

## Summary of Safety and Effectiveness Data (SSED)

### I. GENERAL INFORMATION

Device Generic Name:	Product Code: NIP – Stent, Superficial Femoral Artery
Device Trade Name:	EverFlex™ Self-Expanding Peripheral Stent System
Applicant Name and Address:	ev3 Inc. 3033 Campus Drive, Suite, #N550 Plymouth, MN 55441
Premarket Approval Application (PMA) Number:	P110023
Date of Panel Recommendation:	N/A
Date of Notice of Approval to Application:	March 7, 2012
Expedited:	Not applicable

### II. INDICATION FOR USE

The EverFlex™ Self-Expanding Peripheral Stent System is intended to improve luminal diameter in the treatment of symptomatic *de novo* or restenotic lesions up to 180mm in length in the native Superficial Femoral Artery (SFA) and/or proximal popliteal arteries with reference vessel diameters ranging from 4.5 – 7.5mm.

### III. CONTRAINDICATIONS

- Patients with known hypersensitivity to nickel-titanium
- Patients in whom anticoagulant and/or antiplatelet therapy is contraindicated
- Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or stent delivery system

#### IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the EverFlex™ Self-Expanding Peripheral Stent System labeling (Instructions for Use).

#### V. DEVICE DESCRIPTION

The EverFlex™ Self-Expanding Peripheral Stent System (EverFlex) consists of a self-expanding Nitinol stent premounted on an over-the-wire stent delivery system. The EverFlex stent is a flexible self-expanding Nitinol (nickel-titanium alloy) stent provided in multiple lengths and diameters. **Table 1** lists the available stent diameters and lengths for the EverFlex™ Self-Expanding Peripheral Stent System.

**Table 1: EverFlex Stent Diameters and Lengths**

		Stent Length (mm)								
		20	30	40	60	80	100	120	150	200
Stent Diameter (mm)	6	x	x	x	x	x	x	x	x	x
	7	x	x	x	x	x	x	x	x	x
	8	x	x	x	x	x	x	x	x	x

The stent is laser machined from a continuous non-welded (seamless) piece of Nitinol tubing into an open lattice design. The EverFlex stent cell geometry includes three wave peaks between connection bridges and uses an alternating off-line pattern for the connection bridges which is intended to increase stent flexibility. Tantalum radiopaque markers are located on both ends of the stent to aid in visualization.

The stent is pre-mounted on an 80 or 120 cm working length 6F, .035" over-the-wire (OTW) stent delivery system that is comprised of multiple components as shown in **Figure 1**. Radiopaque markers on the stent delivery system aid in the accurate placement of the stent. Deployment is achieved by pulling the distal delivery system handle proximally, which retracts the outer sheath. The delivery system radiopaque stent retainer holds the stent stationary until the outer sheath is fully retracted to facilitate accurate placement. Upon deployment, the stent achieves its predetermined diameter and exerts a constant outward force to maintain patency in the target vessel.

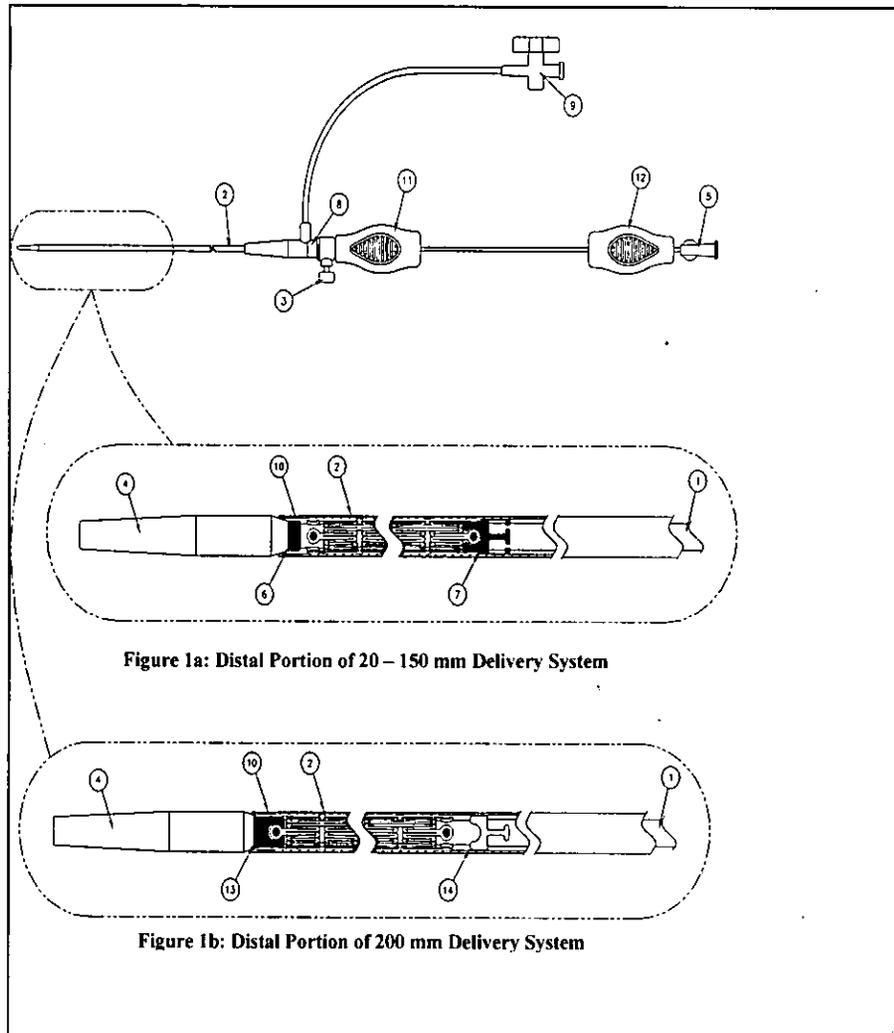


Figure 1a: Distal Portion of 20 – 150 mm Delivery System

Figure 1b: Distal Portion of 200 mm Delivery System

Figure 1 – Delivery System

- |  |   |
|--|---|
| 1. Inner Subassembly                               | 8. Manifold Subassembly                           |
| 2. Outer Subassembly                               | 9. Stopcock                                       |
| 3. Safety Lock                                     | 10. Outer Subassembly Distal Marker Band          |
| 4. Distal Catheter Tip                             | 11. Distal Grip                                   |
| 5. Proximal Hub                                    | 12. Proximal Grip                                 |
| 6. Inner Subassembly Distal Marker Band            | 13. Inner Subassembly Distal Marker Band/Retainer |
| 7. Inner Subassembly Proximal Marker Band/Retainer | 14. Inner Subassembly Proximal Marker/Holder      |

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative practices and procedures for treatment of atherosclerotic disease of the superficial femoral and proximal popliteal arteries include: non-invasive lifestyle modifications (e.g., exercise, weight control, cessation of smoking) and drug therapy, minimally invasive endovascular intervention (e.g., balloon angioplasty, stent placement using other FDA-approved peripheral stents, atherectomy), or surgical bypass.

Each alternative has its own advantages and disadvantages. A patient should fully discuss those alternatives with his/her physician to select the method that best meets expectations and lifestyle.

## **VII. MARKETING HISTORY**

The EverFlex<sup>®</sup> Self-Expanding Peripheral Stent System presented in this PMA is identical to the Protégé<sup>®</sup> EverFlex<sup>™</sup> Self-Expanding Peripheral Stent System commercially available in the EU and the Protégé<sup>®</sup> EverFlex<sup>™</sup> Self-Expanding Biliary Stent System commercially available in the United States. The Protégé<sup>®</sup> EverFlex<sup>™</sup> Self-Expanding Peripheral Stent System has been commercially available in the European Union (EU) since March 2006. The Protégé<sup>®</sup> EverFlex<sup>™</sup> Self-Expanding Biliary Stent System has been commercially available in the United States since March, 2006. The Protégé<sup>®</sup> EverFlex<sup>™</sup> Self-Expanding Peripheral Stent System and the Protégé<sup>®</sup> EverFlex<sup>™</sup> Self-Expanding Biliary Stent System are approved for commercial use in the European Union (EU), Australia, New Zealand, Canada and in additional countries across Asia, Latin America and the Middle East.

