Evaluating the Zilver PTX Stent

Principal investigators discuss the clinical study design and initial results with the Zilver PTX drug-eluting peripheral stent in the SFA.

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Treating superficial femoral artery (SFA) disease remains challenging. Bypass surgery is associated with higher morbidity rates than endovascular therapies, such as percutaneous transluminal angioplasty (PTA) and stenting. However, the success of endovascular therapies is frequently compromised by vessel dissection, recoil, and restenosis. The placement of bare-metal nitinol stents appears to improve initial patency rates compared to PTA alone, but in-stent restenosis remains common and is often difficult to treat.

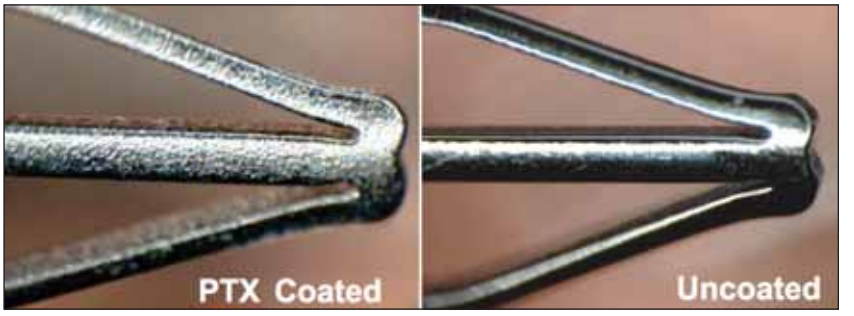

Figure 1. Zilver PTX drug-eluting peripheral stent.

ZILVER PTX DRUG-ELUTING PERIPHERAL STENT

The Zilver PTX drug-eluting peripheral stent (Cook Medical, Bloomington, IN) (commercially available in Europe and currently under US Food and Drug Administration review) is a flexible, self-expanding nitinol stent with a polymer-free paclitaxel coating (Figure 1). Paclitaxel has been shown to prevent neointimal hyperplasia by disrupting normal microtubule function, thereby inhibiting smooth muscle cell migration, proliferation, and extracellular matrix secretion.[1,2] The Zilver PTX stent is enclosed in a sheath before deployment and is coated only on its outer surfaces to help trap the paclitaxel between the stent struts and the vessel wall after the stent is deployed. Moreover, paclitaxel's specific properties make it particularly well-suited for polymer-free local delivery, thereby avoiding the potential inflammatory and thrombotic reactions to polymers. For example, paclitaxel is hydrophobic, which reduces drug delivery to the bloodstream. Paclitaxel is also lipophilic, binds to proteins, and therefore, selectively partitions into arterial walls.[3] Studies have also shown that a single low dose of paclitaxel provides prolonged inhibition of smooth muscle cell proliferation, whereas such results are not achieved with single, even higher doses of sirolimus.[2,4,5] Additionally, the inhibition of smooth muscle cell proliferation occurs at lower paclitaxel doses than those that

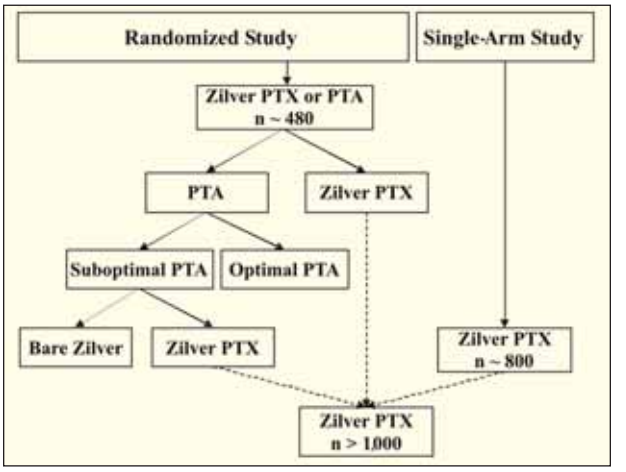

Figure 2. Overview of Zilver PTX clinical studies.

