiography/IVUS substudy.
18 months:	Telephone contact (assessment of medications, hospitalizations, and medical conditions).
2 years:	Clinical assessment: WIQ, EQ-5D, bilateral resting ABI (matching baseline protocol), and Rutherford. Duplex ultrasound for all stent patients and PTA patients in the duplex ultrasound substudy. CBC and blood chemistry for Zilver PTX treatment patients.
3 years:	Clinical assessment: WIQ, EQ-5D, bilateral resting ABI (matching baseline protocol), and Rutherford. Duplex ultrasound for all stent patients and PTA patients in the duplex ultrasound substudy. X-ray for all stent patients.
4 years:	Clinical assessment: WIQ, EQ-5D, bilateral resting ABI (matching baseline protocol), and Rutherford. Duplex ultrasound for all stent patients and PTA patients in the duplex ultrasound substudy.
5 years:	Clinical assessment: WIQ, EQ-5D, bilateral resting ABI (matching baseline protocol), and Rutherford. Duplex ultrasound for all stent patients and PTA patients in the duplex ultrasound substudy. X-ray for all stent patients.
Note: Patients who received a stent as a result of a PTA failure or who experience reintervention of a study stent will continue on the same follow-up schedule, time-indexed from the original study procedure (i.e., the time index will not reset).	

8.2.1 Post-Approval Study Design

This post-approval study will consist of continued follow-up through 5 years for patients enrolled in the randomized IDE clinical study. The EFS rate for patients in the Zilver PTX stent treatment group will be compared to the rate for patients in the PTA control group. The rate of stent fracture and late stent thrombosis for patients treated with the Zilver PTX stent will be closely monitored and evaluated.

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8.3 Sample Size Determination

Current Kaplan-Meier estimates of EFS at 60 months for the Zilver PTX stent treatment group and the PTA control group are 77.8% and 73.6%, respectively. Utilizing StatXact 8.0, an exact non-inferiority test for two binomial populations, delta=0.10, alpha=0.05, and power=0.80 the resulting sample size is 113 per treatment group. This study will follow all available patients through 5 years. The current rate of lost to follow-up and withdrawn patients is less than 5% percent per year, suggesting that adequate patients will be available to assess EFS at 5 years.

8.4 Participation Endpoints of the Post-Approval Study

A patient's follow-up in the study will end after any of the following:

1) Completion of all scheduled clinical and imaging visits, through 5 years
2) Patient withdrawal or lost to follow-up
3) Amputation of the study limb including the study lesion
4) Patient death
5) Closure of the study

8.5 Limitations of the Post-Approval Study

To permit a valid comparison between the treatment and control groups of a clinical study, the sample patient populations in each group must be similar with respect to demographics, extent of disease, and lesion morphology. This is accomplished by requiring that patients meet specified inclusion/exclusion criteria prior to being randomized to an arm of the study. While controlling the homogeneity of the patient population makes it possible to make inferences regarding the effect of the therapy, it may limit the overall range of patients to which the inferences may be applied. Additionally, this study is not designed to provide data beyond the 5-year follow-up.

Historical data is not available from the literature for stent integrity or late stent thrombosis through 5 years following endovascular treatment of the SFA. Additionally, stent integrity and stent thrombosis cannot be compared to patients receiving PTA without stenting. Consequently, in the setting of this post-approval study, these important outcomes will be closely monitored and evaluated to assess the long-term safety of the Zilver PTX stent and the EFS rate will be compared between the treatment and control groups.

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8.6 Safety Monitoring (DSMB and CEC)

The post-approval study will be monitored by a Data Safety Monitoring Board (DSMB) according to a written safety monitoring plan. Safety monitoring will include collecting and reviewing data on major and other adverse events. Section 11.2 lists the possible adverse events associated with this study. A DSMB consisting of independent physicians, who are not investigators in the study, will be convened as applicable to review the incidence rates of adverse events according to standardized procedures.

An independent Clinical Events Committee (CEC) will be established to adjudicate individual adverse events reported during the study. This adjudication will be performed according to standard operating procedures to assess whether the events were due to a pre-existing condition, procedure-related, and/or device-related.

