COOK® MEDICAL

EN
1

Zilver Flex® 35 Vascular Stent

Instructions for Use

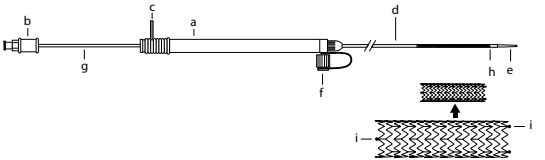

Fig. 1

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 Marker on the Delivery System
i. Gold Radiopaque Markers

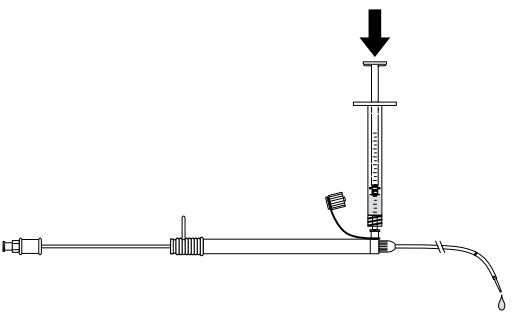

Fig. 2

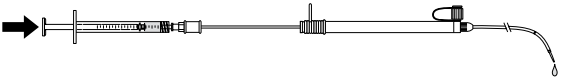

Fig. 3

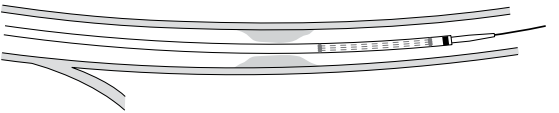

Fig. 4

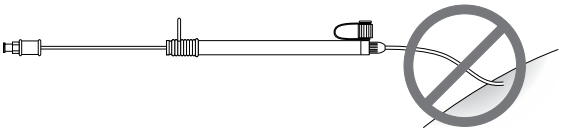

Fig. 5

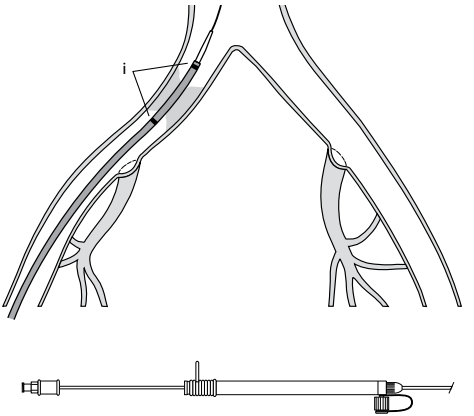

Fig. 6

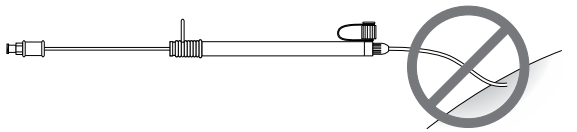

Fig. 7

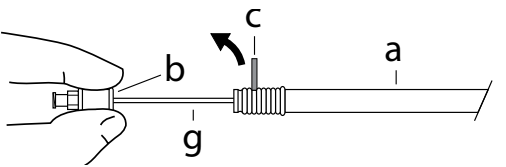

Fig. 8

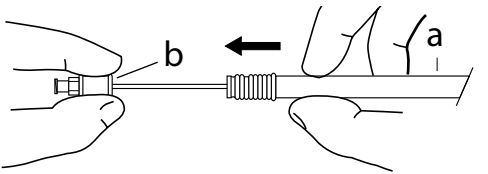

Fig. 9

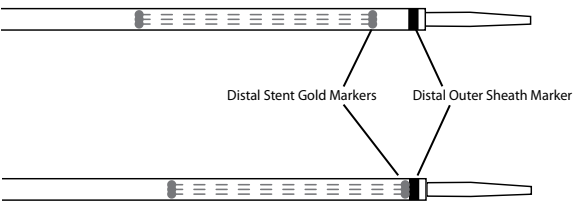

Fig. 10

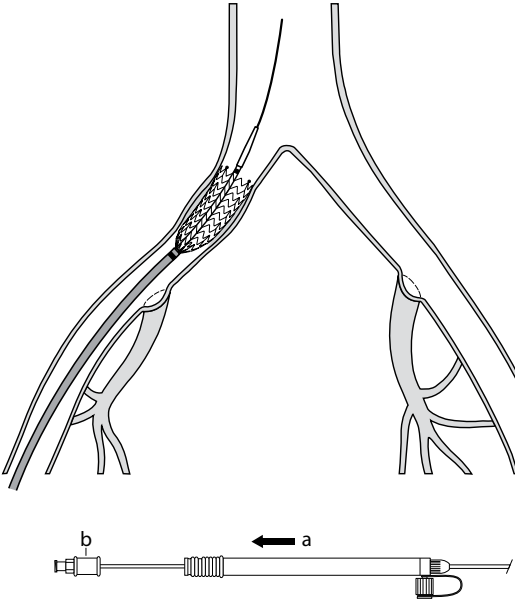

Fig. 11

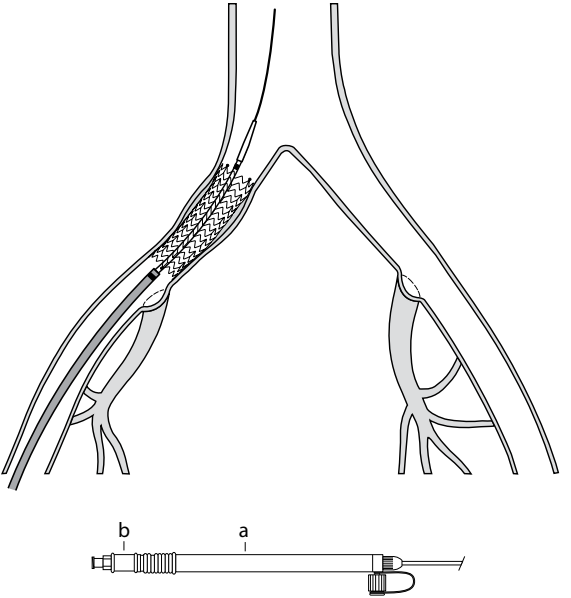

Fig. 12

ZILVER FLEX® 35 VASCULAR STENT

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

Do not re-sterilize.

DEVICE DESCRIPTION

The Zilver Flex 35 Vascular Stent is a self-expanding stent made of nickel titanium alloy (nitinol). The Zilver Flex 35 Vascular Stent comes preloaded in a 2.0 mm (6 Fr) delivery system and is provided with a syringe. The stent has gold radiopaque markers at both ends. Stent deployment is controlled by retraction of the handle. Refer to Tables 1 and 2 below.

