IFU0063-0

# Zilver® PTX® Drug Eluting Stent

## ZILVER® PTX® DRUG ELUTING STENT

**CAUTION: U.S. federal law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).**

## DEVICE DESCRIPTION

The Zilver PTX Drug-Eluting Stent is a self-expanding stent made of nitinol and coated with the drug paclitaxel. It is a flexible, slotted tube that is designed to provide support while maintaining flexibility in the vessel upon deployment. Post-deployment, the stent is designed to impart an outward radial force upon the inner lumen of the vessel, establishing patency in the stented region.
The stent is preloaded in a 6.0 French delivery catheter. Hand-loading of the stent is not possible. Stent deployment is controlled by retraction of the handle while holding the metal cannula stationary.

## MRI Information

Non-clinical testing has demonstrated that the Zilver PTX Drug-Eluting Stent is MR Conditional according to ASTM F2503. A patient with this stent can be scanned safely after placement under the following conditions.

### Static Magnetic Field

- Static magnetic field of 1.5 Tesla or 3 Tesla
- Maximum spatial magnetic gradient of 1600 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for 15 minutes of scanning or less.

The static magnetic field for comparison to the above limits is the static magnetic field that is pertinent to the patient (i.e., outside of scanner covering, accessible to a patient or individual).

**MR-Related Heating**

- 1.5 and 3.0 Tesla Systems: Maximum MR system reported, whole-body-averaged specific absorption rate (SAR) of 2.9 W/kg for 15 minutes of scanning (i.e., per pulse sequence)

**1.5 Tesla Temperature Rise**

In non-clinical testing, single and overlapped Zilver stents of lengths to treat lesions up to 140 mm produced a maximum temperature rise of 3.8°C during 15 minutes of MR imaging (i.e., for one scanning sequence) performed in a MR 1.5 Tesla System (Siemens Magnetom Software Numaris/4) at an MR system reported whole-body-averaged SAR of 2.9 W/kg (associated with a calorimetry measured whole body averaged value of 2.1 W/kg).

**3.0 Tesla Temperature Rise**

In non-clinical testing, single and overlapped Zilver stents of lengths to treat lesions up to 140 mm produced a maximum temperature rise of 4.1°C during 15 minutes of MR imaging (i.e., for one scanning sequence) performed in a MR 3 Tesla System (General Electric Excite, Software 14X.M5) at an MR system reported whole-body-averaged SAR of 2.9 W/kg (associated with a calorimetry measured whole body averaged value of 2.7 W/kg).

**Image Artifacts**

MR image quality may be compromised if the area of interest is within the lumen or within approximately 4 mm of the position of the Zilver PTX Drug-Eluting Stent as found during non-clinical testing using T1-weighted spin echo and gradient echo pulse sequences in a 3.0 Tesla MR system (Excite, General Electric Healthcare, Milwaukee, WI). Therefore, it may be necessary to optimize MR imaging parameters for the presence of this metallic stent.

Cook recommends that the patient register the MR conditions disclosed in this IFU with the MedicAlert Foundation. The MedicAlert Foundation can be contacted in the following manners:

Mail: MedicAlert Foundation International
2323 Colorado Avenue
Turlock, CA 95382
Phone: 888-633-4298 (toll free)

209-668-3333 from outside the US
Fax: 209-669-2450
Web: www.medicalert.org

## INTENDED 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.

## CONTRAINDICATIONS

- Stenoses that cannot be dilated to permit passage of the introducer catheter.
- Stenting of an arterial vessel where leakage from the artery could be exacerbated by placement of a stent.
- Patients with bleeding disorders.
- Women who are pregnant, breastfeeding, or plan to become pregnant in the next 5 years should not receive a Zilver PTX Drug Eluting Stent. It is unknown whether paclitaxel will be excreted in human milk, and there is a potential for adverse reaction in nursing infants from paclitaxel exposure.

## WARNINGS

- Persons with allergic reactions to nitinol may suffer an allergic reaction to this implant.
- Persons allergic to paclitaxel may suffer an allergic reaction to this implant.

## PRECAUTIONS

- This product is intended for use by physicians trained and experienced in diagnostic and interventional vascular techniques. Standard techniques for interventional vascular procedures should be employed.

- Manipulation of the Zilver PTX Drug Eluting Stent requires fluoroscopic control.
- Do not try to remove the stent from the introducer system before use.
- Ensure that the red safety lock is not inadvertently removed until final stent release.
- Deploy the stent over an extra stiff or ultra stiff wire guide.
- Do not push the hub toward the handle during deployment..
- Do not expose the delivery system to organic solvents (e.g., alcohol).
- Do not use power injection systems with the delivery system.
- Do not rotate any part of the system during deployment.
- The device is intended for single use only. Do not resterilize and/or reuse this device.
- Repositioning of the device after deployment is not possible since the introducer catheter cannot be re-advanced over the stent once deployment begins.

## POTENTIAL ADVERSE EVENTS

**Potential adverse events that may occur include, but are not limited to, the following:**

- Allergic reaction to anticoagulant and/or antithrombotic therapy or contrast medium
- Allergic reaction to nitinol
- Atheroembolization (Blue Toe Syndrome)
- Arterial aneurysm
- Arterial rupture
- Arterial thrombosis
- Arteriovenous fistula
- Death
- Embolism
- Hematoma/hemorrhage

- Hypersensitivity reactions
- Infection
- Infection/abscess formation at access site
- Ischemia requiring intervention (bypass or amputation of toe, foot, or leg)
- Pseudoaneurysm formation
- Renal failure
- Restenosis of the stented artery
- Stent embolization
- Stent malapposition
- Stent migration
- Stent strut fracture
- Vessel perforation or rupture
- Worsened claudication/rest pain

Although systemic effects are not anticipated, refer to the Physicians' Desk Reference for more information on the potential adverse events observed with paclitaxel.

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

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

- Myalgia/Arthralgia
- Myelosuppression
- Peripheral neuropathy

## SUMMARY OF CLINICAL INVESTIGATIONS

As detailed below, results from the randomized IDE 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 the PTA control group. Moreover, the rate of event-free survival in the Zilver PTX group was substantially 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.