The Protégé<sup>®</sup> EverFlex<sup>™</sup> Self-Expanding Stent Systems remain in continuous distribution since commercial introduction and have not been withdrawn from marketing in any country.

## **VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

The potential adverse effects (e.g., complications) that may occur and/or require intervention with the use of this device include, but are not limited to:

- Abrupt or sub-acute closure
- Allergic reaction to device materials or procedure medications
- Allergic reaction to Nitinol
- Amputation
- Aneurysm
- Angina
- Arrhythmia
- Arterio-venous fistula
- Artery perforation or rupture
- Bleeding requiring transfusion
- Bruising
- Contrast medium reaction/renal failure
- Death
- Device breakage
- Dissection or intimal flap
- Edema
- Embolism
- Failure to deploy stent
- Fever
- Gastrointestinal bleeding due to anticoagulation
- Hematoma
- Hypertension/Hypotension
- Infection
- Inflammation
- Intraluminal thrombus
- Myocardial Infarction
- Pain
- Partial stent deployment
- Pseudoaneurysm
- Renal failure requiring dialysis
- Renal insufficiency (new or worsening)
- Restenosis
- Sepsis
- Shock
- Stent collapse or fracture
- Stent migration
- Stent misplacement
- Stroke
- Surgical or endovascular intervention
- Thrombosis/occlusion of the stent
- Transient Ischemic Attack
- Venous Thromboembolism
- Vessel spasm

For the adverse events that occurred in the clinical study, please see Section X below.

## **IX. SUMMARY OF PRECLINICAL STUDIES**

### **A. Biocompatibility**

Biocompatibility testing was conducted on the EverFlex™ Self-Expanding Peripheral Stent System. Testing was conducted in accordance with applicable Good Laboratory Practices (21 CFR §58) and ISO 10993-1: 2003 *Biological Evaluation of Medical Devices*. The EverFlex stent was classified per ISO 10993-1, *Biological Evaluation of Medical Devices* as an implant device in permanent contact (> 30 days) with blood. The EverFlex stent delivery system was classified as an externally communicating device in limited contact (< 24 hrs.) with circulating blood. All test results demonstrate that the materials and processes used to manufacture the EverFlex stent and stent delivery system produce a finished device that is biocompatible and suitable for its intended use. **Table 2** summarizes the testing completed on the EverFlex stent and EverFlex stent delivery system.

**Table 2: Summary of Biocompatibility Testing**

Test Performed	Test Description	Stent	Delivery System	Results
Cytotoxicity	ISO MEM Elution Assay with L-929 Mouse Fibroblast Cells	X	X	Pass (Non-toxic)
Sensitization	ISO Guinea Pig Maximization Test (method for biomaterial extracts)	X	X	Pass (Non-sensitizing)
Irritation	ISO Intracutaneous Reactivity Test (Irritation)	X	X	Pass (Non-irritant)
Systemic Toxicity	ISO Acute Systemic Injection Test	X	X	Pass (Non-toxic)
Pyrogenicity	Materials Mediated Rabbit Pyrogen Test	X	X	Pass (Non-pyrogenic)
Hemocompatibility	ASTM Hemolysis Assay – Direct Contact Method	X	N/A	Pass (Non-hemolytic)
Hemocompatibility	ASTM Hemolysis Assay – Extract Method	X	X	Pass (Non-hemolytic)
Hemocompatibility	Complement Activation C3a and SC5b-9	X	X	Pass (Non-activator)
Hemocompatibility	4-Hour Thromboresistance Evaluation in Dogs	Note <sup>1</sup>	X	Pass
Hemocompatibility	Partial Thromboplastin Time (PTT)	N/A	X	Pass
Hemocompatibility	Platelet and Leukocyte Counts	N/A	X	Pass

<sup>1</sup> Evaluated as part of *in vivo* study

Stent thrombogenicity was evaluated as part of other *in vivo* studies conducted to evaluate the safety and effectiveness of the device. The omission of genotoxicity, sub-chronic toxicity, chronic toxicity and carcinogenicity was justified due to the extensive clinical history of the device materials and their well-characterized long-term safety profile, as well as information regarding the processing of the finished device.

The test results demonstrate that the EverFlex stent and stent delivery system are biocompatible and non-pyrogenic.

## **B. In Vitro Product Testing**

*In vitro* bench testing to support the EverFlex™ Self-Expanding Peripheral Stent System was developed based on the device risk assessment and is consistent with FDA *Non-Clinical Tests and Recommended Labeling of Intravascular Stents and Associated Delivery Systems*, April 18, 2010. Because EverFlex is a self-expanding stent, tests recommended specifically for balloon-expandable stents were not conducted. A summary of the tests performed and associated results are provided in **Table 3**.

**Table 3: Summary of In Vitro Product Testing**

Test	Clinical or Functional Relevance	Acceptance Criteria	Summary of Results
Material Composition	Characterize the stent material compositions to assure it is acceptable for the intended use.	Must conform to ASTM F2063 material standards	The stent materials conform to implant material standards ASTM F2063-05 for material composition.
Shape, Memory & Elasticity	The stent must exhibit super elastic properties <i>in vivo</i> and expands to its specified size and shape.	Af temperature must fall within finished stent specification range of 6-32° C	Stents were tested and met established specifications for austenitic finish temperature and the stent exhibits expected shape memory properties.
Corrosion Resistance	The stent must resist corrosion following implantation.	Breakdown potential Eb > 600m ASTM F2129-08	The stent met established specifications for corrosion resistance based on ASTM F2129-08.
Fretting Corrosion	The stent must resist corrosion following implantation due to wear of mated surfaces when overlapped with another stent.	Scanning Electron Microscopy (SEM) analysis showing comparable or less wear than stents from previous accelerated durability testing with successful corrosion resistance results	The stent met the established criteria for fretting corrosion following accelerated durability testing in an overlapped configuration.
Dimensional Verification	The stent diameter must be uniform to achieve adequate wall apposition.	<u>6mm x 20-150mm</u> 0.236" ± 0.012" <u>6mm x 200mm</u> 0.224" – 0.248" <u>8mm x 20-150mm</u> 0.315" ± 0.012" <u>8mm x 200mm</u> 0.303" – 0.327"	The stent dimensions were verified post-deployment and met the established acceptance criteria.
Percent Surface Area of Stent	The metal coverage of the stent must provide sufficient vessel wall contact to help maintain patency.	6-8mm 21 – 27 ± 2%	The stent metal coverage was calculated and met the established design inputs.
Foreshortening	The stent must exhibit minimal foreshortening to assure accurate stent deployment and predictable deployed stent length for the user.	20-150mm: < 10% 200mm: < 5%	Stent lengths were measured in the loaded and unloaded condition. Results showed minimal stent foreshortening and no adverse affect on deployment accuracy or deployed stent length.

Test	Clinical or Functional Relevance	Acceptance Criteria	Summary of Results
Stent Integrity	Post deployment the stent must be free of defects or cracks that may affect long-term performance outcomes.	No cracks or surface defects at 20-40x magnification	Stents were tested and met the established acceptance criteria.
Radial Outward Force	To characterize the force produced by the stent as a function of diameter and assure the force is acceptable for the intended use.	$\geq 3.03$ g/mm	Stents were tested and met the established acceptance criteria were met.
Mechanical Properties	Characterize the stent materials mechanical properties to assure they are acceptable for the intended use.	ASTM F2063-05	The stent materials conform to implant material standards ASTM F2063-05 for mechanical properties.
Strain and Fatigue Analysis/Finite Element Analysis (FEA)	To evaluate strains the stent experiences during processing, deployment and <i>in vivo</i> conditions. To assure the stent does not experience unreasonable strains for the material or the intended use.	Safety Factor >1	Finite element analysis (FEA) results showed strains reasonable for the material and worst-case SFA loading conditions for a ten-year period.  The safety factor is > 1.0.
Accelerated Durability Testing - radial pulsatile loading	The durability of the stent must be tested to assure <i>in vivo</i> real-time use that simulates blood pressure conditions in the human body do not result in stent fractures following 10 years of simulated use.	No Type III, IV or V fractures after 400 million cycles	Following 10 years of simulated use, the results indicated that the stents met the established acceptance criteria.
Accelerated Durability Testing – multi-axial loading	The stent must resist fatigue under simulated <i>in vivo</i> radial loading conditions for an equivalent of 10 years of implant life in both single and overlapped stent conditions	No Type III, IV or V fractures after 10 million cycles	Following 10 years of simulated use, the stents met the established acceptance criteria.
MR Compatibility	To evaluate the MRI safety and compatibility of the implantable stent and ensuring that the stent is not affected by scanning at 1.5 Tesla and 3.0 Tesla field strengths	The presence of the stent must not pose an additional unacceptable risk to patients when subjected to 1.5T and 3.0T magnetic fields	Test results demonstrate the stent does not pose additional risk to patients and may be labeled MR Conditional according to ASTM 2503-05.
Radiopacity	Stent must be visible using angiographic imaging.	Stent visibility was rated on a 1-5 scale with 1 being excellent. Must receive $\leq 3$ to pass	Radiopacity was evaluated during animal studies. Results demonstrated adequate stent visibility using angiographic imaging.