Table 1: Zilver Flex® 35 Vascular Stent features overview[1]

Zilver Flex® 35 Vascular Stent	
Available stent lengths	20, 30, 40, 60, 80, 100, 120, 140, 170, 200 mm
Available stent diameters	5, 6, 7, 8, 9 ,10 mm
Stent material	Nickel titanium alloy (nitinol) with gold markers
Delivery System	
Available delivery system lengths	80, 125 cm
Wire guide compatibility	0.89 mm (0.035 inch)
Delivery system outer diameter	2.0 mm (6 Fr)
Introducer sheath	6 Fr (Minimum ID of 2.0 mm)

[1]Stents of diameter 6–10 mm and length 20–100 mm are indicated for iliac artery use. Stents of diameter 5–8 mm and length 20–200 mm are indicated for above-the-knee femoropopliteal artery use.

Table 2: Stent size selection

Zilver Flex® 35 Vascular Stent above-the-knee femoropopliteal artery indication																					
Stent length (mm)		20		30		40		60		80		100		120		140		170		200	
Delivery system (cm)		80	125	80	125	80	125	80	125	80	125	80	125	80	125	80	125	80	125	80	125
Stent outer diameter (mm)	5	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	6	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	7	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	8	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Zilver Flex® 35 Vascular Stent iliac artery indication																					
Stent length (mm)		20		30		40		60		80		100									
Delivery system (cm)		80	125	80	125	80	125	80	125	80	125	80	125								
Stent outer diameter (mm)	6	x	x	x	x	x	x	x	x	x	x	x	x								
	7	x	x	x	x	x	x	x	x	x	x	x	x								
	8	x	x	x	x	x	x	x	x	x	x	x	x								
	9	x	x	x	x	x	x	x	x	x	x	x	x								
	10	x	x	x	x	x	x	x	x	x	x	x	x								

Performance Characteristics

The function and key features of the device are described below.

Delivery system – the function of the delivery system is to advance the stent through a minimum ID of 2.0 mm (6 Fr) introducer sheath, over a pre-positioned 0.89 mm (0.035 inch) wire guide to its intended location. It maintains the position of the stent during deployment.

The delivery system has the following features (**Fig. 1**):

- Handle – Facilitates the deployment of the stent when the handle is retracted proximally to withdraw the outer sheath.
- Luer hub – Facilitate attachment and detachment of the provided syringe for flushing of the wire guide lumen of the delivery system, prior to introduction to the body. The hub allows the wire guide to exit proximally during introduction.

- Safety lock – Prevents actuation of the handle prior to intended stent deployment. It must be disengaged to initiate deployment at the target location.
- Delivery system outer sheath – The delivery system lengths of 80 cm and 125 cm are used for approach to the target location. The stent is deployed by controlled withdrawal of the outer sheath by retracting the handle towards the hub.
- Tip of delivery system inner catheter:
  - Atraumatic – The tip is designed to be atraumatic to the anatomy.
  - Flexible – The tip is designed to be flexible during introduction and withdrawal from the body.
- Side-arm flushing port – Facilitate attachment and detachment of the provided syringe for flushing of the stent lumen via side arm flushing port of the delivery system.
- Metal cannula – The function of the metal cannula is to allow the handle to travel over it for controlled stent deployment.
- Radiopaque marker band on the delivery system – The radiopaque marker band enables fluoroscopic visibility of the delivery system.

Stent – 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 has the following features:

- The stent is manufactured from nickel titanium alloy (nitinol) enabling it to self-expand at body temperature upon deployment.
- The gold markers on the stent are radiopaque to facilitate visibility under fluoroscopy and to confirm correct placement of the device in the desired position within the vessel.
- The stent is a flexible slotted tube that is designed to provide support while maintaining flexibility in the vessel upon deployment.
- The stent is intended for permanent implant.

Syringe – The Zilver Flex 35 Vascular Stent is provided with a 1 mL or 3 mL syringe depending on the stent size.

- The function of this syringe is to facilitate the flushing of the stent lumen and wireguide lumen.

Device Compatibility

Zilver Flex 35 Vascular device is compatible with the following:

- 0.89 mm (0.035 inch) wire guide
- 6 Fr introducer sheath with minimum ID of 2.0 mm
- Dilation balloons. For pre- and post-dilation, an appropriately sized balloon catheter is recommended
- Saline
- Contrast media*.

* **Note**: The outer part of the delivery system is compatible with contrast media. The device is not to be flushed using contrast media. (Refer to Precautions section)

Patient Population

This device can be used in adult patients with vascular disease of the iliac and above-the-knee femoropopliteal arteries.

Intended User

The product is intended for use by physicians trained and experienced in diagnostic and interventional vascular techniques.

Standard techniques for the interventional vascular procedures should be employed.

Operating Principles

The Zilver Flex 35 Vascular device is placed over a prepositioned 0.89 mm (0.035 inch) wire guide and advanced through a minimum ID of 2.0 mm (6 Fr) introducer sheath to the target location.

The provided syringe is used to flush the stent lumen and wire guide lumen respectively prior to placing the delivery system into the body.

A radiopaque marker band at the distal end of the delivery system provides visibility under fluoroscopy during introduction and deployment of the stent.

Hand-loading of the stent is not possible.

The stent is deployed by retracting the outer sheath using the handle and while holding the hub on the metal cannula stationary.

Full deployment of the stent occurs when the distal end of the sheath has been retracted past the proximal end of the stent.

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.

INDICATIONS FOR USE

The Zilver Flex 35 Vascular Stent is intended for use as an adjunct to percutaneous transluminal angioplasty (PTA) in the treatment of symptomatic vascular disease of the iliac arteries up to 100 mm in length with a reference vessel diameter of 5 to 9 mm. Patients should be suitable candidates for PTA and/or stent treatment.

The Zilver Flex 35 Vascular Stent is intended to improve the luminal diameter in the treatment of de novo or restenotic symptomatic lesions in the native above-the-knee femoropopliteal arteries with reference vessel diameters from 4 to 7 mm and lesion lengths up to 190 mm.

CONTRAINDICATIONS

- Patients who cannot receive appropriate antiplatelet and/or anticoagulant therapy.
- Patients with lesions that prevent complete angioplasty balloon inflation or proper placement of the stent or stent delivery system.