### 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.

### Study Overview

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

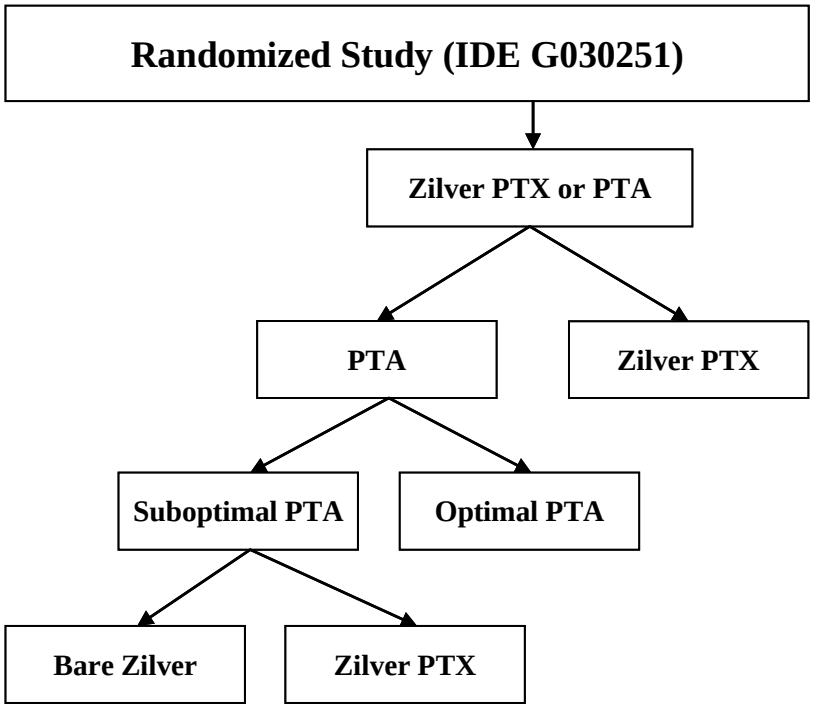



**Figure 1. Patient enrollment**

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 (i.e., equivalent or superior) event-free survival (defined as freedom from the clinical events committee (CEC) adjudicated major adverse events of death, target lesion revascularization, target limb ischemia requiring surgical intervention or surgical repair of the target vessel, and freedom from worsening of the Rutherford classification by 2 classes or to class 5 or 6) at 12 months. The primary effectiveness hypothesis was superior primary patency at 12 months for the Zilver PTX treatment group compared to the PTA control group. Secondary analyses included evaluation of the effectiveness of the Zilver PTX stent compared to a bare metal stent.

Subjects eligible to be enrolled in the study had 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 population but not the intent-to-treat or per-protocol populations. Acute PTA failure was common, occurring in 120 patients in the control group, and these patients underwent a second randomization to provisional stenting with either Zilver PTX stents or bare Zilver stents.

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.

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.

**Demographics**

Baseline patient characteristics were similar between the PTA control group and Zilver PTX treatment group. Demographics (Table 1) and medical history (Table 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 and inflow tract stenosis documented by core lab analysis (Tables 3 – 5).

## Table 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 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.

## Table 3. Baseline angiographic data (core lab 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 4. Lesion location

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

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

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

In summary, lesions were similar between the PTA control group and Zilver PTX treatment group in nearly all parameters. The core laboratory data demonstrated significant differences in lesion calcification and inflow tract stenosis, with lesions in the Zilver PTX treatment group having more

severe calcification and higher inflow tract stenosis. Although the site data indicated that lesions in the Zilver PTX group had a significantly higher baseline percent diameter stenosis, the core lab data demonstrated no difference. While statistically significant, these differences likely do not represent a clinically significant difference between lesions in the treatment and control groups. Moreover, these data indicate that if a difference in lesion characteristics exists, the Zilver PTX treatment group contains potentially more severe lesions and patients with more severe overall peripheral arterial disease—characteristics which would be expected to have an adverse (if any) effect on safety and effectiveness outcomes in the Zilver PTX treatment group.

**Results**

Patient availability for study follow-up through 24 months is summarized in Table 6.

**Table 6. Clinical and imaging follow-up data**

| Follow-up | Eligible for Follow-up[1] | Percent of Data Available | | | Events Occurring Before Next Visit | | | |
|---|---|---|---|---|---|---|---|---|
| | | 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] |
| **PTA Control Group** | | | | | | | | |
| Procedure | 238 | 100.0% (238/238) | 97.5% (117/120)[5] | 86.6% (206/238) | 2 | 3 | 0 | 1 |
| 6-month | 232 | 94.0% (218/232) | 76.5% (13/17)[5,6] | 80.6% (187/232) | 2 | 4 | 2 | 2 |
| 12-month | 222 | 97.3% (216/222) | 76.0% (114/150)[5] | 83.3% (185/222) | 4 | 5 | 0 | 3 |
| 2-year | 210 | 83.3% (175/210) | n/a[8] | 66.7% (84/126)[10] | n/a | | | |
| **Zilver PTX Treatment Group** | | | | | | | | |
| Procedure | 236[7] | 100.0% (236/236) | 96.2% (227/236) | 89.4% (211/236) | 0 | 1 | 1 | 0 |
| 6-month | 234 | 94.0% (220/234) | 86.2% (25/29)[6] | 80.3% (188/234) | 9 | 4 | 4 | 0 |
| 12-month | 217 | 97.7% (212/217) | 84.3% (183/217) | 87.1% (189/217) | 9 | 4 | 3 | 3 |
| 2-year | 198 | 83.8% (166/198) | n/a[8] | 51.0% (101/198) | n/a | | | |

[1] Eligible for follow-up = previous eligibility for follow-up – (previous death + withdrawn + LTF).

[2] Includes cases with at least one of any of the following submitted: clinical form, death form, withdrawn form, or lost to follow-up form.
[3] Includes only ultrasound studies considered diagnostic by the core lab.
[4] Patients who reached an "other endpoint" include 2 patients who received a non-study stent during reintervention 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.

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.

**Safety**

The primary safety endpoint of equivalent or superior safety for the Zilver PTX stent compared to PTA was met with an event-free survival rate at 12 months of 90.4% for the Zilver PTX treatment group and 83.9% for the PTA control group ($p < 0.01$[1]), as illustrated in Figure 2 and Table 7. The most common major adverse event was TLR (Table 8), 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 benefit of the Zilver PTX stent was maintained through 24 months.

[1] Adjusted for multiplicity.