TABLE 1. SUMMARY OF FOLLOW-UP PLANS THROUGH 12 MONTHS

Time Point	Randomized Study		Single-Arm Study
	Control Group (PTA)	**Treatment Group (Zilver PTX)**	**Zilver PTX**
Preprocedure	Clinical assessments	Clinical assessments	Clinical assessments
Procedure	Angiography	Angiography	Angiography
Predischarge	Clinical assessments, ultrasound	Clinical assessments, ultrasound, stent x-rays	Clinical assessments, ultrasound, stent x-rays
6 months	Clinical assessments, ultrasound	Clinical assessments, ultrasound	Clinical assessments, ultrasound, stent x-rays
12 months	Clinical assessments, ultrasound	Clinical assessments, ultrasound, stent x-rays	Clinical assessments, ultrasound, stent x-rays

inhibit endothelial cell proliferation, suggesting that local paclitaxel delivery can inhibit restenosis without preventing re-endothelialization. The ASPECT and ELUTES[6,7] clinical studies demonstrated the benefit of polymer-free, local delivery of paclitaxel from coronary stents, and the FEMPAC[8] and THUNDER[9] clinical studies support the benefit of polymer-free, local delivery of paclitaxel in the SFA. This article describes the designs for both the ongoing randomized and single-arm studies to evaluate the Zilver PTX stent for treating the SFA (Figure 2) and presents initial results from the single-arm study.

RANDOMIZED STUDY DESIGN

To evaluate the safety and effectiveness of the Zilver PTX drug-eluting peripheral stent, a randomized, multicenter, multinational, controlled clinical study was designed to enroll approximately 480 patients with symptomatic de novo or restenotic lesions of the above-the-knee femoropopliteal artery. Patients were required to have clinical symptoms of at least Rutherford class 2, an ankle-brachial index < 0.9, target lesions ≤ 14 cm long with at least 50% stenosis and a reference vessel diameter of 4 to 9 mm, and at least one patent runoff vessel with < 50% stenosis. Major exclusion criteria included untreated significant (> 50%) stenosis or occlusion of the inflow tract, lesions requiring pretreatment with adjunctive devices, and previous stenting of the target vessel. PTA was considered the standard of care at the time of the study design. Accordingly, eligible patients were randomly assigned to either the Zilver PTX (treatment) group or the PTA (control) group (Figure 2). Angioplasty and stent placement were performed via standard techniques. Acute PTA failure (at the time of the procedure) was defined as an inadequate angiographic result of ≥ 30% residual stenosis or hemodynamic result of a ≥ 5-mm Hg mean transstenotic pressure gradient. Before concluding that PTA had acutely failed, the protocol specified that at least one additional 2- to 3-minute balloon dilation of the target lesion be performed. Patients with acute PTA failure were further randomized to receive either an uncoated (bare) Zilver vascular stent(s) or a Zilver PTX stent(s).

TABLE 2. INITIAL RESULTS FROM SINGLE-ARM STUDY

Outcome	12 Months (718 patients, 818 lesions)
Safety (event-free survival)	87%
Effectiveness (freedom from TLR)	89%

Abbreviation: TLR, target lesion revascularization.

The data collection plan through 12 months is summarized in Table 1, with additional data collection continuing through 5 years. An independent clinical events committee (CEC) adjudicated adverse events, and independent core laboratories were used to provide uniform imaging analyses for angiographic, x-ray, and ultrasound data. The primary safety endpoint is event-free survival (EFS) at 12 months. EFS was defined as freedom from the CEC-adjudicated major adverse events of death, clinically driven target lesion revascularization (TLR), target limb ischemia requiring surgical intervention and surgical repair of the target vessel, or worsening of the Rutherford classification by two classes or to class 5 or 6. The primary effectiveness endpoint is primary patency at 12

months, based on either ultrasound core laboratory analysis (with peak systolic flow velocity ratio < 2 representing patency) or angiographic core laboratory analysis (with < 50% diameter stenosis representing patency) when available. Secondary endpoints include the 12-month rates of stent fracture and freedom from TLR.

SINGLE-ARM STUDY DESIGN

To provide additional safety and performance data for the Zilver PTX drug-eluting peripheral stent, a single-arm, multicenter, multinational, controlled clinical study was designed to enroll approximately 760 patients with symptomatic de novo or restenotic lesions of the above-the-knee femoropopliteal artery. The inclusion/exclusion criteria were broader than those criteria for the randomized study. The single-arm study enrolled nearly all comers with de novo or restenotic lesions (including in-stent restenosis) of the above-the-knee femoropopliteal artery, symptoms classified as at least Rutherford class 2, > 50% diameter stenosis, reference vessel diameter 4 to 9 mm, and at least one patent runoff vessel. Eligible patients were treated with up to four Zilver PTX stents, with no limitation on lesion length.