Test	Clinical or Functional Relevance	Acceptance Criteria	Summary of Results
Crush Resistance	The stent must resist localized compression force and return to its original shape.	Crush resistance $\geq 0.07$ lbf.	Stents were tested and met the established acceptance criteria.
Kink Resistance	The stent must be able to reach a radius of curvature suitable for the intended use without kinking.	Smallest kink radius must be $\leq 0.375$ "	Stents were tested and met the established acceptance criteria.
Crossing Profile	To verify the maximum diameter of the stent delivery system and assure compatibility with 6F sheaths.	$\leq 0.0805$ "	Test results met the established acceptance criteria.
Deployment Force	Measure the force required to deploy the stent and verify it meets specifications based on the intended use.	$\leq 3.0$ lbs.	Test results met the established acceptance criteria.
Deployment Accuracy	The delivery catheter must deploy the stent with accuracy at the target location based on the intended use.	Stent must be centered on reference marks within 3mm of the stent nominal implant length	Test results demonstrate the stent may be deployed accurately and met the established acceptance criteria.
Catheter Bond Strengths	Verify the delivery catheter bond strengths meet specifications based on the intended use.	Distal tip to distal inner lumen: $\geq 4.1$ lbs Stainless steel tube to spline: $\geq 2.0$ lbs Distal inner tip tube to spline: $\geq 3.8$ lbs Distal retainer to inner sheath: $\geq 3.0$ lbs <u>200mm Only:</u> Proximal retainer to inner lumen: $\geq 3.0$ Wire lumen to spline tube: $\geq 2.0$	Test results met the established acceptance criteria.
Catheter Flexibility	To verify the stent delivery system is able to flex and track around a bend radius based on the intended use.	The stent/catheter must easily pass through the sheath and around the bend radius without kinking	Test results met the established acceptance criteria.
Torque Strength	Characterize the ability of the	1 rotation	Test results demonstrate

Test	Clinical or Functional Relevance	Acceptance Criteria	Summary of Results
	delivery catheter to withstand torsional forces expected during the intended use.		the delivery catheter withstands expected number of rotations typical for the intended use.

### C. Sterilization, Packaging, & Shelf Life

#### Sterilization

The EverFlex™ Self-Expanding Peripheral Stent System is Ethylene Oxide (EO) sterilized and meets a sterility assurance level (SAL) of 10<sup>-6</sup>. Validation and annual revalidation are completed based on the standards in ISO 11135-1: 2007 *Sterilization of health care products— Ethylene oxide -- Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices Method B: Conservative determination of lethal rate of the sterilization process—overkill approach*.

#### Packaging & Shelf Life

The EverFlex™ Self-Expanding Peripheral Stent System was tested following accelerated aging to an equivalent of three-years under a shelf life protocol. Testing demonstrated that the EverFlex stent and delivery catheter met the established acceptance criteria, and is in compliance with ASTM F1980 for accelerated aging of medical devices. Based on results from this testing, a three-year shelf life was established for the device.

The EverFlex™ Self-Expanding Peripheral Stent System consists of a product tray and a Tyvek pouch. The packaging was tested following accelerated aging to an equivalent of three years under a packaging verification and validation protocol. Test results met the established acceptance criteria. The package testing demonstrated that the packaging system, including the sterile barrier remains intact through sterilization, aging and distribution and is in compliance with ISO 11607-1/2:2006.

### D. Animal Studies

Two *in vivo* studies were performed to demonstrate performance and safety of the EverFlex™ Self-Expanding Peripheral Stent System. Both studies were conducted in accordance with Good Laboratory Practices (GLP) per 21 CFR § 58. **Table 4** provides a summary of the *in vivo* animal testing performed with EverFlex.

**Table 4: Summary of Pre-Clinical Animal Studies**

Study Objective	Study Design	Relevant Findings
<u>Swine Study</u> 1. To evaluate the safety and efficacy of the 20-150mm	<u>Contralateral acute arm</u> evaluated performance of the stent delivery system – 3	All stent delivery and deployment procedures were uneventful with good stent

<p>length EverFlex stent compared to the approved IntraCoil stent</p> <p>2. To evaluate the <i>in vivo</i> performance of the 20-150mm length EverFlex stent and stent delivery system</p>	<p>animals.</p> <p><u>3-day, 30-day, 180-day cohorts</u> evaluated vessel response, stent and delivery system performance and stent fracture resistance – 2, 6, and 6 animals respectively.</p>	<p>apposition and accurate stent delivery. Histologic and morphometric outcomes were generally acceptable and consistent with other animal study outcomes for the vascular region of interest. There were no stent fractures in the 3- and 30-day EverFlex cohort. In the 180-day cohort, 14 of 21 (66%) stents contained fractures.</p>
<p><u>Sheep Study</u></p> <p>1. To evaluate the safety of the 200mm length EverFlex stent</p> <p>2. To evaluate the <i>in vivo</i> performance of the 200mm length EverFlex stent and stent delivery system.</p>	<p><u>Contralateral acute arm</u> evaluated performance of the stent delivery system – 3 animals.</p> <p><u>30-day, 180-day arms</u> delivered from carotid approach; studied stent and delivery system performance and stent fracture resistance – 3 animals w/ 2 stents each in each arm</p>	<p>All stent delivery and deployment procedures were rated as good or better than the control. Histologic and morphometric outcomes were generally acceptable and consistent with other animal study outcomes for the vascular region of interest. Inflammation was acceptably low. Stent fractures were reported in 4 of 8 (50%) of the stented vessels in the 30-day cohort and in 5 of 8 (62%) in the 180-day cohort.</p>

High fracture rates were observed in both animal studies; however, animal studies often present worst case conditions for fracture. For this PMA, the animal testing was comprised of long length stenting and overlapped configurations representing severe anatomic conditions. In addition, experimental studies in small research undulates are often limited by anatomic challenges such as angularity, curvature and taper of the femoral and iliac arteries. Because of the high fracture rates observed in these animal studies and in light of the limitations posed, the available clinical data on stent fracture for the EverFlex stent weighed heavily in the evaluation of fracture rate.

**X. SUMMARY OF PRIMARY CLINICAL STUDY**

Patients were treated between October 26, 2007 and April 23, 2010. The database for this PMA reflected data collected through July 1, 2011 and included 287 subjects. There were 44 investigational sites.

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the EverFlex Nitinol Stent System for improving luminal diameter in the treatment of de novo or restenotic lesions up to 180mm in length in the native superficial femoral artery and/or proximal popliteal arteries with reference vessel diameters ranging from 4.5 – 7.5mm, in the US and Europe under IDE # G070013. Data from this clinical study were the basis for the PMA approval decision. Additional clinical data from two outside the US (OUS) studies (i.e., DURABILITY I and Durability 200) were considered as supporting information. A summary of the IDE clinical study is presented below. The

OUS studies are described in Section XI below.

### A. Study Design

The applicant conducted a study titled the US Study for Evaluating Endovascular Treatments of Lesions in the Superficial Femoral Artery and Proximal Popliteal By using the EverFlex Nitinol Stent System II (DURABILITY II) study. DURABILITY II was a prospective, multi-center, non-randomized, single arm study comparing percutaneous transluminal angioplasty (PTA) and primary stenting with the EverFlex™ stent to performance goals of PTA alone in the treatment of atherosclerotic lesions of the native superficial femoral artery (SFA) or the superficial femoral and proximal popliteal arteries. The safety and effectiveness performance goals were based on an aggregate of published trial data as described by VIVA physicians Inc. (VPI). DURABILITY II was conducted at 40 US and four European investigational sites. A total of 287 subjects were enrolled. Eligible subjects either had stenotic, restenotic (non-stented) or occluded lesions. The reference vessel diameter of the treated subjects was to be 4.5-7.5 mm and the lesion length from 4-18 cm long. Subjects with Rutherford Clinical Categories of 2-4 were included in the study. Subject follow-up occurred at 30 days, 6 months, 1, 2 and 3 years post-procedure. The primary safety endpoint for the study was major adverse event rate at 30 days and the primary effectiveness endpoint was primary stent patency rate at 1 year.