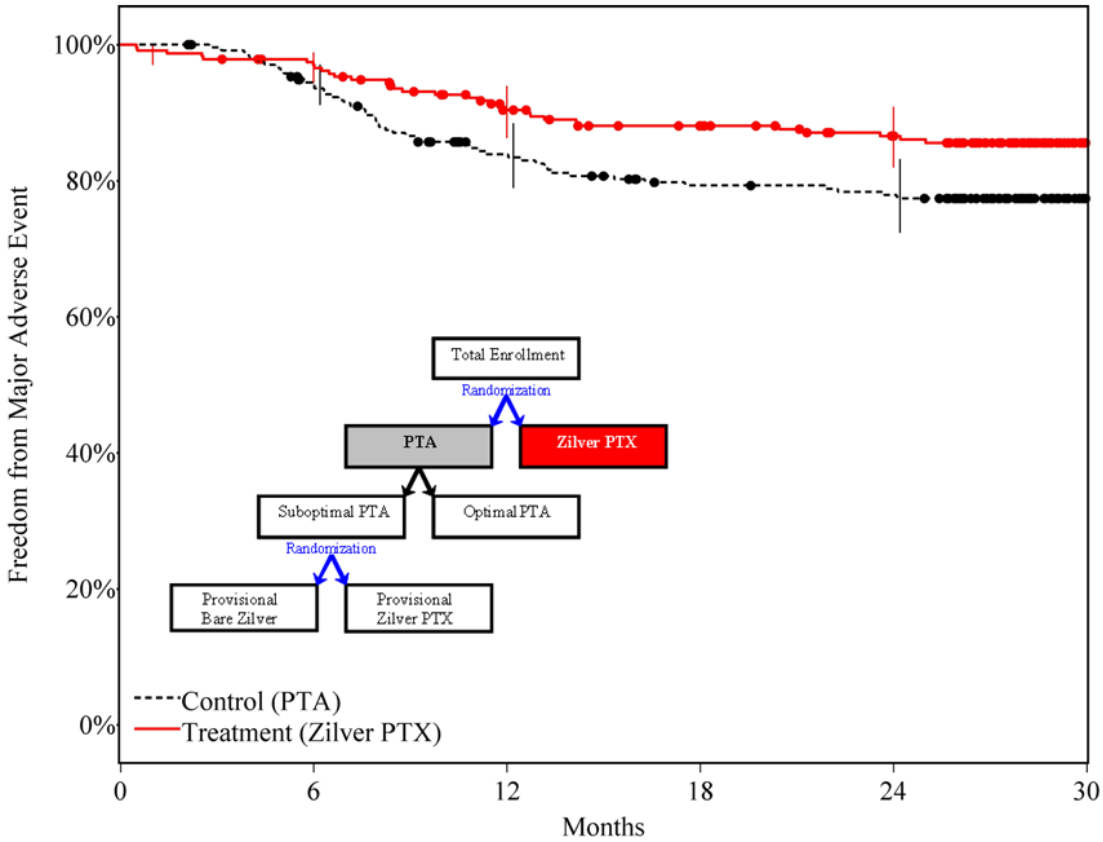



**Figure 2. Kaplan-Meier curve for event-free survival**

**Table 7. Kaplan-Meier estimates for event-free survival at 0, 1, 6, and 12 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 |

**Table 8. Rates of individual major adverse events at 12 months**

| Major Adverse Event | Control (PTA)[1] | Treatment (Zilver PTX)[1] | P-value | Diff. (95% CI)[3] |
|---|---|---|---|---|
| Clinically-driven TLR | 16.3% (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] One patient experienced a worsening Rutherford and a TLR and is included in both categories in this table.
[2] Confidence interval is the difference in percentages.

Table 9 provides a summary of other adverse events through 24 months, not including major adverse events, occurring in the control and treatment groups. No patient deaths were adjudicated by the CEC as related to the study device or procedure.

**Table 9. Adverse events**

| Event Type | Control | | Treatment | |
|---|---|---|---|---|
| | % (n) N = 236 patients | Events | % (n) N = 235 patients | Events |
| **Occurring within 12 months of the study procedure** | | | | |
| 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 |

| Event Type | Control | | Treatment | |
|---|---|---|---|---|
| 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 |
| **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 |

| Event Type | Control | | Treatment | |
|---|---|---|---|---|
| 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 |
| **Occurring between 12 and 24 months following the study procedure** | | | | |
| 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** | | | | |
| 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** | | | | |

| Event Type | Control | | Treatment | |
|---|---|---|---|---|
| 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 ($p < 0.01$), with the most common major adverse event being 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 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.

## Effectiveness

The primary effectiveness endpoint of superior primary patency (conservatively defined as a PSV ratio < 2.0) for the Zilver PTX stent compared to PTA was met ($p < 0.01$[2]) with a primary patency rate at 12 months of 82.7% for the Zilver PTX treatment group and 32.7% for the

[2] Adjusted for multiplicity.

PTA control group, as illustrated in Figure 3 and Table 10. The benefit of the Zilver PTX stent was maintained through 24 months.