A central core lab will be used for image analysis to provide uniformly defined analysis of images. Study monitoring including on-site visits will be conducted for identification of severe adverse events and assurance they are correctly reported to the DSMB and CEC.

8.7 Study Administration

Design of the study was counseled by physicians with peripheral arterial disease (PAD) treatment and clinical study experience. The Global Principal Investigators are Michael Dake, M.D. and Gary Ansel, M.D. The Steering Committee consists of Michael Jaff, D.O.; Lindsay Machan, M.D.; Takao Ohki, M.D.; Richard Saxon, M.D.; and H. Bob Smouse, M.D.

9. Specific Protocol

9.1 Definitions

Please see Appendix A

9.2 Inclusion and Exclusion Criteria

Patients were screened to ensure they met the inclusion/exclusion criteria for the study; assessments of inclusion and exclusion criteria were based on data available pre-operatively

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and/or by visual estimates made during the procedure. Patients were required to sign an informed consent document prior to participating in the study.

Inclusion Criteria:

- Patient has signed and dated the informed consent.
- Patient has up to 2 documented stenotic or occluded atherosclerotic lesions (< 14 cm long) of the above-the-knee femoropopliteal artery, up to one in each limb, that meet all of the inclusion criteria and none of the exclusion criteria.
- Patient has reference vessel diameter of 4-9 mm.
- Patient has a de novo or restenotic lesion(s) with > 50% stenosis documented angiographically and no prior stent in the target lesion.
- Patient has symptoms of peripheral arterial disease classified as Rutherford Category 2 or greater
- Patient has a resting ABI < 0.9 or an abnormal exercise ABI if resting ABI is normal. Patient with incompressible arteries (ABI > 1.2) must have a TBI < 0.8.
- Patient agrees to return for a clinical status assessment and duplex ultrasound post-procedure and at 6 months, 12 months, and 2, 3, 4 and 5 years.
- Patient agrees to x-rays at post-procedure and at 12 months, 3 years, and 5 years.
- Patient agrees to return for angiography and/or IVUS at 12 months, if required as part of the angiographic/IVUS substudy
- Patient agrees to be contacted by telephone at 1, 3, 9 and 18 months to assess clinical status.

Exclusion Criteria:

- Patient is < 18 years of age.
- Patient is pregnant or breast-feeding.
- Patient is simultaneously participating in another investigational drug or device study. The patient must have completed the follow-up phase for the primary endpoint of any previous study at least 30 days prior to enrollment in this study.
- Patient has significant stenosis (> 50%) or occlusion of inflow tract (proximal ipsilateral, iliofemoral, or aortic lesions) not successfully treated before this procedure (success is measured as < 30% residual stenosis).

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- Patient has undergone an unsuccessful arterial interventional treatment of the legs (i.e., the treatment resulted in > 30% residual stenosis of a treated lesion) within 30 days prior to the study procedure.
- Patient has experienced complications of an arterial access site in the legs within 30 days prior to the study procedure.
- Patient has any planned surgical or interventional procedure within 30 days after the study procedure.
- Patient has a planned procedure involving arterial interventional treatment of the study leg(s) within the 12-month follow-up period.
- Patient has had previous stenting of the target vessel.
- Patient has a medical condition or disorder that would limit life expectancy to less than 1 year or that may cause noncompliance with the protocol or confound the data analysis.
- Patient has a known left ventricular ejection fraction < 30%.
- Patient has a known New York Heart Association Classification of 3 or 4.
- Patient has had a myocardial infarction within the last 90 days.
- Patient has serum creatinine > 2.0 mg/dL, is in chronic renal failure, or is on hemodialysis or chronic peritoneal dialysis.
- Patient in whom antiplatelet and/or anticoagulant therapy is contraindicated.
- Patient has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions.
- Patient has known hypersensitivity or contraindication to aspirin, antiplatelet medication, contrast dye, paclitaxel, or nitinol that, in the opinion of the investigator, cannot be adequately premedicated.
- Patient has a history of aortic aneurysm > 4 cm (treated or untreated).
- Patient has a history of iliac aneurysm > 2 cm (treated or untreated).
- Patient lacks at least one patent vessel of runoff with < 50% stenosis throughout its course.
- Patient has untreated angiographically-evident thrombus in the target lesion.
- Patient has a bypass graft with an anastomosis in the target vessel.
- Patient has lesions requiring atherectomy (or ablative devices), cutting balloons, cryoplasty balloons, or any other advanced device to facilitate stent delivery.
- Patient has an untreated systemic or local infection or infection treated for less than 10 days prior to procedure

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10. Measurements and Data Collection

Study data will be collected on standardized case report forms or via an electronic data capture system.