#### 1. DURABILITY II Clinical Inclusion and Exclusion Criteria

Subjects enrolled in the DURABILITY II study were required to meet the following general and angiographic **inclusion** criteria. Potential study Subjects who meet any of the following general and angiographic **exclusion** criteria were not eligible for enrollment in the study

**Table 5: Inclusion and Exclusion Criteria**

Inclusion Criteria	Exclusion Criteria
<ol style="list-style-type: none"> <li>1. Has stenotic, restenotic (from PTA or adjunct therapy, not including stents or stent grafts), or occluded lesion(s) located in the native superficial femoral artery or superficial femoral and proximal popliteal arteries suitable for primary stenting.</li> <li>2. Has a Rutherford Clinical Category Score of 2, 3 or 4.</li> <li>3. Is willing to comply with all follow-up evaluations at the specified times.</li> <li>4. Is ≥ 18 years old.</li> <li>5. Provides written informed consent prior to enrollment in the study.</li> <li>6. Target lesion(s) located within the native SFA/proximal popliteal: distal point at least 3 cm above the cortical margin of the femur and proximal point at least 1 cm below the origin of the <i>profunda femoralis</i> measured by straight</li> </ol>	<ol style="list-style-type: none"> <li>1. Has undergone previous implantation of stent(s) or stent graft(s) in the target vessel.</li> <li>2. Has a contraindication or known allergy to antiplatelet therapy, anticoagulants, thrombolytic drugs, contrast media or any other drug used in study according to the protocol.</li> <li>3. Has known hypersensitivity to nickel-titanium.</li> <li>4. Has bleeding diathesis, coagulopathy, known hypercoagulable condition, or refuses blood transfusion.</li> <li>5. Is female with childbearing potential not taking adequate contraceptives or currently breastfeeding.</li> <li>6. Has life expectancy of less than 1 year.</li> <li>7. Has planned use of cutting balloon, scoring balloon, thrombectomy, atherectomy, brachytherapy or laser devices during procedure.</li> <li>8. Has previously been enrolled in the</li> </ol>

Inclusion Criteria	Exclusion Criteria
<p>posteroanterior (PA) view for distal lesions, ipsilateral oblique view for proximal lesions.</p> <p>7. Evidence of <math>\geq 50\%</math> stenosis or restenosis (from PTA or adjunct therapy, not including stents or stent grafts), or occlusion of target lesion(s).</p> <p>8. Target lesion(s) total length is <math>\geq 4</math> cm and <math>\leq 18</math> cm as determined by a spatially calibrated internal measurement using a device with known distance between radiopaque markers (e.g. marker catheter, balloon catheter, marker wire) and is amenable to stenting with a single stent.</p> <p>9. Target vessel diameter is <math>\geq 4.5</math> mm and <math>&lt; 7.5</math> mm.</p> <p>10. There is evidence of at least one runoff vessel to the ankle/foot of the limb to be treated that does not also require treatment for significant (<math>&gt; 50\%</math> stenosis or occlusion) stenosis during the index procedure.</p>	<p>DURABILITY II study.</p> <p>9. Has received endovascular treatment of target lesion by percutaneous transluminal angioplasty or any other means (except stents/stent grafts) of previous endovascular treatment (e.g. cutting balloon, scoring balloon, cryoplasty, thrombectomy, atherectomy, brachytherapy or laser devices) within six months of the index procedure.</p> <p>10. Has any planned surgical intervention or endovascular procedure 14 days before or 30 days after the index procedure.</p> <p>11. Is currently participating in an investigational drug or another device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints.</p> <p>12. Has one of the following co-morbid conditions:</p> <ul style="list-style-type: none"> <li>◆ History of severe liver disease (i.e. ascites, esophageal varices, liver transplant)</li> <li>◆ Known or suspected active infection</li> <li>◆ Undergoing hemodialysis for kidney failure</li> <li>◆ Undergoing immunosuppressant therapy</li> <li>◆ Elevated creatinine level on most recent test (<math>&gt; 2.5</math> mg/dl)</li> <li>◆ New York Heart Association Classification of III or IV with hospitalization for decompensated heart failure within 3 months</li> <li>◆ Recent (within 30 days) myocardial infarction</li> <li>◆ Recent (within 30 days) hemorrhagic or ischemic stroke</li> <li>◆ Acute thrombophlebitis or deep venous thrombosis in the limb to be treated</li> <li>◆ Any other co-morbid condition that in the judgment of the physician precludes safe percutaneous intervention</li> </ul> <p>13. Has symptomatic contralateral femoral disease.</p> <p>14. Exchangeable guidewire cannot cross the target lesion and re-enter true vessel lumen distal to lesion(s).</p> <p>15. Presence of significant (<math>&gt; 50\%</math> stenosis or occlusion) ipsilateral common femoral stenosis.</p> <p>16. Aneurysmal target vessel.</p> <p>17. Presence of an acute intraluminal thrombus at the proposed lesion site.</p> <p>18. Perforation, dissection or other injury of the access or target vessel requiring additional stenting or surgical intervention prior to start of PTA procedure.</p> <p>19. Focal popliteal disease in the absence of femoral disease.</p>

2. DURABILITY II Study Conduct

All subjects were scheduled to return for follow-up evaluations at 30 days, 6 months, 1, 2 and 3 years post-procedure. **Table 6** provides a summary of the specific study requirements at each stage of the study.

**Table 6: Study Assessment Schedule and Requirements**

Assessment Schedule (Timeframe Window)	Baseline (45 days prior, labs 30 days prior)	Procedure	Pre- Discharge	30 Days (25-40 Days)	6 Months (150-210 Days)	1 Year (335-395 Days)	2 Years (685-775 Days)	3 Years (1050-1140 Days)
Medical history	X							
Physical exam	X							
Concomitant medication use	X	X	X	X	X	X	X	X
Clinical status by Rutherford Clinical Category	X			X		X		
Ankle-brachial index	X			X	X	X	X	X
Walking Impairment Questionnaire	X			X	X	X	X	X
Treadmill exercise test (Gardner protocol)						X*		
Duplex ultrasound				X		X	X	X
Angiogram		X						
Laboratory tests	X							
X-ray (fracture assessment)						X	X	X
Adverse event evaluation		X	X	X	X	X	X	X

\*Treadmill exercise testing was only required for subjects enrolled under protocol v3.0, v4.0 and v5.0.

3. Clinical Endpoints

The primary safety endpoint was the Major Adverse Event (MAE) rate at 30 days, defined as clinically-driven target lesion revascularization (TLR), amputation of treated limb, or all-cause mortality. Secondary safety endpoints included:

- Major adverse event rate at 30 days for single-stent subjects
- Major adverse event rate at 1 year
- Stent fracture rate at 1 year
- Decline in Rutherford Clinical Category (RCC) at 30 days, defined as a decline in clinical status indicated by an increase of one or more in RCC compared to baseline.

The primary effectiveness endpoint was the primary stent patency rate at 1 year, defined as a binary duplex ultrasound ratio < 2.0 at the stented target lesion with no clinically-driven reintervention within the stented segment. Duplex ultrasound was evaluated by an independent core laboratory and clinically-driven reintervention was adjudicated by the Clinical Event Committee (CEC). Secondary effectiveness endpoints included:

- Primary patency rate at 1 year for single stent subjects
- Device success, defined as the ability to deploy the stent as intended at the treatment site.
- Improvement of Rutherford Clinical Category at 1 year, defined as an improvement in clinical status indicated by a decrease of one or more in RCC.
- Increase of ankle-brachial index at 1 year, defined as an increase in ABI compared to baseline in subjects with compressible arteries and baseline ABI < 0.9.
- Assisted primary patency at 1 year, defined as a binary duplex ultrasound ratio < 2.0 maintained by repeated percutaneous intervention completed prior to complete vessel closure.
- Secondary patency at 1 year, defined as a binary duplex ultrasound ratio < 2.0 maintained by repeat percutaneous intervention after occlusion of the target lesion.
- Duplex ultrasound  $\leq 2.4$  primary patency at 1 year, defined as a binary duplex ultrasound ratio  $\leq 2.4$  at the stented target lesion with no clinically-driven reintervention without the stented segment.
- Absolute claudication distance improvement at 1 year, defined as the increase in walking distance determined by a graded treadmill exercise test in subjects enrolled under protocol versions 3.0, 4.0, and 5.0 who did not have iliac disease treated at the same time of the index procedure compared to baseline.
- Walking Improvement at 1 year, defined as an increase in Walking Impairment Questionnaire score in subjects who did not have iliac disease treated at the time of the index procedure compared to baseline.