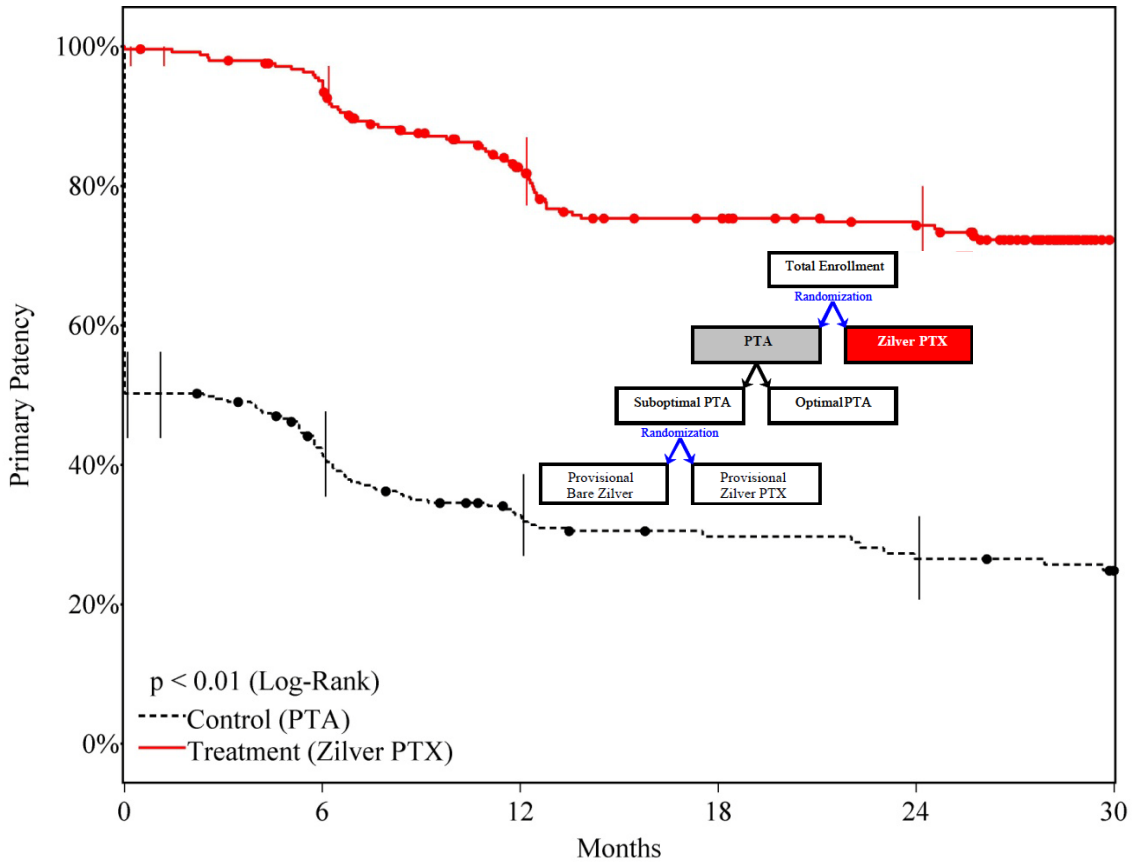



**Figure 3. Kaplan-Meier curve for primary patency**

**Table 10. Kaplan-Meier estimates for primary** patency at 0, 1, 6, and 12 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 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 4 and Table 11, there was a significant difference in patency outcomes between the groups ($p < 0.01$[3]), with the Zilver PTX group exhibiting a higher primary patency rate at 12 months of 90.2% compared to 72.9% for the bare Zilver group. The benefit of the Zilver PTX stent was maintained through 24 months with a 24-month patency rate of 83.4% for the Zilver PTX group compared to 64.1% for the bare Zilver group. Therefore, stenting with the paclitaxel-coated Zilver PTX stent is significantly more effective in maintaining primary patency through 24 months than stenting with a bare (uncoated) stent—indicating that the PTX® coating has a significant effect, and further supporting the effectiveness of the Zilver PTX stent.

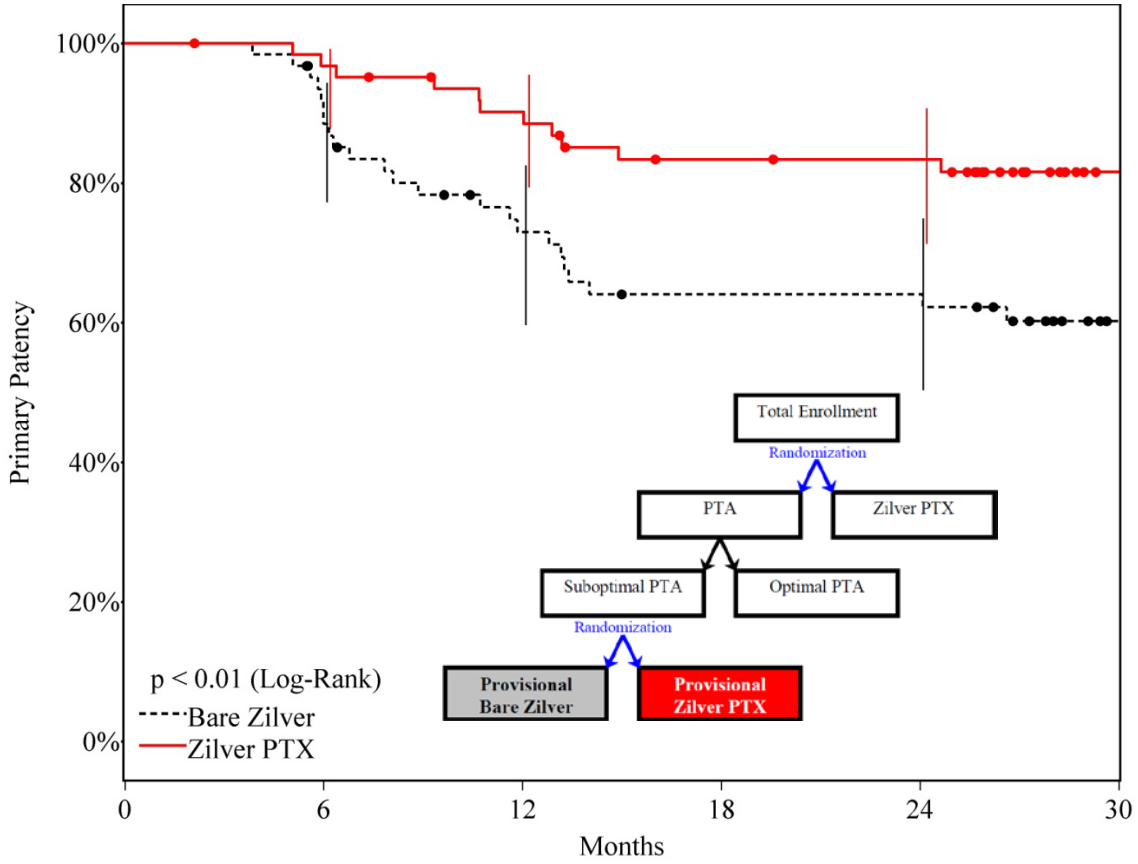



**Figure 4. Kaplan-Meier estimate plot for primary patency for provisional bare Zilver vs. provisional Zilver PTX (ITT)**

[3] Adjusted for multiplicity.

**Table 11. Kaplan-Meier estimates for bare Zilver vs. Zilver PTX**

| Months Post-procedure | Primary Patency Estimate | | Standard Error | | Cumulative Failed | | Cumulative Censored | | Number Remaining | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Bare Zilver | Zilver PTX | Bare Zilver | Zilver PTX | Bare Zilver | Zilver PTX | Bare Zilver | Zilver PTX | Bare Zilver | Zilver PTX |
| 0 | 100.0% | 100.0% | 0.0% | 0.0% | 0 | 0 | 0 | 0 | 62 | 63 |
| 1 | 100.0% | 100.0% | 0.0% | 0.0% | 0 | 0 | 0 | 0 | 62 | 63 |
| 6 | 88.4% | 96.8% | 4.1% | 2.2% | 7 | 2 | 2 | 1 | 53 | 60 |
| 12 | 72.9% | 90.2% | 5.8% | 3.8% | 16 | 6 | 5 | 3 | 41 | 54 |
| 24 | 64.1% | 83.4% | 6.3% | 4.8% | 21 | 10 | 6 | 7 | 35 | 46 |

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

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

**Secondary Endpoints**

Secondary endpoint analyses include procedural success, the patient-centered measure of freedom from 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).