WARNINGS

- The stent contains nickel titanium alloy (nitinol), which may cause an allergic reaction in individuals with nickel sensitivity.
- This single use device is not designed for re-use. Attempts to reprocess, re-sterilize, and/or to re-use may lead to contamination with biological or chemical agents and/or mechanical integrity failure of device.
- The stent is intended for permanent implant.
- Visually inspect the integrity of the sterile packaging. Do not use if the sterile packaging is damaged or unintentionally opened before use.
- Visually inspect the device with particular attention to kinks, bends and breaks. If an abnormality is detected that would prohibit proper working condition, do not use. Please notify Cook Medical for a return authorization.
- Flow restrictions remaining after stent deployment (e.g., residual proximal or distal stenosis or dissection, or poor distal outflow) may increase the risk of stent thrombosis. Inflow and outflow should be assessed at procedure completion and additional measures considered (e.g., additional PTA (percutaneous transluminal angioplasty), adjunctive stenting, or distal bypass) if necessary to maintain good inflow and outflow.

PRECAUTIONS

Prior to Use

- Use of this device is restricted to a trained healthcare professional.
- This product is intended for use by physicians trained and experienced in diagnostic and interventional vascular techniques. Standard techniques for placement of an arterial introducer sheath and wire guide should be employed during use of the vascular stents.
- Do not use the stent system past the expiration date specified on the package.
- Store the device in a dry location.
- Pre-dilatation of the lesion and vessel prior to stent placement is optional and at the discretion of the physician.
- Device not indicated for use in the treatment of in-stent restenosis.
- Prior to the insertion of the balloon catheter and post implant procedure, appropriate antiplatelet and anticoagulant therapy should be administered.
- When more than one stent is required, resulting in stent-to-stent contact, stent materials should be of similar composition (i.e., nickel titanium alloy (nitinol)).

Device Handling

- Manipulation of the Zilver Flex 35 Vascular Stent requires high resolution fluoroscopic control.
- Do not use power injection system with the delivery system.
- Do not expose any part of the delivery system to organic solvents (e.g., alcohol).
- Do not flush the device with contrast media.
- Do not attempt to remove the stent from the delivery system before use.
- A 0.89 mm (0.035 inch) wire guide should be used during tracking, deployment, and removal to ensure adequate support of the system. Using a smaller diameter wire guide may ultimately result in partial deployment of the stent. Possible outcomes of partial deployment are:
    - Prolonged procedure (e.g., additional exposure to radiation/contrast).
    - Additional stent required.
    - Secondary intervention (e.g., vessel incision).
- If resistance is met during advancement of the delivery system, do not force passage. Remove the delivery system and replace with a new device. Continuing to force passage may ultimately cause partial deployment of the stent. Possible outcomes of partial deployment are:
    - Prolonged procedure (e.g., additional exposure to radiation/contrast).
    - Additional stent required.
    - Secondary intervention (e.g., vessel incision).
- The long-term outcome following repeat dilatation of endothelialized stents is unknown.
- Safety and effectiveness have not been demonstrated in:
    - Patients with a history of bleeding diathesis or coagulopathy
    - Patients with a history of iliac aneurysm
    - Patients with a known pregnancy
    - Lesions located within or beyond a bypass graft
    - Pediatric patients.

Stent Placement

- Avoid stent placement that may obstruct access to a vital side branch.
- Do not rotate any part of the delivery system during deployment.
- Ensure that the safety lock is not inadvertently removed prior to intended stent deployment.
- Prior to stent deployment, it is important to straighten the proximal portion of the delivery system as much as possible and to keep the handle in a stable position.
- If high resistance is felt when beginning deployment, do not force deployment. Carefully withdraw the delivery system without deploying the stent and replace with a new device.
- Repositioning of the Zilver Flex 35 Vascular Stent is not possible. The delivery system outer sheath cannot be re-advanced over the stent once deployment begins.
- Do not push the hub toward the handle during deployment. Pull the handle toward the hub during deployment.
- If placement of multiple stents is required in a patient to cover the length of the lesion, 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.
- Once stent deployment has begun, the stent must be fully deployed.

Device Removal

- Following stent deployment, if resistance is met during the withdrawal of the delivery system, carefully remove the delivery system and wire guide together as a unit.
- If resistance is still encountered during removal of the delivery system and wire guide as a unit, remove the wire guide, delivery system and introducer sheath together as a unit.

Post Procedure

- Periodic evaluation of the device is recommended during the indwell period.

- Damage/dislodgement of a placed stent may occur with additional procedures.
- Use caution when re-crossing a stent to avoid stent damage or migration.

MRI SAFETY INFORMATION

This symbol means the device is MR Conditional

A patient with the COOK Medical Zilver Flex® 35 Vascular Stent may be safely scanned under the following conditions. Failure to follow these conditions may result in injury to the patient.

Name/Identification of device	COOK Medical Zilver Flex® 35 Vascular Stent
Nominal value(s) of Static Magnetic Field [T]	1.5 T or 3 T
Maximum Spatial Field Gradient [T/m and gauss/cm]	24 T/m (2,400 gauss/cm)
RF Excitation	Circularly Polarized (CP)
RF Transmit Coil Type	Whole body transmit coil, Head RF transmit-receive coil
Maximum Whole Body SAR [W/kg]	2.0 W/kg (Normal Operating Mode)
Limits on Scan Duration	2.0 W/kg whole body average SAR for 15 minutes of continuous RF (a sequence or back to back series/scan without breaks)
MR Image Artifact	The presence of the COOK Medical Zilver Flex® 35 Vascular Stent may produce an image artifact. Some manipulation of scan parameters may be needed to compensate for the artifact.

If information about a specific parameter is not included, there are no conditions associated with that parameter.

POTENTIAL ADVERSE EVENTS

Potential adverse events that may occur: abrupt stent closure • allergic reaction to anticoagulant and/or antithrombotic therapy or contrast medium • allergic reaction to nickel • amputation • angina/coronary ischemia • arrhythmia • arterial aneurysm • arterial rupture • arteriovenous fistula • atheroembolization (blue toe syndrome) • death • embolism • fever • hematoma/hemorrhage • hypersensitivity reactions • hypotension/hypertension • infection/abscess formation at access site • intimal injury/dissection • ischemia requiring intervention (bypass or amputation of toe, foot or leg) • myocardial infarction (MI) • occlusion • pain/discomfort • pseudoaneurysm formation • pulmonary embolism • renal failure • restenosis of the stented artery • septicemia/bacteremia • stent malapposition • stent migration • stent strut fracture • stroke • thrombosis • tissue necrosis • vasospasm • worsened claudication/rest pain.

HOW SUPPLIED

This device is supplied ethylene oxide (EO) sterilized in a peel-open pouch. Following sterilization, the pouch is further packaged into a product box.