## **B. Accountability of PMA Cohort**

A total of 287 subjects signed the informed consent and were enrolled in the DURABILITY II study. **Table 7** shows the patient accountability for all follow-up timepoints. **Tables 8 and 9** show detailed patient accountability for the 30-day and 12-month visits, respectively.

**Table 7: Summary of Subject Compliance**

Time	Compliance
Pre-discharge	100% (287/287)
30 Days	98% (280/287)
6 Months	96% (275/287)
1 Year	92% (263/287)
2 Year	81% (72/89)
3 Year	79% (11/14)

**Table 8: 30-Day Follow-Up Compliance**

30-day Follow-Up	N=287
Available	280/287 (98.0%)
Unavailable	7/287 (2.4%)
Died	0/287 (0.0%)
Lost-to-Follow-Up (LTFU)	0/287 (0.0%)
Missed Visit	5/287 (1.7%)
Withdrew	2/287 (0.7%)

**Table 9: 12-Month Follow-Up Compliance**

12-Month Follow-Up	N=287
Available	263/287 (91.6%)
Unavailable	24/287 (8.4%)
Died	9/287 (3.1%)
Lost-to-Follow-Up (LTFU)	6/287 (2.1%)
Missed Visit	3/287 (1.0%)
Withdrew	6/287 (2.1%)

**C. Study Population Demographics and Baseline Parameters**

Baseline demographic and clinical characteristics for all subjects enrolled in the DURABILITY II study are summarized in **Table 10**.

**Table 10: Demographics and Baseline Clinical Characteristics**

Subject Characteristics	N=287
Age (yrs.)	
Mean $\pm$ SD (N)	67.7 $\pm$ 10.7 (287)
Range (min, max)	(39.4, 93.3)
Male	66.2% (190/287)
Race	
White/Caucasian	88.9% (255/287)
African	7.7% (22/287)
Asian	0.7% (2/287)

Subject Characteristics	N=287
Hispanic	2.4% (7/287)
Other	0.3% (1/287)
Risk Factors	
Diabetes	42.5% (122/287)
Type I	3.1% (9/287)
Type II	39.4% (113/287)
Hyperlipidemia	86.1% (247/287)
Hypertension	88.2% (253/287)
Renal Insufficiency	9.8% (28/287)
Current smoker	39.0% (112/287)
Medical History	
Angina	17.4% (50/287)
Arrhythmia	13.9% (40/287)
Congestive heart failure (CHF)	9.4% (27/287)
Stroke	6.3% (18/287)
Transient ischemic attack (TIA)	4.9% (14/287)
Myocardial infarction	20.9% (60/287)
Non-healing ischemic ulcer in the lower extremities	1.4% (4/287)
Amputation of the lower extremities	1.0% (3/287)
Previous interventions in the superficial femoral or popliteal arteries	41.1% (118/287)
Clinical Characteristics	
Rutherford Clinical Category	
2=Moderate claudication	39.4% (113/287)
3=Severe claudication	55.7% (160/287)
4=Ischemic rest pain	4.5% (13/287)
5=Minor tissue loss	0.3% (1/287)
Ankle Brachial Index	
Mean $\pm$ SD (N)	0.69 $\pm$ 0.19 (281*)
Range (min, max)	(0.06, 1.38)
*ABI not available for 6 subjects due to non-compressible arteries	

**Table 11** presents baseline characteristics (assessed by the angiographic core laboratory except as otherwise noted), including lesion location, length and pre-procedure vessel diameter. Results for lesion length are consistent with the differences in methodology, with mean lesion length of 109.6 mm reported by the site investigators and 89.1 mm reported by the core laboratory. Per site assessment, normal-to-normal lesion was determined by measuring the length of the target lesion from healthy tissue to healthy tissue. In contrast, 20-to-20 lesion length was determined by the core laboratory, measuring between the proximal and distal points at which the lesion was 20% stenosed. The mean percent diameter stenosis was 85.8%, and the lesion distribution included 48.1% occluded lesions and 43.2% severely calcified lesions.

**Table 11: Baseline Target Lesion Characteristics**

Lesion Characteristics	N=287
SFA Location	
Superior SFA	27.5% (79/287)
Inferior SFA	70.4% (202/287)
Popliteal	2.1% (6/287)
Lesion length (mm) (Normal-to-normal)*	
Mean $\pm$ SD (N)	109.6 $\pm$ 45.0 (287)

Lesion Characteristics	N=287
Range (min, max)	(10.0, 180.0)
Lesion Length (mm) (20-to-20)	
Mean ± SD (N)	89.1 ± 44.8 (287)
Range (min, max)	(7.3, 200.9)
Pre-procedure Reference Vessel Diameter (mm)	
Mean ± SD (N)	4.8 ± 0.9 (287)
Range (min, max)	(2.7, 8.0)
Pre-procedure Minimum Lumen Diameter (mm)	
Mean ± SD (N)	0.7 ± 0.8 (287)
Range (min, max)	(0.0, 2.7)
Pre-procedure Diameter Stenosis (%)	
Mean ± SD (N)	85.8 ± 16.2 (287)
Range (min, max)	(50.7, 100.0)
Occlusion	48.1% (138/287)
Bend	100.0% (287/287)
Calcification	
None/Mild	30.0% (86/287)
Moderate	26.8% (77/287)
Severe	43.2% (124/287)
Ulcerated	10.5% (30/287)
Aneurysm	1.0% (3/287)
* Normal-to-normal lesion length assessed per site investigator	

The total number of subjects who withdrew from the study, were lost to follow-up, or died, regardless of follow-up visit or visit-window status through the duration of the study are provided in **Table 12**.

**Table 12: Subjects who have exited the study**

Exited Study	Subjects
Died	4.9% (14/287)
Lost-to-Follow-Up (LTFU)	2.1% (6/287)
Withdrew	3.8% (11/287)
<b>Total</b>	<b>10.8% (31/287)</b>

## D. Safety and Effectiveness Results

### 1. Safety Endpoints

The primary analysis of safety was based on the 284 subjects available for the 30-day evaluation. The key safety outcomes for this study are presented below. Adverse effects are reported in **Tables 13 and 14**.

The primary safety endpoint was MAE rate at 30 days. MAE was defined as clinically-driven target lesion revascularization (TLR), amputation of treated limb, or all-cause mortality, as adjudicated by CEC. Among the 284 subjects for whom 30 day MAE data were available, the rate was 0%. The 97.5% upper

confidence bound was 1.1%, which is less than the performance goal of 12%. Therefore, the primary safety endpoint was met. Per protocol three (3) subjects who did not have reported MAEs prior to 30 days and who did not complete the 30 day follow-up visit and were without any further follow-up information were not included in the analysis.

Additional safety endpoints are discussed below.

Decline in Rutherford Clinical Category at the 30-day follow-up visit was not observed in any subjects.

The 1-year MAE rate was 16.8%(46/273) and is presented in **Table 13**.

**Table 13: Major Adverse Event Rate at 1 Year**

<b>1-Year MAE</b>	<b>N = 273*</b>
Subjects with MAE at 1-Year	16.8% (46/273) [50]
Death	2.9% (8/273) [8]
Amputation of treated limb	0.0% (0/273) [0]
Clinically driven target lesion revascularization	13.9% (38/273) [42]
* Denominator for 1-year MAE included subjects who had completed the 1-year follow-up visit (263), or who had not completed the visit but whose 1-year visit window had closed (3), or those who did not complete the 1-year visit but had an MAE prior to 1 year (7).	