The data collection plan through 12 months is summarized in Table 1, with additional data collection continuing through 2 years. An independent CEC adjudicated adverse events. The primary endpoint is EFS as defined for the randomized study. Secondary endpoints include the 12-month rates of stent fracture, freedom from TLR, and primary patency.

INITIAL RESULTS

Enrollment and 12-month follow-up for both the randomized study and the single-arm study are complete, and data analysis is underway. The available results from the single-arm study are summarized here.

A total of 787 patients were enrolled in the single-arm study, and 900 lesions were treated with Zilver PTX stents. The average lesion length was 9.9 ± 8.2 cm; 40% of the lesions were classified as TASC 2000[14] C or D, and 38% of the lesions were totally occluded. In addition, 24% of the lesions had been previously treated, and almost two-thirds of those (ie, 15% of the total lesions) had been previously stented. Radiographic follow-up at 12 months was obtained for approximately 91% of the stents in patients available for evaluation,

TABLE 3. THE BENEFIT OF PACLITAXEL COATING

Study Name (Stent)	Inclusion Criteria From Cited Study	TLR at 12-Month Follow-Up		Relative Reduction in TLR for Zilver PTX Stent
		From Cited Study	For Matching Subset From Zilver PTX Single-Arm Study	
RESILIENT[10] (LifeStent, Bard Peripheral Vascular, Inc., Tempe, AZ)	• No in-stent restenosis • Lesion length < 15 cm • Rutherford class 1 to 3	13% (n = 153)	6% (n = 467)[a]	54%
FAST[11] (Luminexx, Bard Peripheral Vascular, Inc.)	• De novo lesions • Length 1 to 10 cm • Multiple lesions < 10 cm total • ≥ 70% DS	15% (n = 127)	6% (n = 282)[b]	60%
DURABILITY[12] (Protégé EverFlex, ev3 Inc., Plymouth, MN)	• No in-stent restenosis • Lesion length ≤ 14 cm • Rutherford class 2 to 4	21% (n = 134)	6% (n = 474)[c]	71%
STRIDES[13] (Dynalink-E everolimus eluting stent, Abbott Vascular, Santa Clara, CA)	• Single SFA lesion • No in-stent restenosis • Lesion length 3 to 17 cm • Rutherford class 2 to 5	20% (n = 104)	6% (n = 315)[d]	70%

Abbreviation: DS, diameter stenosis.
[a]Not included: in-stent restenosis, lesions > 15 cm, and Rutherford class > 3.
[b]Not included: restenotic lesions and lesions < 1 cm or > 10 cm.
[c]Not included: in-stent restenosis and Rutherford class < 2 or > 4.
[d]Not included: in-stent restenosis, lesions > 17 cm or < 3 cm, and Rutherford class < 2 or > 5.

and the 12-month fracture rate was 1.6% (23/1,413 stents).

As shown in Table 2, the 12-month EFS rate was 87% (627/718 patients). Four deaths occurred within 30 days of the initial procedure and were counted as procedure-related by definition. Four patients had Rutherford classification worsen to class 5, and one patient had a toe amputated. The most common protocol-defined major adverse event was TLR. However, as Table 2 shows, 89% of lesions were free from TLR at 12 months.

Table 3 compares the performance of the Zilver PTX stent with the published performance of other current bare-metal, self-expanding nitinol stents and an everolimus-eluting stent. Specifically, the results for subsets of patients from the single-arm Zilver PTX study having inclusion/exclusion criteria matching those used in each of the cited studies were compared to the results of each cited study.[10-13] These comparisons show that the Zilver PTX stent reduces the 12-month rate of TLR by between 54% to 70%.

CONCLUSION

Given the difficult patient population treated, which includes a substantial percentage of patients with total occlusions, restenotic lesions, lesions with in-stent restenosis, and TASC C and D lesions, the initial results from the single-arm study demonstrate an excellent safety profile (87% 12-month EFS rate) for the Zilver PTX stent. Furthermore, the results show excellent stent integrity (98.4% of stents were fracture free) and a very favorable performance (54%–70% reduction in TLR rate) compared to outcomes reported for other current bare-metal and drug-eluting stents. These initial data support the safety and effectiveness of the Zilver PTX drug-eluting peripheral stent for treating de novo or restenotic lesions of the above-the-knee femoropopliteal artery. ■

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