10.1 Post-approval Follow-up Activities

3-year clinic visit (1095 ± 60 days)
An office visit should be completed including a functional status assessment via the Walking Impairment Questionnaire and EQ-5D as well as an ABI matching baseline protocol and a Rutherford classification. All stent patients, as well as a subset of 50 patients overall in the PTA group, will be evaluated with duplex ultrasound at this time. X-ray will be obtained for all stent patients (bare Zilver and Zilver PTX).

4-year clinic visit (1460 ± 90 days)
An office visit should be completed including a functional status assessment via the Walking Impairment Questionnaire and EQ-5D as well as an ABI matching baseline protocol and a Rutherford classification. All stent patients, as well as a subset of 50 patients overall in the PTA group, will be evaluated with duplex ultrasound at this time.

5-year clinic visit (1825 ± 90 days)
An office visit should be completed including a functional status assessment via the Walking Impairment Questionnaire and EQ-5D as well as an ABI matching baseline protocol and a Rutherford classification. All stent patients, as well as a subset of 50 patients overall in the PTA group, will be evaluated with duplex ultrasound at this time. X-ray will be obtained for all stent patients (bare Zilver and Zilver PTX).

10.2 Lost to Follow-up

To ensure maximum follow-up, sites will be expected to attempt contacting a patient for follow-up via telephone, mail, and through the last known contact for the patient. Only when each attempt has been unsuccessful should a patient be considered lost to follow-up.

11. Risk Analysis

Events associated with the natural course of PAD and its treatment with standard of care (PTA or stenting) could be experienced by patients not participating in this study, and therefore, are not considered increased for patients participating in the study. These events include allergic reaction to contrast

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medium including renal failure, arterial rupture, arteriovenous fistula, atheroembolization, death, embolism, infection or abscess formation at the access site, ischemia requiring intervention, renal failure, above-the-knee femoropopliteal spasm, stent strut fracture, stent migration, tissue necrosis, vessel perforation or rupture and worsened claudication/rest pain. Monitoring for stent strut fracture will occur in this trial via flat-plate x-ray at 1, 3 and 5 years.

Oversight by the DSMB will allow for detection and assessment of any new information that may affect the known risk/benefit profile.

11.1. Potential for Adverse Reactions due to Paclitaxel

The vast majority of the paclitaxel on the Zilver PTX stent is delivered to tissue within 1 day following stent implantation and after 2 months only 0.1% of the initial quantity remains on the stent and < 0.5% of the peak level remains in the stented artery. Based on these pharmacokinetic data, there is no paclitaxel expected to remain on the stent or in the artery in the post-approval follow-up time period of 3 to 5 years post-procedure. Therefore, there is no expected risk of adverse reaction due to the paclitaxel drug coating in this post-approval study.

11.2 Adverse Events

The following is a list of adverse events considered to have sufficient risk to be considered potential risks to subjects enrolled in this study. All of these events will be captured by sites on data forms, monitored, tracked and analyzed. This high level of monitoring includes field monitors as well as the participation of an independent Data Safety Monitoring Board which sets notification rules for the study based on the number of each events that occur and an independent Clinical Events Committee which adjudicates the clinical events. All monitors as well as members of the DSMB and CEC will be made aware of the potential for these events.