Procedural success (< 30% residual stenosis) was significantly higher ($p < 0.01$) in the Zilver PTX treatment group (95.0%; 229/241) compared to the PTA control group (57.7%; 143/248), demonstrating that the Zilver PTX stent is effective in establishing patency.

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.

**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 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 12.

**Table 12. Pharmacokinetic substudy groups**

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

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

A parametric curve was fit to the data and the maximum observed plasma paclitaxel concentration ($C_{max}$), time to maximum concentration ($T_{max}$), area under the plasma concentration-time curve (AUC), half-life ($t_{1/2}$), and paclitaxel total clearance ($CL_{plasma}$) were estimated, along with 95% confidence intervals (Table 13). Additionally, a curve was fit to previously reported pharmacokinetic results obtained for animals implanted with Zilver PTX stents with a total of 876 µg paclitaxel coating per animal, and $C_{max}$, $T_{max}$, AUC, $t_{1/2}$, and $CL_{plasma}$ were estimated.

**Table 13. Pharmacokinetic parameters (with 95% confidence intervals)**

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

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

The results show that pharmacokinetics of paclitaxel in humans were similar to previously reported results in animals 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 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. Patients in the substudy required angiography at the 12-month follow-up and substudy patients in the Zilver PTX treatment group also required 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 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 and this excellent concordance between angiography and ultrasound confirms the validity of duplex ultrasound for assessing patency in the absence of angiography.

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

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 agreement with previously reported results from animal studies. The angiographic substudy indicated a high correlation of angiography and ultrasound for

assessing lesion patency, confirming the validity of duplex ultrasound for assessing patency in the absence of angiography. The IVUS substudy found no aneurysm or stent malapposition at the 6-month or 12-month follow-ups and a low rate of aneurysm and stent malapposition immediately post-stenting (2.4%), which was associated with pre-existing aneurysms prior to stent implantation and was not associated with clinical sequelae. In conclusion, the results from these substudies support the safety and effectiveness of the Zilver PTX stent.

**Stent Integrity**

Zilver stent integrity 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 16, 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 16. 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% |
| 12 months | 457 | 4 | 0.9% |

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

**Results Summary**

Event-free survival at 12 months was 90.4% in the Zilver PTX treatment group and 83.9% in the PTA control group, with the most common major adverse event being TLR, which occurred significantly more often in the PTA control group (16.3%) 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 treatment with the Zilver PTX stent is as safe as or safer

than treatment with PTA ($p < 0.01$) and that the Zilver PTX stent provides a significantly higher rate of primary patency compared to PTA ($p < 0.01$). These results support the safety and effectiveness of the Zilver PTX stent for the treatment of symptomatic vascular disease of the above-the-knee femoropopliteal arteries.

Additionally, stenting with the paclitaxel-coated Zilver PTX stent is significantly more effective ($p < 0.01$) in maintaining primary patency through 12 months 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 previously reported results from animal studies. The angiographic substudy indicated a high correlation between angiography and ultrasound for assessing lesion patency, confirming the validity of duplex ultrasound for assessing patency in the absence of angiography. The IVUS substudy found no aneurysm or stent malapposition at the 6-month or 12-month follow-ups and a low rate of aneurysms and stent malapposition immediately post-stenting (2.4%), which was associated with pre-existing aneurysms prior to stent

implantation and was not associated with clinical sequelae. In conclusion, the results from these substudies support the safety and effectiveness of the Zilver PTX stent.

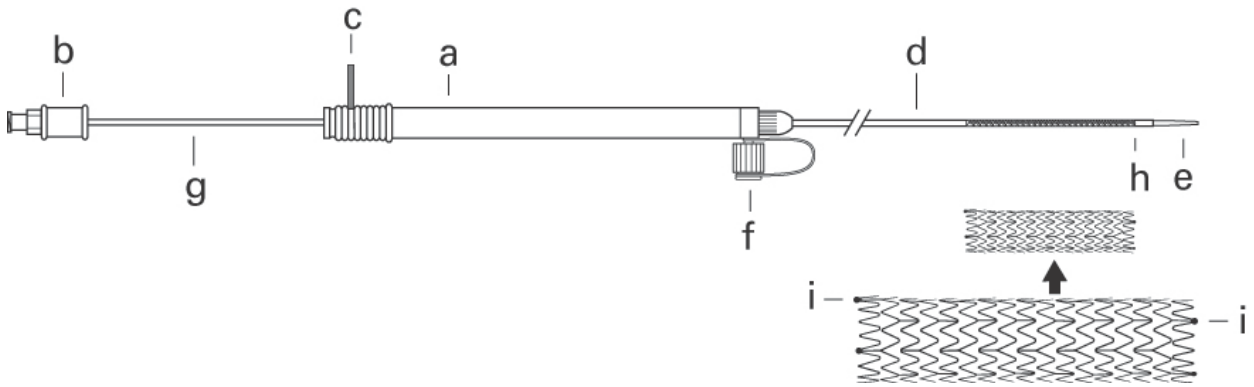
The stent fracture rate was low (0.9%) and the safety and effectiveness outcomes for patients with a stent fracture indicate that the stent fractures did not adversely affect patient safety or the effectiveness of the Zilver PTX stent. These results further support the safety of the Zilver PTX stent.

**Conclusions**

The results of the Zilver PTX randomized clinical study provide a reasonable assurance of safety and effectiveness for the Zilver PTX Drug-Eluting Stent in the treatment of symptomatic vascular disease of the above-the-knee femoropopliteal arteries. Specifically, the event-free survival rate for the Zilver PTX treatment group has been shown to be statistically non-inferior to the PTA control group. Moreover, the rate of EFS in the Zilver PTX group was substantially 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 is 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. 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.

## PRODUCT RECOMMENDATIONS

Placement of this vascular stent requires advanced skills in interventional vascular procedures. The following instructions will give technical guidance, but do not obviate formal training in the use of the device.




a. Handle
b. Hub
c. Safety Lock
d. Delivery System: Outer Sheath
e. Tip of Delivery System Inner Catheter
f. Side-arm Flushing Port
g. Metal Cannula
h. Radiopaque Markers on the Delivery System
i. Gold Radiopaque Markers

**Figure 5**

**Multiple Stent Placement**
If placements of multiple stents are required in a patient, to cover the length of the lesion, the following recommendations should be considered:

- In relation to the lesion site, the distal area of narrowing should be stented first, followed by the proximal locations (i.e., a second stent should be placed proximally to the previously placed stent).
- Stents placed in tandem must overlap to allow for complete coverage of the lesion.
- The effect of implanting more than four Zilver PTX Drug-Eluting Stents in a patient has not been clinically evaluated.