**Adverse effects that occurred in the PMA clinical study:**

There have been 14 subject deaths reported in the study. All deaths have been classified by the CEC as unrelated to the study device, study index procedure or study requirement.

**Table 14** provides a summary of the adverse events documented in the study. The data are presented as a percentage of subjects experiencing an AE followed by the total number of events in brackets.

**Table 14: Summary of Adverse Events**

<b>Adverse Event</b>	<b>Events at &lt;= 30 days<sup>†</sup></b>	<b>Events at &lt;= 1 Year<sup>††</sup></b>	<b>Total Events<sup>†††</sup></b>
Total Subjects with AEs	45.3% (129/285) [210]	86.1% (242/281) [756]	87.8% (252/287) [1111]
Allergic reaction	1.4% (4/285) [4]	1.8% (5/281) [5]	1.7% (5/287) [5]
Amputation	0.4% (1/285) [1]	0.7% (2/281) [2]	1.4% (4/287) [4]
Angina	0.4% (1/285) [1]	4.3% (12/281) [13]	7.0% (20/287) [22]
Arrhythmia	0.7% (2/285) [2]	2.8% (8/281) [9]	3.8% (11/287) [12]
Arterial dissection/perforation	14.0% (40/285) [42]	15.3% (43/281) [49]	15.0% (43/287) [51]

Adverse Event	Events at ≤ 30 days <sup>†</sup>	Events at ≤ 1 Year <sup>††</sup>	Total Events <sup>†††</sup>
Bleeding disorders (including GI, lymphatic)	1.8% (5/285) [5]	5.0% (14/281) [15]	6.6% (19/287) [22]
Cerebrovascular accident		1.8% (5/281) [5]	2.8% (8/287) [8]
Death <sup>*</sup>		0.7% (2/281) [2]	1.4% (4/287) [4]
Edema	1.8% (5/285) [5]	5.0% (14/281) [14]	6.6% (19/287) [22]
GI bleeding	0.4% (1/285) [1]	1.4% (4/281) [4]	2.1% (6/287) [6]
Hematoma at vascular access site	3.9% (11/285) [11]	3.9% (11/281) [11]	3.8% (11/287) [11]
Hypertension/hypotension	2.1% (6/285) [6]	4.3% (12/281) [12]	4.9% (14/287) [16]
Infection, local or systemic including bacteremia or septicemia	0.4% (1/285) [1]	3.6% (10/281) [11]	5.6% (16/287) [22]
Myocardial infarction		1.1% (3/281) [3]	2.1% (6/287) [6]
Other Cardiac Disorders	0.7% (2/285) [2]	8.5% (24/281) [26]	9.8% (28/287) [34]
Other GU Disorders	0.7% (2/285) [2]	3.2% (9/281) [10]	4.9% (14/287) [17]
Other Gastrointestinal Disorders	3.2% (9/285) [11]	12.8% (36/281) [52]	13.9% (40/287) [69]
Other Musculoskeletal disorders	4.6% (13/285) [15]	14.9% (42/281) [52]	20.2% (58/287) [81]
Other Respiratory Issues	0.4% (1/285) [1]	10.7% (30/281) [34]	14.6% (42/287) [54]
Other Vascular Disorders	5.3% (15/285) [16]	21.7% (61/281) [81]	32.1% (92/287) [133]
Percutaneous revascularization	0.4% (1/285) [1]	4.3% (12/281) [14]	4.5% (13/287) [17]
Pseudoaneurysm	1.4% (4/285) [4]	1.4% (4/281) [4]	1.4% (4/287) [4]
Renal Insufficiency/Failure		1.1% (3/281) [3]	1.4% (4/287) [4]
Restenosis	1.4% (4/285) [4]	21.7% (61/281) [66]	32.8% (94/287) [113]
Slow/no flow during procedure	0.7% (2/285) [2]	0.7% (2/281) [2]	0.7% (2/287) [2]
Stent/Vessel thrombosis	0.4% (1/285) [1]	3.6% (10/281) [11]	4.2% (12/287) [13]
Vessel spasm	0.4% (1/285) [1]	0.4% (1/281) [1]	0.3% (1/287) [1]
Other	18.9% (54/285) [71]	46.3% (130/281) [245]	51.6% (148/287) [358]

<sup>†</sup> Denominator for events at ≤ 30 days included subjects who had completed the 30-day follow-up visit or those who did not complete the 30-day visit but had an AE prior to 30 days.

<sup>††</sup> Denominator for events at ≤ 1 year included subjects who had completed the 1-year follow-up visit or who had not completed the visit but whose 1-year visit window had closed, or those who did not complete the 1-year visit but had an AE prior to 1 year.

<sup>†††</sup> Denominator for total events included all enrolled subjects.

\* Count of AEs labeled "death" is less than total number of study deaths since death may be attributable to other AEs.

### Stent Fracture Analysis

X-rays on 260 stents (248 subjects) were available for analysis by the angiographic core laboratory for stent fractures at 1 year. Stent fractures identified by the core laboratory were evaluated and classified by the Stent Fracture Committee. One

subject had a class V fracture<sup>1</sup> in the single stent implanted. The stent fracture rate was 0.4% (1/260) at 1 year (**Table 15**).

**Table 15: Stent Fracture at 1 Year**

	N=260 *
Stent Fracture	0.4% (1/260)
Class I – Single tine fracture	0.0% (0/260)
Class II - Multiple tine fractures	0.0% (0/260)
Class III – Stent fracture(s) with preserved alignment of the components	0.0% (0/260)
Class IV - Stent fracture(s) with mal-alignment of the components	0.0% (0/260)
Class V- Stent fracture(s) in a trans-axial spiral	0.4% (1/260)
* Denominator was number of stents in 248 subjects who had completed the 1-year follow-up visit and for whom evaluable X-rays were available.	

## 2. Effectiveness Endpoints

The analysis of effectiveness was based on the 226 evaluable at the 12-month time point. Key effectiveness outcomes are presented in **Tables 17 to 19**.

The primary effectiveness endpoint was primary stent patency, defined as PSV ratio < 2.0 at the stented target lesion as measured by duplex ultrasound at the 1-year follow-up visit (335-395 days post procedure) and no clinically-driven TLR within the stented segment within 1 year of the procedure. The primary effectiveness analysis was specified to occur using the first 232 single-stent subjects. Because the primary safety analysis was pre-specified to occur using all 287 enrolled subjects, safety and effectiveness data from the 287-patient Intent-to-Treat cohort were presented during review of the PMA, using the same endpoints and definitions as previously submitted. This analysis yielded similar results as the analysis of the first 232 single-stent subjects, and was found more informative. Therefore, the results of the analysis of the full cohort are presented.

Primary stent patency was evaluated in all enrolled subjects with evaluable 1-year data (N=226, excluding out-of-window duplexes) and was achieved in 67.7% (153/226) of the subjects. The 97.5% lower confidence bound of 61.2% is greater than the PG of 57%. Therefore, the primary effectiveness endpoint was met and the null hypothesis is rejected.

In twenty-seven (27) subjects, the 1-year duplex data were evaluable but obtained out of the 1-year follow-up visit window. If the 27 subject with out-of-window

<sup>1</sup> Jaff M, Dake M, Pompa J, Ansel G, Yoder T. Standardized evaluation and reporting of stent fractures in clinical trials of noncoronary devices. *Catheter Cardiovasc Interv.* Sep 2007;70(3):460-462.

duplexes were included in the analysis, the primary stent patency would be achieved in 68.4% (173/253) of the subjects.

The primary effectiveness endpoint at 1-year was not available in 34 subjects (287-253=34). **Table 16** displays the reasons for the missing data.