- Abrupt stent closure
- Allergic reaction to anticoagulant and/or antithrombotic therapy or contrast medium
- Amputation
- Atheroembolization (Blue Toe Syndrome)
- Arterial aneurysm
- Arterial rupture
- Arterial thrombosis
- Arteriovenous fistula
- Death

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- Dissection
- Distal arterial occlusion
- Drug reactions including allergic reaction to contrast medium including renal toxicity
- Embolism
- GI bleeding from anticoagulation/antiplatelet medication
- Hematoma/hemorrhage
- Hypersensitivity reactions
- Infection
- Infection/abscess formation at access site
- Ischemia requiring intervention (bypass or amputation of toe, foot, or leg)
- Myocardial infarction
- Myelosuppression
- Pseudoaneurysm formation
- Renal failure
- Restenosis of the stented artery
- Stent embolization
- Stent malapposition
- Stent migration
- Stent strut fracture
- Stroke
- Vessel spasm
- Thrombosis
- Tissue necrosis
- Total occlusion of the above-the-knee femoropopliteal artery
- Worsened claudication/rest pain

12. Statistical Methods

General Analysis

Statistical analyses will be performed using SAS® for Windows® (release 8.2 or higher), or other widely accepted statistical software. Clinically relevant baseline variables will be tabulated and compared between patients assigned to the two treatment groups. Categorical variables will be assessed using appropriate contingency table analyses (chi-square or Fisher's exact test) and multivariate logistic regression to assess the importance of the covariates. Continuous variables will be tested using unpaired Student's *t*-test or Wilcoxon rank-sum test, depending on variable

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distribution, and linear regression where appropriate. Survival analysis techniques such as Kaplan-Meier or Cox proportional hazards will be incorporated if censoring of data occurs.

Primary Endpoint Analysis

The primary safety endpoint will be assessed using a Z-statistic with a non-inferiority margin of 10%. The Z-statistic is given by

$$Z = \frac{EFS_{PTX} - EFS_{PTA} + \delta}{SE}$$

where,

EFS_{PTA} = Kaplan-Meier estimated event-free survival at 12 months post-procedure for the PTA per-protocol cohort

EFS_{PTX} = Kaplan-Meier estimated event-free survival at 12 months post-procedure for the Zilver PTX per-protocol cohort

δ = minimum difference of practical interest (in this case $\delta = 0.10$)

SE = Standard Error

$$= \sqrt{V\left(EFS_{PTA}\right) + V\left(EFS_{PTX}\right)}$$

where $V(EFS_{PTX})$ and $V(EFS_{PTA})$ are the estimates of the variances of the Kaplan-Meier estimates using the Greenwood formula.

The primary safety null hypothesis will be rejected in favor of the alternative if $EFS_{PTX} - EFS_{PTA} > z_{\alpha} SE - \delta$, for $\alpha = 0.05$.

Analysis of the primary endpoint will occur on the per-protocol set of patients. That is, for the PTA group, this is all patients randomized to receive PTA at first randomization; excluding those patients who did not receive initial PTA treatment. For the PTX group this is all patients randomized to receive Zilver PTX stent at first randomization; excluding those patients who did not receive a Zilver PTX stent

13. Monitoring Procedures

The study will be monitored in accordance with written standard operating procedures consistent with 21 CFR 812 and other applicable regulations. Written procedures for monitoring the investigation are maintained by the monitor.

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Name and Address of the Monitor

Jennifer Kerr (or designee)
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Appendix A - Definitions

ABI – Ankle-brachial index. Ankle systolic pressure/brachial systolic pressure. 0.9-1.2 = normal, < 0.9 = peripheral arterial disease, < 0.4 = severe peripheral arterial disease (ischemic pain and ulceration). ABI > 1.2 is likely due to incompressible arteries and is commonly observed in association with long-standing diabetes mellitus, extreme old age, or calcinosis.

ABI, Exercise – ABI measured one minute post-exercise at 3.5 km/hr and 12% grade for five minutes or until symptoms develop. Abnormal exercise ABI is defined as a drop of ≥ 25% from resting ABI.

Above-the-knee Femoropopliteal Artery – Includes the SFA (located below the bifurcation from the external iliac artery) and the popliteal artery above the plane of the femoral epicondyles. To avoid involvement of the common femoral artery, the proximal end of the stent should be placed at least 1 cm below the origin of the bifurcation into the SFA. To avoid involvement of the below-the-knee popliteal artery, the distal end of the stent should be placed above the plane of the femoral epicondyles.