## INSTRUCTIONS FOR USE

### Stent Sizing

1. Determine the proper stent size after complete diagnostic evaluation. The stent deployment must be performed under fluoroscopic control. Measure the length of the target lesion to determine the length of the stent required. Allow for the proximal and distal aspects of the stent to cover the entire target area.

**NOTE:** The Zilver PTX Drug Eluting Stent is designed not to shorten upon deployment. Bench testing has shown that on average, the stent length increases from pre-deployment to post-deployment by approximately 2.5%.

The stent is recommended for use in above-the-knee femoropopliteal arteries having reference vessel diameter from 4 mm to 9 mm.

Measure the diameter of the reference vessel (proximal and distal to the lesion) and use the LARGEST reference diameter as your basis for choosing the appropriate stent size.

The stent size should be selected so that the unconstrained stent diameter is at least 1 mm larger than the reference vessel diameter and no more than 2 mm larger than the reference vessel diameter.

### Introduction of the Stent

1. Gain access to the site using a 6.0 French (2.0 mm) or larger introducer sheath.
2. Introduce the extra or ultra stiff 0.035 inch (0.89 mm) wire guide through the introducer sheath across the distal segment of the target lesion.
3. Predilatation before stent placement is optional and at the discretion of the physician.

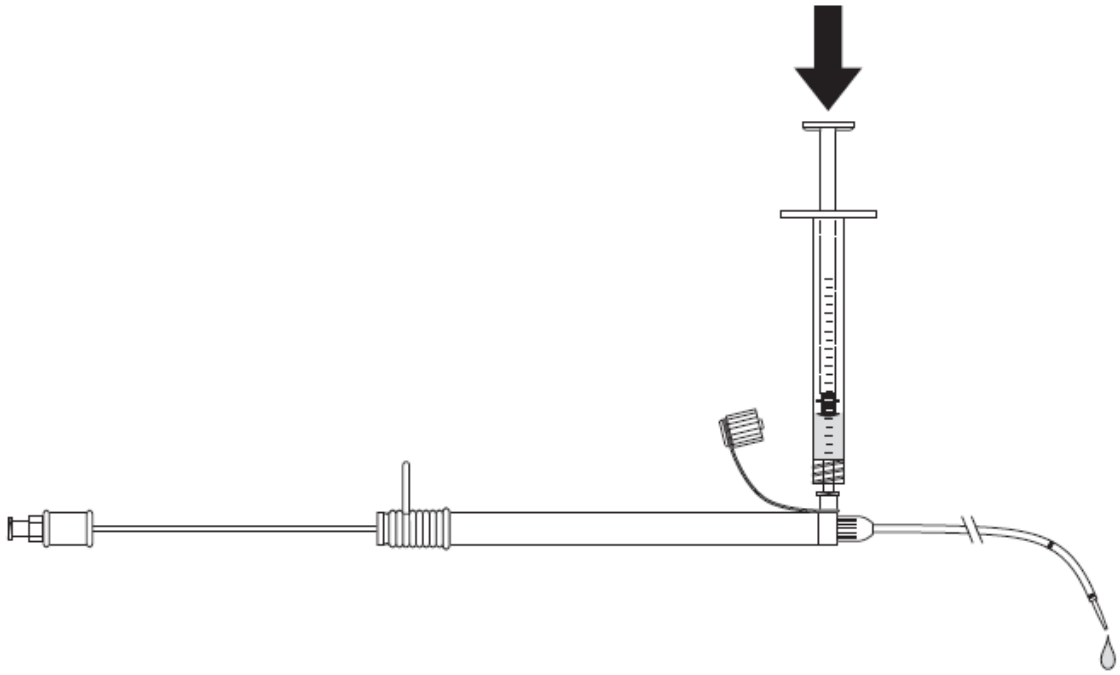


**Figure 6**

4. Immediately before placing the stent delivery system into the body, use the 1 ml syringe included in the inner package to flush the delivery system with saline through the side-arm flushing port. Flush only until a few drops of saline exit the distal tip, between the delivery system inner catheter and outer sheath. (Figure 6)

   Use the 1 ml syringe to flush the wire guide lumen with saline through the hub (**Figure 7**).

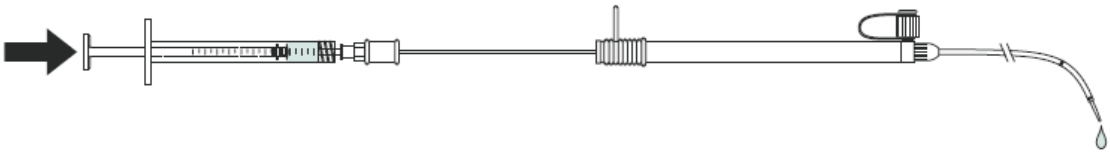


**Figure 7**

**The time between flushing and stent deployment should be minimized, and must be no longer than 5 minutes.**

5. Under fluoroscopy, advance the delivery system over the wire guide through the introducer sheath until the distal gold radiopaque markers on the stent are beyond the target lesion site (Figure 8).

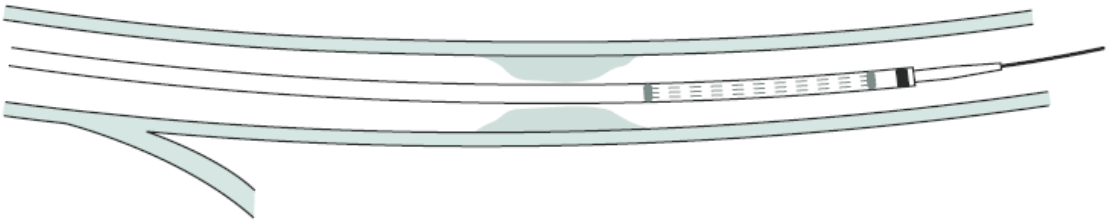


**Figure 8**

**Alignment of the Stent**

1. Before stent alignment, it is important to:
    a. Straighten the proximal part of the delivery system as much as possible (Figure 9)
    b. Remove any slack in the delivery system
    c. Keep the handle in a stable position.