**Table 16: Reasons for Missing Data**

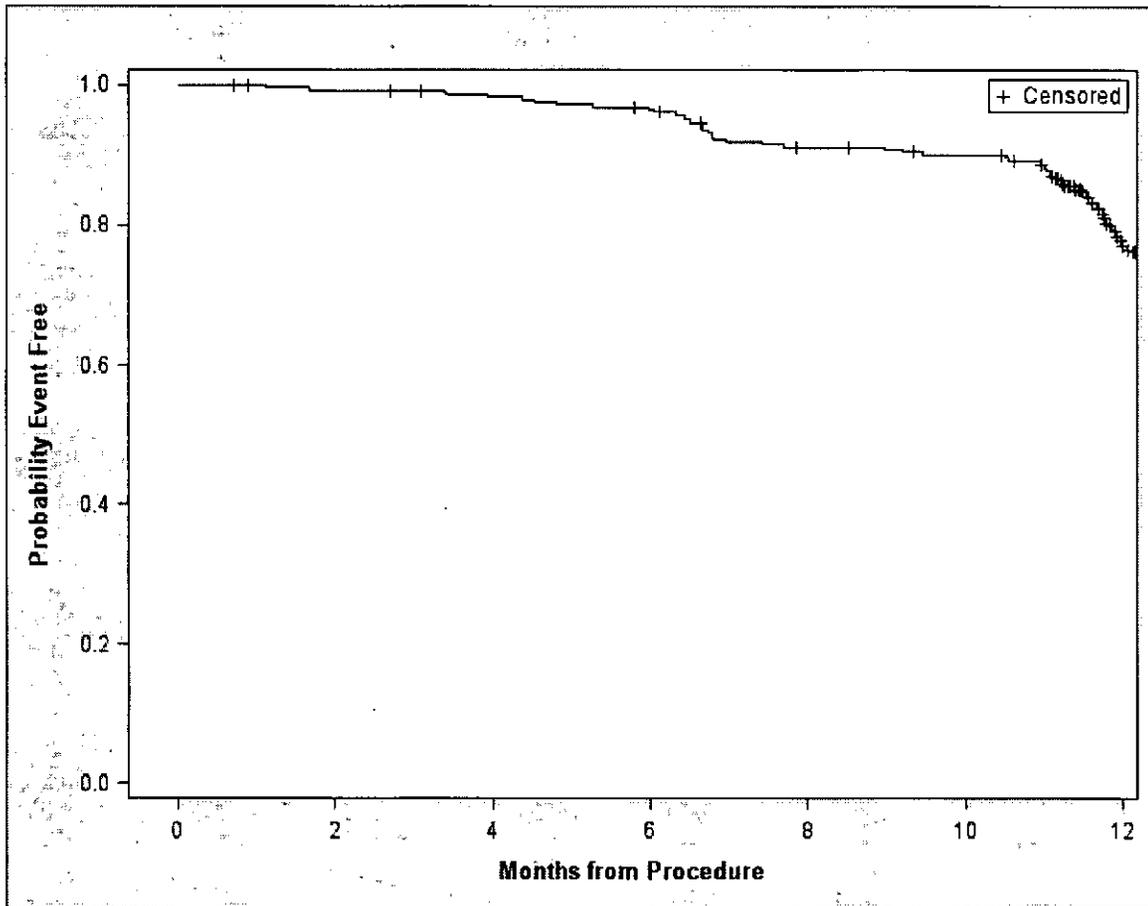
Reason	Subjects
Exited study	21
Non-diagnostic duplex at 1-year	10
Missed 1-year visit	2
Missing 1-year duplex scan	1
<b>Total</b>	<b>34</b>

**Table 17: Summary of Primary Effectiveness Endpoint**

Primary Effectiveness Endpoint	Primary Stent Patency Rate	99.26% Lower Confidence Bound	Performance Goal	Objective Met
Single-stent & multi-stent subjects (Exclude Out-of-Window Duplex)	67.7% (153/226)	61.2%	57.0%	Yes
Single-stent & multi-stent subjects (Include Out-of-Window Duplex)	68.4% (173/253)	62.3%	57.0%	Yes

The primary stent patency rate was also analyzed using the Kaplan-Meier method. The analysis cohort consisted of all enrolled subjects.

As presented in **Figure 2** and **Table 18**, the freedom from loss of primary patency at 1 year was 77.2%.



**Figure 2: Freedom from Loss of Primary Patency**

**Table 18: Probability of Freedom from Loss of Primary Patency**

Month	# At Risk	Cumulative# Events	Cumulative Censored	Probability Event Free	95% CI
0	287	0	0	100%	-
1	285	0	2	100%	-
6	273	9	5	96.8%	94.0%-98.3%
12	181	61	45	77.2%	71.7%-81.8%

DURABILITY II included stents available in lengths up to 200 mm, while lesions up to 180 mm were eligible for enrollment, and the study was anticipated to include a substantial proportion of longer and more challenging lesions. **Table 19** displays primary patency rates and freedom from loss of primary patency at 1 year by lesion length through lesion lengths greater than 180 mm.

**Table 19: Primary Patency at 1-Year by Core Lab-Assessed Lesion Length**

	Lesion Length 0-150 mm	Lesion Length >150-180 mm	Lesion Length >180 mm
Primary Patency	71.8% (145/202)	50.0% (8/16)	0.0% (0/8)
Kaplan-Meier analysis of freedom from loss of primary patency	80.8%	65.0%	14.8%

**Secondary Effectiveness Endpoints**

The following table provides a summary of results from the evaluation of secondary effectiveness endpoints.

**Table 20: Summary of Secondary Effectiveness Endpoints**

Variables	1 Year
Device Success	99.3% (302/304 <sup>§</sup> )
Improvement of Rutherford Clinical Category at 1 Year-Changes from baseline	
% with improvement of 1 or more categories	83.5% (218/261)
Increase of Ankle-Brachial Index at 1 Year-Change from baseline (%)	
Mean ± SD (N)	0.25 ± 0.23 (222)
Assisted Primary Patency at 1 Year*	86.9%
Secondary Patency at 1 Year *	87.3%
Duplex Ultrasound ≤ 2.4 Primary Patency at 1 Year*	77.9%
Absolute Claudication Distance Improvement at 1 Year**	
Absolute Claudication Distance-Change from baseline to 1 year (% of subjects with improvement)	69.0% (20/29)
Mean ± SD (N)	0.08 ± 0.28 (29)
Walking Improvement Questionnaire at 1 Year	
Score for pain, aching, or cramps in calves or buttocks-Change from baseline to 1 year (%max)	
Mean ± SD (N)	33.7 ± 34.8 (239†)
Walking Distance Score –Change from baseline to 1 year (%max)	
Mean ± SD (N)	37.1 ± 40.6 (205†)
Walking Speed Score –Change from baseline to 1 year (%max)	
Mean ± SD (N)	18.6 ± 25.5 (169†)
Stair Climbing Score –Change from baseline to 1 year (%max)	
Mean ± SD (N)	24.7 ± 38.3 (199†)
<sup>§</sup> The denominator includes 303 implanted stents plus one stent that could not be successfully deployed and was removed. * Evaluated by the Kaplan-Meier method in all enrolled subjects. ** Assessed in subjects enrolled under protocol versions 3.0, 4.0 and 5.0 † Subject counts for “Changes from baseline” included subjects with available WIQ data both at baseline and at 1 year.	

### 3. Subgroup Analyses

#### Applicability to Pediatric Populations

Peripheral artery disease is not typically found in pediatric populations. Accordingly, the safety and effectiveness of the ev3 EverFlex Self-Expanding Peripheral Stent System in pediatric populations was not studied in the DURABILITY II clinical study.

#### DURABILITY II Study Results by Gender/Sex

The DURABILITY II trial accrued a total of 97 (33.8%) female and 190 (66.2%) male subjects. This distribution is representative of that seen in other studies involving PAD. A total of 95 (33.5%) female and 189 (66.5%) male subjects were evaluable for the primary safety endpoint of major adverse events (MAE) at 30 days. Female and male subjects had similar MAE rate (0.0% and 0.0%) with an overall MAE rate of 0.0%. In addition, the primary effectiveness endpoint of primary stent patency at 12 months was evaluable in 76 (33.6%) female and 150 (66.4%) male subjects. Primary stent patency rate was 68.4% in females and 67.3% in males for an overall rate of 67.7%. These findings indicate similar safety and effectiveness outcomes for males and females.

## **XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION**

### DURABILITY I Study

DURABILITY I (Study Measuring the Durability of the PROTÉGÉ® EverFlex™ Stent in Lesions of the Superficial Femoral Artery), was a multi-center, non-randomized, prospective study. It was designed to evaluate the safety and effectiveness of the EverFlex stent in the treatment of *de novo*, restenotic or reoccluded SFA lesions in symptomatic PAD patients. The study enrolled 151 subjects (151 target lesions) between August 2006 and June 2007 at 13 centers in Europe.