Adverse Event, Major (MAE) – Includes death, target lesion revascularization (see definition of "target lesion revascularization (TLR)"), target limb ischemia requiring surgical intervention (bypass or amputation of toe, foot, or leg), surgical repair of the target vessel (e.g., vessel dissection or perforation requiring surgery) and prolonged existing hospitalization.

Anaphylaxis – Any allergic reaction following the introduction of a substance, that is characterized by dyspnea, clinically significant hypotension, shock, angioedema, dermal eruption, generalized urticaria, and/or death.

Blue Toe Syndrome (atheroembolization) – Atherothrombotic microembolism of the lower extremities with painful cyanotic discoloration of the toes.

Blood Chemistry – Venous blood evaluation (SMA-12).

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Classification of Lesion Morphology (TASC):

Type A femoropopliteal lesions – Single stenosis up to 3 cm in length, not at the origin of the SFA or the distal popliteal artery.

Type B femoropopliteal lesions – Single stenoses or occlusions 3-5 cm long, not involving the distal popliteal artery; heavily calcified stenoses up to 3 cm in length; multiple lesions, each less than 3 cm (stenoses or occlusions); single or multiple lesions in the absence of continuous tibial runoff to improve inflow for distal surgical bypass.

Type C femoropopliteal lesions – Single stenosis or occlusion longer than 5 cm; multiple stenoses or occlusions, each 3-5 cm, with or without heavy calcification.

Type D femoropopliteal lesions – Complete common femoral artery or SFA occlusions or complete popliteal and proximal trifurcation occlusions.

Dissection Grades:

A – Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.

B – Filling defect parallel to the lumen of the vessel disappearing with the passage of contrast material.

C – Dissection protruding outside the lumen of the vessel persisting after passage of contrast material.

D – Spiral shaped filling defect with delayed runoff of the contrast material in the distal vessel.

E – Persistent luminal filling defect with delayed anterograde flow.

F – Filling defect accompanied by total occlusion.

Event-free Survival – Freedom from the CEC-adjudicated major adverse events (Adverse Events, Major; see definition) including worsening of the Rutherford classification by 2 classes or to class 5 or 6. Failure of Event-free Survival occurs when a) the CEC adjudicates a major adverse event as device and/or procedure related; b) the CEC adjudicates a revascularization as clinically driven target lesion failure (i.e., TLR); or c) the Rutherford classification worsens by 2 classes or to class 5 or 6.

EQ-5D – A self-administrated, health-related quality of life measure including the following five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression.

Hematoma/Hemorrhage – A localized collection of blood, usually clotted, in an organ, space, or tissue, due to a break in the wall of a blood vessel; bleeding into an extravascular space, which

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could be outside the body. A serious adverse event hematoma or hemorrhage is one requiring transfusion, surgical intervention, or causing death.

Infection of Access Site – Typically presents with erythema, edema, heat, pain, tenderness and purulent discharge. (Note: cultures of the wound are not required.)

Limb Loss – Amputation of a leg, either above the knee or below the knee, including amputation of the foot or toes.

Minimum Lumen Diameter (MLD) – Mean minimum lumen diameter (mm) from 2 orthogonal views.

Myocardial Infarction (Non-Q-Wave) – Clinical evidence of elevated peak CK values greater than three times the upper limit of normal with elevated CK-MB fraction (above the institution's upper limit of normal) in the absence of new pathological Q-waves.

Myocardial Infarction (Q-Wave) – Post-procedure presence of new Q-waves greater than 0.04 seconds in 2 contiguous leads with elevation of CK greater than three times the upper limit of normal and MB fraction greater than the upper limit of normal.

***New York Heart Association Classification*:**
Class I – The patient has cardiac disease but without resulting limitations of ordinary physical activity. Ordinary physical activity (i.e., walking several blocks or climbing stairs) does not cause undue fatigue, palpitation, dyspnea, or anginal pain. Limiting symptoms may occur with marked exertion.
Class II – The patient has cardiac disease resulting in slight limitation of ordinary physical activity. Patient is comfortable at rest. Ordinary physical activity such as walking more than two blocks or climbing more than one flight of stairs results in limiting symptoms (e.g., fatigue, palpitation, dyspnea, or anginal pain).
Class III – The patient has cardiac disease resulting in marked limitation of physical activity. Patient is comfortable at rest. Less than ordinary physical activity (i.e., walking one to two blocks or climbing one flight of stairs) causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV – The patient has dyspnea at rest that increases with any physical activity. Patient has cardiac disease resulting in inability to perform any physical activity without discomfort. Symptoms of cardiac insufficiency or anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

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Occlusion – No flow identified within the arterial segment by ultrasound and/or angiogram.