PATIENT PREPARATION

Selection of Stent

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.

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.

Note: If multiple stents are required to cover the length of the lesion, please refer to the Multiple Stent Placement section of the instructions for use for further recommendations.

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 Zilver Flex Vascular Stent is designed not to shorten upon deployment. Bench testing has shown that on average, the stent length decreases from pre-deployment to post-deployment by 0.4% to 0.9%.

Table 3: Stent sizing and length change

Reference Vessel Diameter (mm)	Labeled Stent Diameter (mm)	Mean Stent Length Change upon Deployment[1]
4	5	-0.4% to -0.9%
4–5	6	
5–6	7	
6–7	8	
7–8	9	
8–9	10	

[1]Negative value indicates shortening upon deployment.

INSTRUCTIONS FOR USE

Access

1. Visually inspect the integrity of the sterile packaging. Do not use if the sterile packaging is damaged or unintentionally opened before use.
2. Visually inspect the device with particular attention to kinks, bends and breaks. If an abnormality is detected that would prohibit proper working condition, do not use.
3. Gain access at the appropriate site utilizing a minimum ID of 2.0 mm (6 Fr) introducer sheath.
4. Introduce a 0.89 mm (0.035 inch) wire guide through the introducer sheath across the distal segment of the target lesion.
5. Predilate if necessary. Remove the balloon catheter, leaving the wire guide in place.
6. Immediately before placing the delivery system into the body, use the provided syringe (1 mL for 20–140 mm length and 3 mL for 170–200 mm length) to flush the delivery system with saline through the side-arm flushing port. Flush until a few drops of saline exit the distal tip, between the delivery system outer sheath and inner catheter. (**Fig. 2**)
7. Use the provided syringe (1 mL for 20–140 mm length and 3 mL for 170–200 mm length) to flush the wire guide lumen with saline through the hub. (**Fig. 3**)
8. Place the delivery system over the wire guide.
9. Under fluoroscopy, insert the delivery system through the introducer sheath and advance the delivery system until the distal outer sheath radiopaque marker band is past the lesion (**Fig. 4**). **Note**: If resistance is met during advancement of the delivery system over the wire guide, remove the delivery system and replace with a new device.
10. Straighten the proximal part of the delivery system as much as possible (**Fig. 5)** and keep the handle in a stable position.
11. Pull back on the stent delivery system under fluoroscopy until the radiopaque markers on the stent are at the desired position. The stent is now ready to be deployed. (**Fig. 6**)

Deployment of the Stent

12. Before stent deployment, it is important to keep the proximal part of the delivery system as straight as possible (**Fig. 7**) and to keep the handle in a stable position, while maintaining stent marker alignment with the intended deployment location.
13. The stent expansion must be performed under fluoroscopic control.
14. Hold the hub on the metal cannula steady. To deploy the stent, remove the red safety lock. (**Fig. 8**)
15. Hold the hub end (b) stationary. The stent will be deployed as the handle (a) is gently pulled toward the hub (b) (**Fig. 9**). The movement of the radiopaque marker band on the delivery system relative to the stent gold markers indicates the progress of the deployment. (**Fig. 10**) **Note**: Full deployment of the stent length will occur when the distal end of the outer sheath has been retracted past the proximal part of the stent. **Note:** If high resistance is felt when beginning deployment, do not force deployment. Carefully withdraw the delivery system without deploying the stent and replace with a new device.

16. As deployment occurs, continue sliding the handle (a) toward the hub (b) in a slow, smooth and consistent fashion. (**Fig. 11**)
    Note: Once stent deployment has begun, the stent must be fully deployed. Repositioning of the Zilver Flex 35 Vascular Stent is not possible since the delivery system 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.
17. The stent is fully deployed when the handle (a) reaches the hub (b). (**Fig. 12**)
18. Delivery system removal – Do not advance outer sheath after the stent has been deployed. Delivery system can be removed without recapturing tip. Check for delivery system integrity post removal from the patient.
19. Perform an arterial angiogram to ensure proper placement of the device. **Note:** 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. Select an appropriate size PTA balloon catheter and dilate the lesion with conventional technique. The inflation diameter of the PTA balloon used for post dilatation should approximate the diameter of the reference vessel. Remove the PTA balloon from the patient.
20. Introducer sheath and wire guide may be removed at this point.

Multiple Stent Placement

If placement of more than one stent is required, the following recommendations should be considered:

a. When more than one stent is required, resulting in stent-to-stent contact, stent materials should be of similar composition.
b. 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 proximal to the previously placed stent).
c. Stents placed in tandem must overlap to allow for complete coverage of the lesion.

DISPOSAL OF DEVICES

This device may be contaminated with potentially infectious substances of human origin and should be coiled for disposal in accordance with institutional guidelines.

SERIOUS INCIDENT REPORTING

If any serious incident has occurred in relation to the device this should be reported to Cook Medical and the competent authority of the country where the device was used.

SUMMARY OF CLINICAL INVESTIGATIONS

The Zilver Vascular stent was subject of a single arm Investigational Device Exemption study which is described in detail below. Results from the study support the safety and effectiveness of the Zilver Vascular stent and Zilver Flex Vascular Stent in diameters of 6–10 mm and lengths of 20–100 mm in treatment of symptomatic vascular disease of the iliac arteries. The Zilver Flex Vascular Stent was subject of a prospective analysis of data accumulated in the bare metal arm of the Zilver PTX Randomized Controlled Trial (RCT), the Zilver Flex Vascular Study, and the Zilver Flex Post Market Study (PMS) in Japan. The analysis supports the safety and effectiveness of the Zilver Flex Vascular Stent in diameters of 5–8 mm and lengths of 20–200 mm in the treatment of above-the-knee femoropopliteal arteries.

Single Arm Clinical Study (Iliac Artery Study)

A pilot study of the safety of the Zilver Vascular Stent enrolled 20 patients at four investigative sites and provided justification for initiation of a pivotal study to assess the safety and effectiveness of the Zilver Vascular Stent.

A total of 151 patients at 24 U.S. investigative sites were enrolled in a pivotal study to evaluate the safety and effectiveness of the Zilver Vascular Stent for use as an adjunct to percutaneous transluminal angioplasty (PTA) in the treatment of symptomatic vascular disease of the iliac arteries. The following is a summary of the pivotal study.