The primary objective of the study was to evaluate the long-term effectiveness and integrity of a single EverFlex stent in SFA lesions  $\leq 14$  cm. The primary endpoint was freedom from  $> 50\%$  restenosis at 12 months as indicated by an independently verified peak systolic velocity ratio (PSVR)  $< 2.5$  in the target vessel with no reintervention. If ultrasound data were unavailable or inconclusive, available angiographic data were used in place of the ultrasound data to determine freedom from  $>50\%$  restenosis.

The primary patency rate at 12 months was 72.2%. The target lesion revascularization rate was 20.9% at 12 months. Stent fractures were found in 10 of 123 subjects with available x-ray data, resulting in a 12-month stent fracture rate of 8.1%. Elongation of the EverFlex stent during implantation was identified in 90% (9/10) of the fractured stents at 12 months. Implantation technique was identified as an influential factor of

subsequent stent fracture.<sup>2</sup> Outcomes from the DURABILITY I study are summarized in the Table 21.

**Table 21: Summary of DURABILITY I Study Outcomes**

<b>Endpoint</b>	<b>Subjects</b>	<b>Percentage</b>
<b>Primary Endpoint</b> Primary patency, defined as primary Patency at 12 months	96/133	72.2%
<b>Secondary Endpoints</b>		
<b>Technical Success</b> Defined as the ability to cross the target lesion with the device and deploy the stent as intended at the treatment site.	151/151	100%
<b>Initial arteriographic success</b> Defined as arteriographic evidence of improvement in luminal diameter to < 30% residual stenosis AND/OR an increase of ≥ 50% in luminal diameter immediately following stent placement	144/151	95.4%
<b>Follow up clinical success at 12 months</b> Defined as an improvement of Rutherford classification	123/134	91.8%
<b>Secondary Patency</b> Defined as a diameter stenosis < 50% by Duplex ultrasound, regardless of reintervention during follow-up.	115/129	89.1%
<b>Fracture rate as determined by X-ray</b>	10/123	8.1%
<b>Major Adverse Clinical Events (MACE)</b>		
Death	9/151	6.0%
Myocardial infarction,	3/151	2.0%
Stroke	2/151	1.3%
Emergent surgical revascularization of the target vessel	3/151	2.0%
Repeat vascularization of the target vessel,	30/151	18.5%
Bleeding complication (Access site complications)	2/151	1.3%
Total*	42/151	27.8%
*Total is presented in number of patients with MACEs		

#### DURABILITY 200 Study

DURABILITY 200 was an investigator-sponsored, prospective nonrandomized study performed at two centers in Belgium designed to evaluate primary stenting with the Protégé EverFlex 200mm long self-expanding nitinol stent in femoropopliteal TransAtlantic Inter-Society Consensus (TASC) C and D lesions of at least 150mm in

<sup>2</sup> Bosiers M, Torsello G, Gissler HM, et al. Nitinol stent implantation in long superficial femoral artery lesions: 12-month results of the DURABILITY I study. *J Endovasc Ther.* Jun 2009;16(3):261-269.

length<sup>3</sup>. The primary study endpoint, primary patency at 12 months, defined as the absence of hemodynamically significant stenosis on duplex ultrasound imaging (systolic velocity ratio  $<2.4$ ) at the target lesion and without target lesion revascularization (TLR)  $< 12$  months. Stent fracture occurrence was assessed at the 12-month follow-up by conventional x-ray imaging. Between March 2008 and June 2009, 100 patients with 100 symptomatic TASC C and D femoropopliteal lesions were treated with at least one 200-mm-long EverFlex stent. The average lesion length was 242 mm (range, 160-450mm). Placement of one stent was reported in 49 patients (49%), two stents in 44 subjects (44%), and three stents in seven (7%).

The primary patency rate by Kaplan-Meier estimate at 12 months was 64.8%. The 12-month freedom from target lesion revascularization by Kaplan-Meier estimate was 68.2%. Stent fractures were identified in 6 of 100 patients, resulting in a 12-month stent fracture rate of 6%.

## **XII. PANEL MEETING RECOMMENDATION**

In accordance with the provisions of Section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

## **XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES**

### **A. Safety Conclusions**

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above. Among the 284 subjects for whom data on the primary safety endpoint (i.e., 30 day MAE rate) were available, the rate was 0%. The 97.5% upper confidence bound was 1.1%, which is less than the performance goal of 12%. Therefore, the primary safety endpoint was met.

### **B. Effectiveness Conclusions**

The primary effectiveness endpoint, primary stent patency, was evaluated in all enrolled subjects with evaluable 1-year data and was achieved in 67.7% of the subjects. In addition, an analysis of the patency rate by lesion length showed an even greater patency rate of 71.8% for shorter lesions. The 97.5% lower confidence bound of the primary effectiveness endpoint was 61.2%, which is greater than the prespecified performance goal of 57%. Therefore, the primary effectiveness endpoint was met.

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<sup>3</sup> Bosiers M, Deloose K, Callaert J, Moreels N, Keirse K, Verbist J, Peeters P. One-year results with the Protégé EverFlex 200-mm-long nitinol stent (ev3) in TransAtlantic Inter-Society Consensus C and D femoropopliteal lesions: Durability-200 study. *J Vasc Surg.* May 31.

### C. Overall Conclusions

The preclinical and clinical studies indicate that the EverFlex Self-Expanding Peripheral Stent System meets or exceeds safety and performance specifications. The multicenter clinical study results demonstrate that the EverFlex Self-Expanding Peripheral Stent System is safe and effective for the treatment of moderate to long lesions in the native superficial femoral and proximal popliteal arteries. Results from preclinical and clinical evaluations provide valid scientific evidence and reasonable assurance that the device is safe and effective; therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the labeling and Instructions for Use (IFU).

### XIV. CDRH DECISION

CDRH issued an approval order on March 7, 2012. The final conditions of approval cited in the approval order are described below.

In addition to the general conditions outlined, the sponsor must conduct two post-approval studies, as described below:

1. *DURABILITY PAS*: The study must be conducted as per approved protocol CP-1001, Version 1.0, located at P110023/A005. The study will consist of a prospective, multi-center, non-randomized, single-arm, study of newly enrolled US patients treated with the EverFlex Self-Expanding Stent System.

The primary study objective is to evaluate the longer-term safety and effectiveness of the EverFlex Self-Expanding Stent System for the treatment of atherosclerotic lesions in the native superficial femoral artery or the superficial femoral and proximal popliteal arteries over a three-year period. The primary endpoint for this trial is the composite of freedom from acute death, amputation, and target lesion revascularization at 36 months post-procedure.

The secondary endpoints will include adverse events, the individual components of the primary endpoint (acute death, amputation, and target lesion revascularization), device success, improvement in Rutherford clinical category, improvement in ankle-brachial index, and walking improvement.

The study population will consist of adult patients with lesions up to 180 mm in length in the native superficial femoral artery or the superficial femoral and proximal popliteal arteries.

A total of 169 patients must be enrolled. This sample size will ensure precision of the stent fracture rate at 1 year with a 95% confidence interval of 1.3% to 7.9%, assuming a proportion of 4.6% and 10% attrition at 1 year. Also, assuming that

the true 36-month composite primary endpoint rate is 55% (with a performance goal of greater than 35%) and 30% attrition at 36 months, the resulting 118 evaluable subjects are greater than the 79 required to power the primary endpoint.

The sponsor was advised that the results from this study should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement.

The sponsor is required to submit PAS Progress Reports every six months during the first two years and annually thereafter. The reports should clearly be identified as Post-Approval Study Report. Two copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order"  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm>

2. *Continued Follow-up of the Premarket Cohort:* In addition to the post-approval study enrolling new US patients as outlined above, the sponsor must continue follow-up of patients from your premarket cohort (DURABILITY II, G070013) through 3 years post-procedure. The goals and endpoints of this follow-up study will be identical to that described above with respect to the DURABILITY PAS.

The sponsor must collect clinical outcomes as outlined in the respective investigational plans submitted in G070013, analyzing and reporting on these findings as agreed upon in the Analysis Plan, Version #1, located at P110023/A005.

The sponsor was advised that the results from this study should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement.

The sponsor is required to submit PAS Progress Reports annually until study completion. The reports should clearly be identified as Post-Approval Study Report. Two copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

## **XV. APPROVAL SPECIFICATION**

Directions for use: See device labeling. (*See General hints*)

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.