Percent Diameter Stenosis (%DS) – 100 x (1-(MLD/RVD)), where MLD = minimum lumen diameter and RVD = reference vessel diameter.

PSV Ratio – The ratio of the peak systolic velocity (PSV) in the target lesion to that of the proximal reference vessel.

PTA Failure, Acute – One or more of the following documented at the time of the procedure:

a) an inadequate angiographic and/or hemodynamic result as defined by a 30% or greater diameter stenosis (the stenosis may be due to residual stenosis, recoil, dissection, or intimal flaps, for example);
b) a 5 mmHg or greater mean trans-stenotic pressure gradient measured with a pressure wire or ≤ 4 Fr catheter; or
c) acute occlusion of the vessel.

PTA Failure, Long-term – ≥ 50% diameter stenosis including the region within ± 5 mm proximal and/or distal to the target lesion within 12 months of the index PTA procedure, confirmed and documented by duplex ultrasound or angiography .

Reference Vessel Diameter, Proximal (RVD_{prox}) – Diameter of normal segment immediately proximal to the treated region.

Reference Vessel Diameter, Distal (RVD_{dist}) – Diameter of normal segment immediately distal to the treated region.

Renal Failure – Acute or progressive renal insufficiency leading to the need for dialysis.

Renal Insufficiency – A rise in creatinine of more than 30% above the pre-procedure level resulting in a creatinine level > 2.0 mg/dl that does not spontaneously resolve.

Restenosis – Recurrence of ≥ 50% diameter stenosis within ± 5 mm proximal and/or distal to the target lesion as measured by duplex ultrasound (PSV > 2) or angiography (note: in cases where both imaging modalities are available, the angiography will take precedence).

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Rutherford Categories –

Class 0 – Asymptomatic, no hemodynamically significant occlusive disease.

Class 1 – Mild claudication.

Class 2 – Moderate claudication.

Class 3 – Severe claudication.

Class 4 – Ischemic rest pain.

Class 5 – Minor tissue loss.

Class 6 – Major tissue loss.

Stent Strut Fracture Types –

Type 0 – No strut fractures.

Type I – Single strut fracture only.

Type II – Multiple single strut fractures that can occur at different sites.

Type III – Multiple strut fractures resulting in complete transection of the stent, without displacement of the stent segments.

Type IV – Multiple strut fractures resulting in displacement of segments of the stent*.

*Note: Type IV includes spiral fractures that could result in stent displacement without complete transection.

Superficial Femoral Artery (SFA) – Terminal branch of the common femoral artery with the profunda femoris artery which passes down the anteromedial portion of the thigh through the femoral triangle to the opening in the adductor magnus muscle (adductor hiatus) where it becomes the popliteal artery.

Symptoms of PAD – Include but are not limited to: claudication (leg or hip pain during walking which stops when at rest), numbness, tingling or weakness in the legs, burning or aching pain in feet or toes at rest, sore on leg or foot that will not heal, cold legs or feet, color change in skin of legs or feet, or loss of hair on legs.

Target Lesion Revascularization (TLR) – A re-intervention performed for ≥ 50% diameter stenosis (confirmed by angiography) within ± 5 mm proximal and/or distal to the target lesion after documentation of recurrent clinical symptoms of PAD following the initial procedure.

TBI – Toe-brachial index. Toe systolic pressure/brachial systolic pressure. ≥ 0.8 = normal, < 0.8 = peripheral arterial disease.

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Thrombosis **–** Ultrasound, angiographic, or clinically proven complete arterial occlusion of thrombotic origin.

Walking Impairment Questionnaire (WIQ) **–** A measure of patient-perceived walking performance for patients with PAD and/or intermittent claudication. This questionnaire estimates walking distance, walking speed and stair-climbing capacity. Improvement is defined as an increase of walking distance.

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