Study Endpoints

This prospective, non-randomized study of the Zilver Vascular Stent for the treatment of stenotic or occlusive lesions of the external or common iliac arteries was intended to establish the rate of major

adverse events (MAE) at 9-month clinical follow-up as the primary study endpoint compared to an Objective Performance Criterion (OPC) derived from literature of recent studies in similar patient populations. The MAE rate of the OPC was set to be not greater than 16%, with a 9% delta. Secondary endpoints included acute procedure success, 30-day clinical success, 9-month patency rate based on ultrasound examination, ankle-brachial index, and 9-month functional status as measured by the walking impairment questionnaire.

Patient Population

Patients eligible to enroll in this study had up to two documented stenotic (≤10 cm long) or occluded (≤5 cm long) atherosclerotic lesions of the external iliac or common iliac artery on opposite sides. Lesions could be either de novo or restenotic. Patients with previously stented lesions were excluded. Characteristics of the patients enrolled in this study, including age, gender, medical history as well as angiographic characteristics of the treated lesions (pre-procedure), are included in Tables 4 and 5.

Table 4: Characteristics of patients implanted with the Zilver Vascular stent

Baseline Characteristics		Patients (N=151)	
Age (Mean years ± SD)		67 ± 8.9	
Male Gender		93	61.6%
Smoking Status	Past	79	52.3%
	Current	65	43.0%
Diabetes		46	30.5%
Hypercholesterolemia		109	72.2%
Hypertension		117	77.5%
Carotid Disease		49	32.5%
Renal Disease		23	15.2%
Pulmonary Disease		50	33.1%
Use of Antiplatelets		116	76.8%
CHF Class 3 or 4		7	4.6%
Previous MI		47	31.1%

Table 5: Angiographic characteristics of the lesions prior to treatment with the Zilver Vascular stent

Angiographic Characteristics	Lesions (N=177)	Mean ± SD
Lesion Length (mm)	168	32.9 ± 18.8
RVD (mm)	171	7.4 ± 1.5
In-Stent MLD (mm)	171	2.7 ± 1.4
% Diameter In-Stent Stenosis	171	64.5 ± 15.2

Methods

All patients underwent PTA (predilatation) of the target lesion prior to deployment of the stent. Up to two lesions per patient on opposite sides were stented with no more than two stents per lesion. Patients had an angiogram prior to and immediately following stent placement. Duplex ultrasound to assess patency of the stented artery and common femoral artery was performed no more than three days following the procedure. The protocol recommended each hospital follow its standard protocol with respect to pre- and post-procedure medication; based on previous published studies, clopidogrel was suggested before and post-procedure for 6 months. Patients underwent clinical follow-up at 1 and 9 months post-procedure. Clinical follow-up at 1 month included measurement of ABI on the treated side as well as completion of a walking impairment questionnaire. Follow-up at 9 months included measurement of ABI on the treated side as well as completion of the walking impairment questionnaire, and an ultrasound to evaluate patency. In addition, patients were contacted by telephone at 6 months post-procedure. All data were recorded on case report forms at the investigative sites. Independent core laboratories were to analyze angiographic and ultrasonic imaging.

Results

The primary study endpoint is the major adverse event (MAE) rate occurring within 9 months post-procedure. Major adverse events include death, MI (non-Q-wave and Q-wave), target lesion

revascularization, and limb loss on the same side as the treated lesion. Success of the study required that the MAE rate be less than or equal to a predetermined objective performance criterion (OPC) of 16%. All MAEs were also adjudicated with respect to their relationship to the study device by an independent Clinical Events Committee.

Table 6 presents the adverse events and complications reported in the pivotal study. Events that occurred while the patients were hospitalized and cumulative events through 9 months post-implant are presented. There were a total of 8 deaths, 3 myocardial infarctions (MI), 1 target lesion revascularization, and 1 limb loss. Two patients experienced 2 events each as discussed below. All patients have completed their 9-month follow-up or reached a study endpoint. Five (5) of the 151 patients (3.3%) have been confirmed as withdrawn or lost to follow-up. Therefore, there were 146 evaluable patients available for assessment of MAE within the entire 9-month follow-up period. This number (146) exceeds the sample size of 130 patients determined *a priori* to be necessary to provide at least 80% power for this measure.

Table 6: Adverse events/complications observed in patients implanted with the Zilver Vascular stent

Adverse Event/Complication	In-Hospital	Cumulative thru 9 Months
Death[1]	2.6% (4/151)	5.3% (8/151)
MI (Non-Q-Wave and Q-Wave)[1]	0.7% (1/151)	2.0% (3/151)
Target Lesion Revascularization	0.0% (0/151)	0.7% (1/151)
Limb Loss[1]	0.0% (0/151)	0.7% (1/151)
Arterial Aneurysm/Rupture	0.0% (0/151)	0.0% (0/151)
Blood Loss Requiring Transfusion	3.3% (5/151)	4.6% (7/151)
Blue Toe Syndrome	0.0% (0/151)	0.7% (1/151)
Drug/Allergic Reactions Requiring Antibiotics	0.7% (1/151)	0.7% (1/151)
Embolism	0.0% (0/151)	0.0% (0/151)
Hematoma at Access Site Requiring Intervention	1.3% (2/151)	1.3% (2/151)
Hemorrhagic Stroke with Deficit	0.0% (0/151)	0.0% (0/151)
Iliac Artery Spasm	0.0% (0/151)	0.0% (0/151)
Iliofemoral Bypass Graft Surgery	0.0% (0/151)	1.3% (2/151)
Infection/Abscess Formation	0.0% (0/151)	3.3% (5/151)
Pseudoaneurysm or AV Fistula at the Access Site	2.0% (3/151)	3.3% (5/151)
Thrombosis of Culprit Lesion	0.0% (0/151)	0.7% (1/151)
Tissue Necrosis Requiring Debridement	0.7% (1/151)	4.0% (6/151)
Worsened Claudication/Rest Pain	0.7% (1/151)	7.3% (11/151)

[1]Two patients experienced multiple major adverse events. One patient had a non-Q-wave MI on day 87 followed by a limb loss on day 119; and another had an MI on day 3 followed by death on day 8.

Rates for CEC-adjudicated related events, as well as total events, are shown in Table 7. Of primary interest is the MAE rate at 9 months post-procedure for events adjudicated by the Clinical Events Committee as related to the device or the procedure. This rate is 2.7% (4/146). For related and non-related events combined, the total MAE rate is 7.5% (11/146). These study results demonstrate that the MAE rate of the Zilver Vascular Stent is not greater than the target value of 16%.