**Figure 9**

2. The stent alignment must be performed under fluoroscopic control.

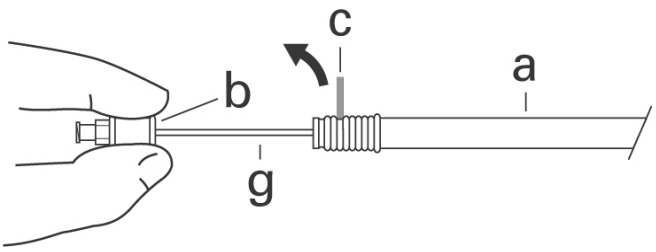


**Figure 10**

3. Remove the red safety lock (**c**) while holding the hub (**b**) on the metal cannula (**g**) steady. (Figure 10)

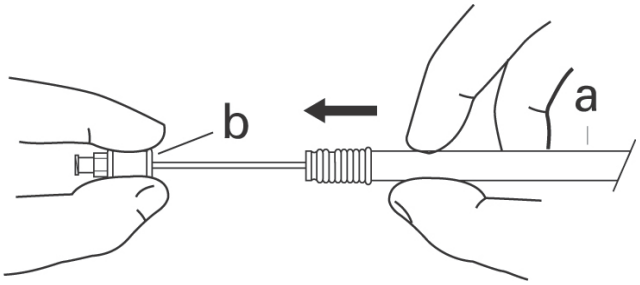



**Figure 11**

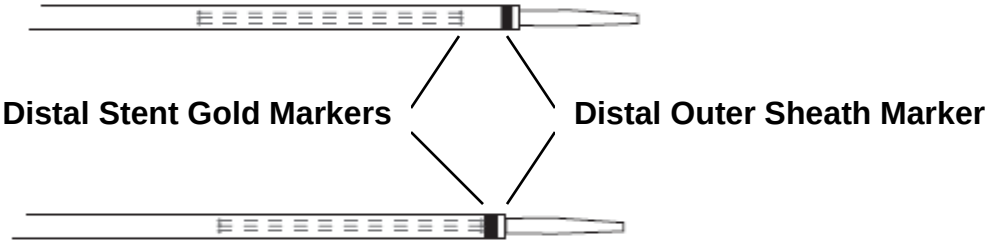



**Figure 12**

4. Hold the hub (**b**) steady. Slowly pull the handle (**a**) toward the hub (**b**) (Figure 11) until the distal outer sheath marker overlaps the distal stent gold markers. (Figure 12)

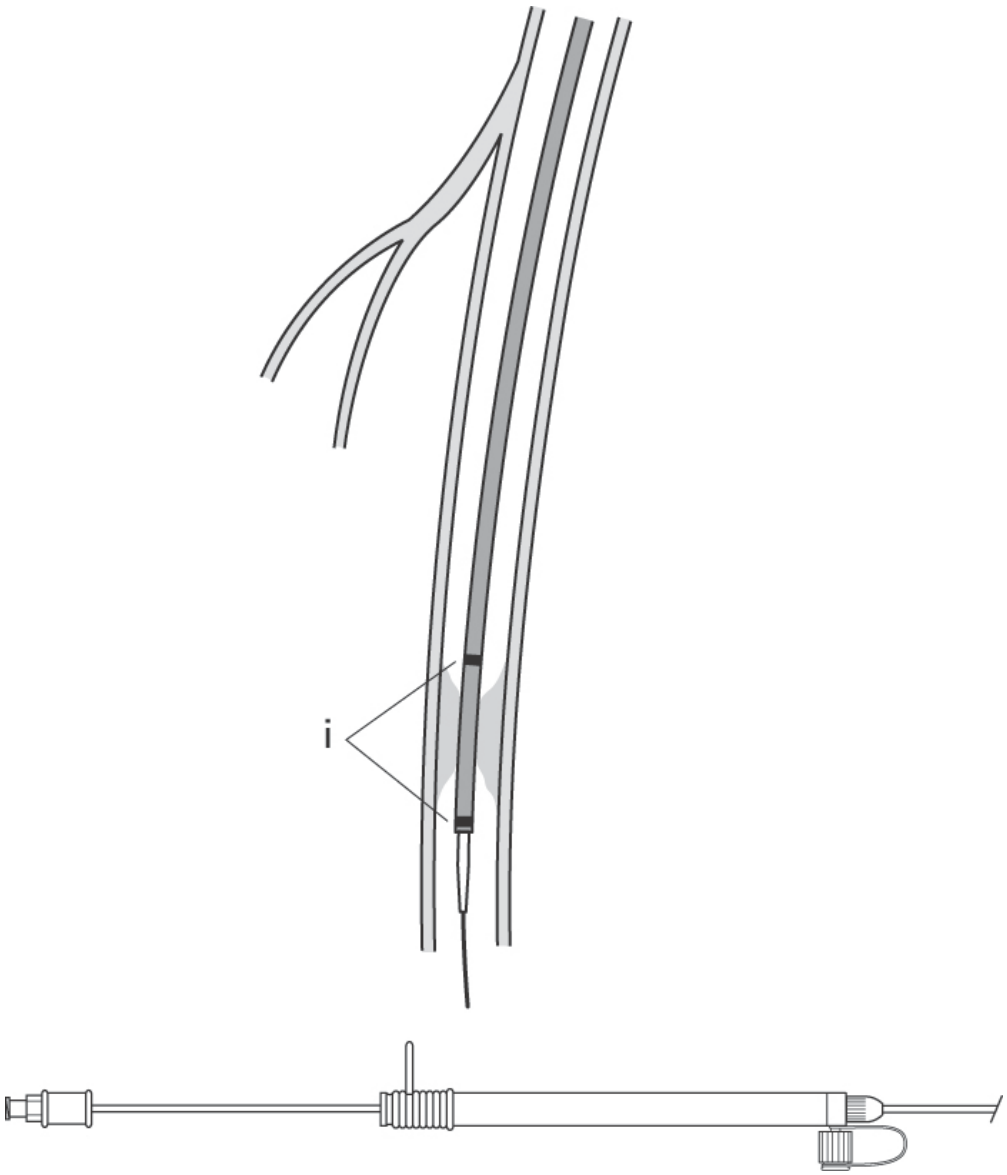



**Figure 13**

5. Align the radiopaque stent markers (i) to the desired position. (Figure 13) The stent should now be ready to be deployed.

**Deployment of the Stent**

1. Before stent deployment, it is important to:
    a. Straighten the proximal part of the delivery system as much as possible (Figure 14)
    b. Remove any slack in the delivery system

c. Keep the handle in a stable position.