Table 7: Summary of protocol-defined major adverse events observed in 146 patients implanted with the Zilver Vascular stent

Major Adverse Event	Related Events (CEC-Adjudicated)		All Events	
	N	%	N	%
Death[1]	3	2.0	8	5.5
MI (Non-Q-Wave and Q-Wave)	0	0.0	1	0.7
TLR	1	0.7	1	0.7
Limb Loss[2]	0	0.0	1	0.7
Total	4	2.7	11	7.5

[1]One patient experienced an MI 5 days prior to the death.

[2]One patient experienced a non-Q-wave MI 32 days prior to the limb loss.

Table 8 focuses on all (related and non-related) observed major adverse events and demonstrates that for evaluable patients (n=146), the MAE rate is 7.5% (11 of 146). A more conservative analysis of all evaluable patients counts all patients who withdrew from the study and all who were lost to follow-up as Major Adverse Events. In this conservative approach, the MAE rate becomes 10.6% (16 of 151). By both methods of analysis, the MAE point estimate rate is below the OPC target value of 16%. This indicates that the primary study endpoint was met.

Table 8: Rates for all major adverse events within 9 months post-procedure

	Pivotal Study Result		OPC	
	Point Estimate	2-sided 95% CI Upper Bound	Target Value	Upper Limit
All enrolled patients[1]	16/151 (10.6%)	16.6%		
Evaluable patients[2]	11/146 (7.5%)	13.1%	16%	25%

[1]Five patients who could not be assessed at 9 months (i.e., 1 withdrawn and 4 lost to follow-up) were imputed as experiencing MAE as a worst case analysis.

[2]Major adverse events in 7 of the 11 patients reported with MAE were adjudicated by an independent Clinical Events Committee as not related to the device or the procedure.

Effectiveness of the Zilver Vascular Stent was confirmed by clinical and imaging assessment post-procedure and at follow-up time points. Effectiveness measures included acute procedure success, 30-day clinical success, ankle-brachial index, patency, and 9-month functional status measured by the walking impairment questionnaire. These measures are summarized in Table 9.

Table 9: Effectiveness measures for patients implanted with the Zilver Vascular stent

Effectiveness Measure	Pre-Procedure	Post-Procedure	One-Month	Nine-Month
Acute Procedure Success		93.3% (140/150)[1]		
30-day Clinical Success			94.0% (141/150)	
ABI[2]	0.68 ± 0.23 (N=154)	0.88 ± 0.29 (N=152)	0.86 ± 0.20 (N=140)	0.87 ± 0.21 (N=137)
Patency of Stented Lesion		99.2% (123/124)		92.9% (105/113)
Walking Distance Score	20.1 ± 28.8 (N=147)		63.5 ± 38.3 (N=138)	55.8 ± 40.1 (N=124)
Walking Speed Score	25.6 ± 29.2 (N=141)		63.1 ± 37.4 (N=131)	56.7 ± 37.5 (N=119)

[1]One patient was excluded from the analysis due to placement of a non-study stent during the procedure.

[2]There were 177 treated lesions in the study that occurred in 170 limbs.

N=number of limbs treated.

Acute procedure success was defined in the protocol as "vessel with <30% residual stenosis determined angiographically immediately after stent placement and no major clinical events before discharge." Furthermore, patients with multiple treated vessels are considered to be acute procedure failures if any of their treated vessels are ≥30% stenosed. The acute procedure success was 93.3% for the pivotal study. Ten patients experienced acute procedure failure. Six of the 10 failures had ≥30% residual stenosis, and the remaining 4 patients experienced major adverse events (3 deaths and 1 MI) prior to hospital discharge. Two of the 3 deaths, and the MI, were adjudicated as procedure-related by the Clinical Events Committee.

Thirty-day clinical success was defined in the protocol as "vessel with <30% residual stenosis immediately after stent placement and no major clinical events within 30 days of implant." Thirty-day clinical success was 94.0% for the pivotal study. Nine patients out of the ten patients that were considered to be acute procedure failures were also 30-day clinical failures.

ABIs were measured pre-procedure, post-procedure, and at 1- and 9-month follow-up. ABI was seen to improve from pre- to post-procedure, as well as from pre-procedure to 1-month and 9-month follow-ups. After the procedure, ABI was little changed at 1-month follow-up and 9-month follow-up relative to the post-procedure value. These findings suggest that the improvement achieved immediately after stent placement is maintained up to 9 months post-procedure.

Ultrasound was performed no more than 3 days post-procedure and at 9-month follow-up to assess treated vessel patency within the stented region. Patency rates were high both post-procedure and at the 9-month follow-up (99.2% and 92.9%, respectively). Imaging was not performed, or was inadequate for assessment, for 53 lesions immediately post-procedure and for 52 lesions at follow-up.

The Walking Impairment Questionnaire is a measure of patient-perceived walking performance for patients with PAD and/or intermittent claudication. Distance and speed scores are calculated by expressing each patient's score as a percentage of the maximum score possible, with higher scores indicating a patient's perception of greater walking distance and/or speed. Table 9 presents the walking distance and speed scores pre-procedure, at 1-month follow-up, and 9-month follow-up. The walking distance and speed both increased from pre-procedure to 1-month follow-up, and from pre-procedure to 9-month follow-up. From 1- to 9-month follow-up there is a slight decrease in both scores. These decreases may be due to progression of the disease rather than directly related to stent performance. More importantly, walking distance and speed at 9-month follow-up continues to be improved relative to pre-procedure values.

Sub-analysis of Patients with Overlapping Stents

According to the study protocol, patients were eligible to receive up to 2 stents per lesion. As a result, some patients received overlapping stents to treat a single lesion. Twenty-four patients (15.9%) received at least 1 pair of overlapping stents. Comparisons were made between results from patients with non-overlapping stents and patients with overlapping stents. Patients with overlapping stents were slightly older with a greater proportion of males. Although patients with overlapping stents had a lower incidence of diabetes, they had a greater incidence of high cholesterol, hypertension, and carotid, renal, and pulmonary disease. Of the 11 major adverse events that occurred within 9 months post-procedure, 4 of the events occurred in patients with overlapping stents. However, according to the CEC, none of these 4 events were iliac repair related. Acute procedure success rate and 30-day clinical success were 87.5% and 91.7%, respectively, for patients with overlapping stents. Trends in ABIs were similar to patients with non-overlapping stents, showing an increase in ABI pre-procedure to post-procedure and maintenance of ABI post-procedure to 9-month follow-up. Treated vessel patency was high for patients with overlapping stents post-procedure and at 9-month follow-up (100% and 82.4%, respectively). Of those patients with overlapping stents, imaging was not performed, or was inadequate for assessment, for 13 lesions immediately post-procedure and for 11 lesions at follow-up. Walking impairment scores, including distance and speed, improved for patients with overlapping stents from pre-procedure to 1-month follow-up and pre-procedure to 9-month follow-up. From 1- to 9-month follow-up time points, patients with overlapping stents had no significant changes in their walking distance and speed scores. In summary, despite more prevalent comorbid conditions, effectiveness measures such as acute procedure success, 30-day clinical success, ABIs, patency, and walking distance and speed scores were improved for patients with overlapping stents. These measures are summarized in Table 10.

Table 10: Effectiveness measures for patients implanted with overlapping Zilver Vascular stents

Effectiveness Measure	Pre-Procedure	Post-Procedure	One-Month	Nine-Month
Acute Procedure Success		87.5% (21/24)		
30-day Clinical Success			91.7% (22/24)	
ABI[1]	0.65 ± 0.24 (N=24)	0.84 ± 0.28 (N=23)	0.86 ±0.26 (N=23)	0.80 ±0.24 (N=18)
Patency of Stented Lesion		100% (20/20)		82.4% (14/17)
Walking Distance Score	20.7 ± 30.7 (N=24)		53.5 ±43.3 (N=24)	52.8 ± 40.0 (N=17)
Walking Speed Score	17.2 ± 25.0 (N=20)		55.9 ± 44.3 (N=22)	48.3 ± 42.8 (N=16)

[1]N=Number of limbs treated.

Prospective Analysis (Above-the-Knee Femoropopliteal Artery Studies)

To support the safety and effectiveness of the Zilver Flex stent in the treatment of above-the-knee femoropopliteal arteries, a prospective analysis of clinical data from three previously completed clinical studies was conducted. These clinical studies included the bare metal stent (i.e., Zilver Flex) arm of the Zilver PTX randomized controlled trial (RCT) in the U.S., Germany and Japan, the Zilver Flex Vascular Stent Study in Germany, and the Zilver Flex Post-Market Study (PMS) in Japan (Zilver Flex Japan PMS). In these studies, the Zilver Flex stent was utilized for the treatment of de novo or restenotic lesions of the above-the-knee femoropopliteal artery. In the Zilver PTX RCT and the Zilver Flex Vascular Stent Study, inclusion and exclusion criteria were generally consistent; there were

no exclusion criteria for the Zilver Flex Japan PMS but enrollment of symptomatic patients. A brief overview of the three Zilver Flex stent clinical studies is summarized in Table 11 below.

Table 11: Zilver Flex stent clinical study overview

	Zilver PTX RCT (Zilver Flex patients)	Zilver Flex Vascular Study	Zilver Flex Japan PMS
Purpose	Patients experiencing acute PTA failure in the Zilver PTX RCT underwent secondary randomization. Long-term safety and effectiveness of Zilver Flex in treatment of de novo or restenotic lesions of above-the-knee femoropopliteal arteries.	Prospective, single arm post market study of the safety and long-term effectiveness of the Zilver Flex stent for the treatment of de novo or restenotic lesions of the above-the-knee femoropopliteal artery.	Prospective, single arm post market study to collect real world data and evaluate the long-term safety and effectiveness of the Zilver Flex stent in the above-the-knee femoropopliteal artery.
Number of patients / Number of lesions	55/57	110/112	188/200
Key study criteria	• De novo or restenotic lesion with ≥50% diameter stenosis • No prior stent in lesion • Lesion length ≤ 140 mm	• De novo or restenotic lesion with ≥50% diameter stenosis • No prior stent in lesion • Up to two stents placed to treat the lesion	• No exclusion criteria • Consecutive patients with symptomatic peripheral arterial disease involving the above-the-knee femoropopliteal arteries were enrolled
Devices used	5–8 mm diameters 20–80 mm lengths	5–8 mm diameters 40–200 mm lengths	6–8 mm diameters 20–140 mm lengths
Safety and effectiveness data collected	•Target lesion revascularization •Thrombosis •Stent integrity •Primary patency •Clinical improvement •Clinical benefit •Vascular adverse events	• Target lesion revascularization • Thrombosis • Stent integrity • Primary patency • Clinical improvement • Clinical benefit • Vascular adverse events	• Target lesion revascularization • Thrombosis • Stent integrity • Primary patency • Clinical improvement • Clinical benefit • Vascular adverse events
Follow-up	5 years	5 years	3 years
Safety oversight	CEC; DSMB Site adjudication for device and procedure related adverse events	CEC; DSMB Site adjudication for device and procedure related adverse events	CEC[1] Site adjudication for device and procedure related adverse events
Imaging review	Independent core laboratory: duplex ultrasound, angiography, and X-ray	Independent core laboratory: duplex ultrasound, angiography, and X-ray	Site: site-assessed stent fractures were sent to an independent core laboratory for review
Study compliance	ICH GCP, JGCP, ISO 14155, 21 CFR 812, 21 CFR 56, 21 CFR 50	ICH GCP, JGCP, ISO 14155, 21 CFR 812	Japanese Good Postmarket Surveillance Practice Regulations
NCT number	NCT00120406	NCT00827619	NCT02254356

[1]All deaths reported in the Zilver Flex Japan PMS were adjudicated by the CEC; adverse events were not adjudicated by the CEC.

Analysis Endpoints

The primary safety endpoint was defined as the combined rate of freedom from all-cause death, amputation, or target vessel revascularization (TVR) at 30 days. The VIVA performance goal was prospectively chosen to evaluate safety of the Zilver Flex stent for the above-the-knee femoropopliteal arteries in the as-treated patient population. In this approach, safety was assessed by comparing the combined rate of freedom from all-cause death, amputation, or TVR at 30 days post-procedure for the Zilver Flex Vascular Stent to the VIVA performance goal of 88%. Using the VIVA performance goal of 0.88, an alpha of 0.025, a power of 0.8, and an exact one sided test for superiority, the minimum required sample size was 29 patients.

The primary effectiveness endpoint was defined as 1-year freedom from target lesion revascularization (TLR). The SPEED Objective Performance Goal (OPG) for the SFA was prospectively

chosen to evaluate effectiveness of the Zilver Flex stent for the above-the-knee femoropopliteal arteries in the as-treated patient population. In this approach, effectiveness was assessed by comparing the 1 year freedom from TLR rate for all patients with an SFA lesion treated with the Zilver Flex Vascular Stent to the SPEED OPG of 83.2%, with a margin of 5%, making the null proportion equal to 78.2%. Using the SPEED OPG of 0.832 for BMS, a margin of 0.05, an alpha of 0.025, a power of 0.8, and an exact one-sided test, the minimum required sample size was 206 patients.