**Figure 14**

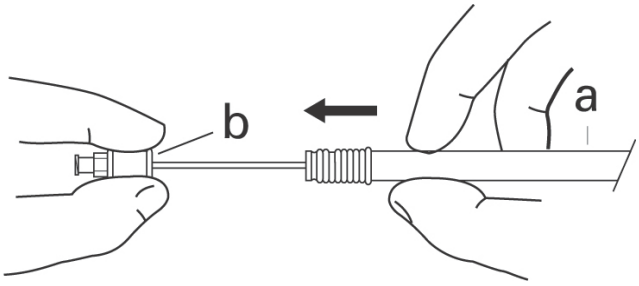



**Figure 15**

2. Hold the hub (**b**) steady. The stent will be deployed as you pull the handle (**a**) toward the hub (**b**). (Figure 15)

   **NOTE:** Care should be taken to hold the hub (**b**) stationary and to remove any slack in the introducer catheter to ensure the stent is not stretched or compressed lengthwise during deployment (i.e., so that the stent is deployed to its proper length). Full deployment of the stent length will occur when the distal end of the sheath has been retracted past the proximal part of the stent**.**

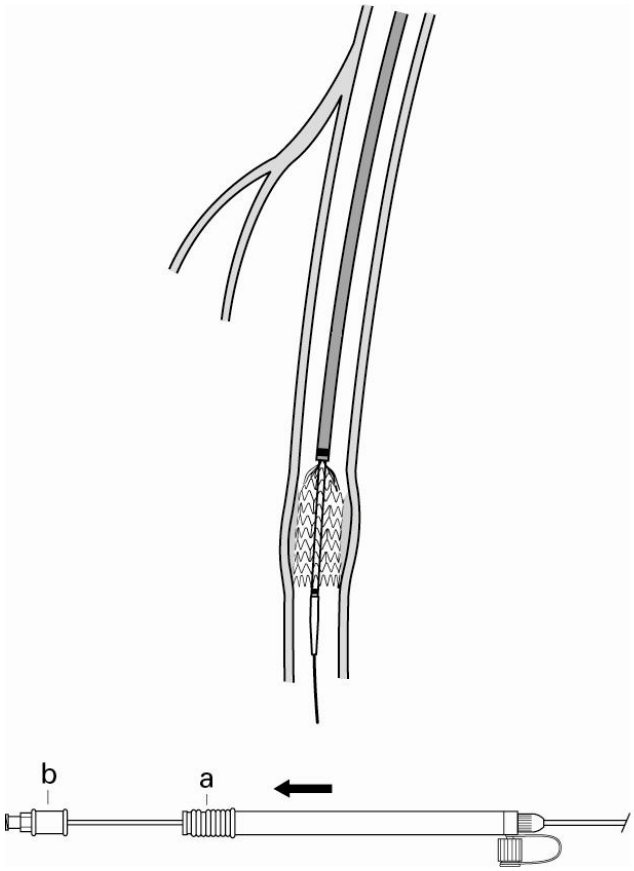



**Figure 16**

3. As deployment occurs, continue sliding the handle (**a**) toward the hub (**b**) in a slow, smooth and consistent fashion. (Figure 16)

   **NOTE:** Once stent deployment has begun, the stent must be fully deployed. Repositioning of the Zilver PTX Drug Eluting Stent is not possible since the delivery system's outer sheath cannot be re-advanced over the stent once deployment begins. Refer to the **Multiple Stent Placement** section of these Instructions For Use for information on missed lesions.

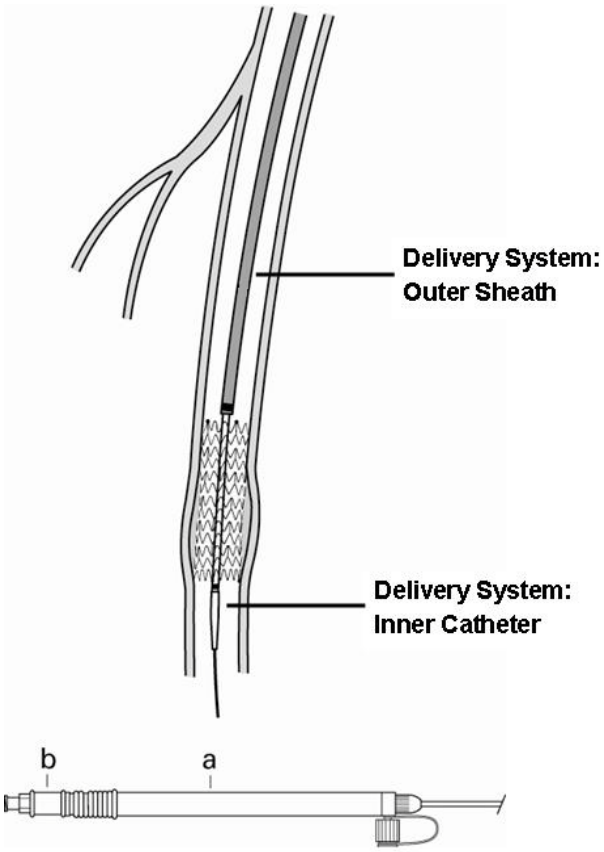



**Figure 17**

4. The stent is fully deployed when the handle (**a**) reaches the hub (**b**). (Figure 17)

**Post Stent Deployment**

1. Remove the delivery system.

   **NOTE:** If resistance is met during the withdrawal of the inner catheter through the stent, re-advance the outer sheath over the inner catheter to its pre-deployment position. Withdraw the system in this position.

2. Perform an arterial angiogram to verify full deployment of the device. If incomplete expansion exists within the stent at any point along the lesion, post-deployment balloon dilatation (standard PTA) can be performed at the discretion of the physician.
3. Remove the wire guide and introducer sheath from the patient.

4. Close the entry wound as appropriate.

## HOW SUPPLIED

Supplied sterilized by ethylene oxide gas in peel-open packages. Intended for one-time use. Sterile if package is unopened or undamaged. Do not use the product if there is doubt as to whether the product is sterile. Store in a dark, dry, cool place. Avoid extended exposure to light. Upon removal from package, inspect the product to ensure no damage has occurred.

## REFERENCES

These instructions for use are based on experience from physicians and (or) their published literature. Refer to your local Cook sales representative for information on available literature.

PHT

**This symbol on the label indicates that this device contains phthalates.**

**Use By**

**Single Use**

**Date of Manufacture**

LOT

**Lot Number**

**Keep away from direct sunlight**

**Keep Dry**

**Consult IFU**

**Attention See IFU**

| STERILE | EO |
|---|---|

**Sterilized using Ethylene oxide**

**Rx ONLY**

CE
0088

MANUFACTURER

**Cook Ireland Ltd.**
**O'Halloran Road**
**National Technology Park**
**Limerick, Ireland**

**US Distributor**

**Cook Medical Incorporated**
**400 Daniels Way**
**Bloomington, IN 47404**
**USA**

**www.cookmedical.com**

**© COOK 2010**

**September 2011**
**IFU0063-0**