Analysis Results in the Combined Clinical Cohort

The Zilver Flex Vascular Stent was used to treat 353 patients with 369 de novo or restenotic lesions of the above-the-knee femoropopliteal artery in a combined clinical cohort from three clinical studies. The number of patients exceeded the minimum sample size required to analyze the endpoints.

A total of 533 Zilver Flex stents were implanted during the index procedure in the combined clinical cohort. The device sizes used span the range of available device sizes, both in stent diameter and in stent length. In the combined clinical cohort, a mean number of 1.6 ± 0.8 stents were implanted per patient and a mean number of 1.4 ± 0.7 stents were implanted per lesion.

The mean patient age was 70.4 ± 10 years (range: 40-94 years). The majority of patients were male (71.1%) and had claudication (Rutherford classification 0-3, 77.8%) at baseline. The average lesion length was 107.3 ± 81.3 mm. Baseline patient demographics, medical history, and lesion characteristics for the combined clinical cohort are shown in Tables 12 and 13.

Table 12. Demographics and medical history

Baseline Variable	Combined Cohort (N = 353)
Age (years, mean ± SD (N, range))	70.4 ± 10 (353, 40–94)
Male	71.1% (251/353)
Myocardial infarction[1]	14.5% (24/165)
Congestive heart failure[1]	6.1% (10/165)
Diabetes	43.9% (155/353)
Type I[1]	3.9% (6/152)
Type II[1]	96.1% (146/152)
Hypercholesterolemia	57.5% (203/353)
Hypertension	79.0% (279/353)
Carotid disease	39.1% (95/243)
Renal disease	34.2% (83/243)
Chronic renal failure[1]	36.4% (68/187)
Pulmonary disease	8.5% (30/353)
Smoking	
Never	25.2% (89/353)
Quit/Past	44.8% (158/353)
Current	30.0% (106/353)
Rutherford Classification[1]	
0–3	77.8% (263/338)
4–6	22.2% (75/338)

[1]Data not available for all patients.

Table 13: Baseline lesion characteristics (best available)

Lesion Characteristic	Combined Cohort (N = 369)
Lesion length (mm, mean ± SD (n, range))	107.3 ± 81.3 (369, 7–393)
RVD (mm, mean ± SD (n, range))	5.4 ± 1.0 (369, 2–8.4)
Percent diameter stenosis (%, mean ± SD (n, range))	90.5 ± 12.4 (369, 41.1–100)

The primary safety analysis was based on the combined rate of freedom from all-cause death, amputation, or TVR at 30 days post-procedure for the Zilver Flex Vascular Stent. At 30 days, 98.0% of patients (346/353) treated with the Zilver Flex Vascular Stent remained free from death, amputation, or TVR. Through 30 days, there were four amputations and three TVR events in the 353 patients; there were no deaths. The combined rate of freedom from all-cause death, amputation, or TVR at 30 days

post-procedure compares favorably to the established VIVA performance goal of 88%, with a *p*-value <0.01 indicating that the performance goal for safety was met.

The primary effectiveness analysis was based on the 12-month freedom from TLR rate for the Zilver Flex Vascular Stent. TLR was defined as a reintervention performed for ≥50% diameter stenosis within ± 5 mm of the study lesion after recurrent clinical symptoms of PAD. At 12 months, 87.2% of patients (307/352) treated with the Zilver Flex Vascular Stent were free from TLR. The rate of freedom from TLR is high with a lower bound of the 95% confidence interval (CI) exceeding the derived performance goal of 78.2%, indicating that the effectiveness endpoint met the pre-defined criteria.

Table 14 outlines the primary safety and effectiveness outcomes and additional safety and effectiveness outcomes (namely, 12-month measures of freedom from thrombosis, stent integrity, all-cause mortality, primary patency, clinical improvement, and clinical benefit) from the combined clinical cohort treated with the Zilver Flex Vascular Stent. Taken together, these 12-month clinical outcomes support the safety and effectiveness of the Zilver Flex Vascular Stent for treatment of patients with lesions of the above-the-knee femoropopliteal artery.

Table 14: Results for outcomes assessed

Outcome Assessed	Definition	Results (n/N) or (# events, # patients at risk)
Safety Outcomes		
Primary safety: 30-day safety	Freedom from all-cause death, amputation, or TVR at 30 days post-procedure.	98.0% (346/353)
12-month freedom from thrombosis[1]	Based on imaging or clinically proven complete occlusion of the study lesion occurring post-index procedure.	98.8% (4, 304)
12-month stent integrity[1]	Freedom from stent fracture through 12 months.	99.6% (2, 464)
12-month all-cause mortality[1]	Death through 12 months.	3.0% (10, 308)
Effectiveness Outcomes		
Primary effectiveness: 12 month freedom from TLR[1]	Freedom from reintervention performed for a ≥ 50% stenosis within ±5 mm of the study lesion after recurrent clinical symptoms of PAD.	87.2% (307/352) 89.1% (35, 277)
12-month primary patency[1]	Assessed by duplex ultrasound (peak systolic velocity ratio (PSVR) ≤ 2.4) and/or angiography (< 50% stenosis) and the absence of reintervention within the study lesion post-index procedure. In the absence of a duplex ultrasound with a PSVR, a best available assessment of patency was used.	85.9% (46, 249)
12-month clinical improvement	An improvement in Rutherford score by at least 1 class between pre-procedure and the 12-month clinical assessment.	84.7% (222/262)
12-month clinical benefit[1]	Freedom from persistent or worsening symptoms of ischemia (i.e., claudication, rest pain, ulcer or tissue loss) after the initial study treatment.	93.5% (21, 291)

[1] Kaplan-Meier estimate

Table 15 shows effectiveness outcomes through 3 years. The long-term clinical outcomes support the effectiveness of the Zilver Flex stent for treatment of patients with lesions of the above-the-knee femoropopliteal artery.

Table 15: Outcomes assessed through 3 years

Long-term Outcome		Kaplan-Meier Estimate (# events, # patients at risk)
2-year outcomes	Freedom from TLR	82.1% (56,228)
	Clinical benefit	90.4% (30,249)
3-year outcomes	Freedom from TLR	79.2% (63,155)
	Clinical benefit	89.6% (32,179)

EN This symbol indicates the wire guide size

Rx ONLY

STERILE | EO

COOK IRELAND LTD.
O'Halloran Road
National Technology Park
Limerick, Ireland

cookmedical.com

IFU0073-6

2025-09