SUMMARY OF SAFETY AND EFFECTIVENESS DATA

1. General Information

Device Generic Name:	Carotid Stent
Device Trade Name:	Protégé® GPS™ Carotid Stent System Protégé® RX Carotid Stent System
Applicant's Name and Address:	ev3 Inc. 9600 54th Avenue North Plymouth, MN 55442

Premarket Approval (PMA) Application Number: P060001

Date of Panel Recommendation: None

Date of Notice of Approval to Applicant: January 24, 2007

2. Indications for Use

The Protégé® GPS™ Carotid Stent System and the Protégé® RX Carotid Stent System, used in conjunction with ev3 embolic protection devices, are indicated for the treatment of patients at high risk for adverse events from carotid endarterectomy who require percutaneous carotid revascularization and meet the criteria outlined below:

- Patients with carotid artery stenosis (≥ 50% for symptomatic patients by ultrasound or angiography or ≥ 80% for asymptomatic patients by ultrasound or angiography) of the common or internal carotid artery, AND
- Patients must have a reference vessel diameter within the range of 4.5mm and 9.5mm at the target lesion.

3. Contraindications

The Protégé® GPS™ and Protégé® RX Carotid Stent Systems are contraindicated for use in:

- Patients in whom anticoagulant, antiplatelet therapy or thrombolytic drugs are contraindicated.
- Patients with severe vascular tortuosity or anatomy that would preclude the safe introduction of a guidewire, guide catheter, sheath, embolic protection system, or stent system.
- Patients with known hypersensitivity to nickel or titanium.
- Patients with uncorrected bleeding disorders.
- Lesions in the ostium of the common carotid artery.

4. Warnings and Precautions

The warnings and precautions can be found in the Instructions for Use for the Protégé® GPS™ and Protégé® RX Carotid Stent Systems.

5. Device Description

Protégé® GPS™ Carotid Stent

The Protégé® GPS™ Carotid Stent is a self-expanding stent composed of nitinol (nickel-titanium alloy). The stent is laser machined from a continuous seamless piece of nitinol tubing into an open lattice design. There are no welds, joints or bonds used in the construction of the stent. Tantalum radiopaque markers are located on both ends of the stent to aid in visualization. The stent is premounted on a delivery catheter designed for femoral access. Upon deployment, the stent achieves its predetermined diameter and exerts a constant, gentle outward force to establish patency in the carotid artery. The same Protégé® GPS™ Carotid Stent is used for both the Protégé® GPS™ and Protégé® RX Carotid Stent Systems.

Protégé® GPS™ and Protégé® RX Carotid Stent Delivery Systems

The Protégé® GPS™ Carotid Stent System is a single-use catheter with an outer sheath that constrains the stent onto the catheter shaft and lowers the stent profile. The system is inserted through a guide catheter or sheath and tracked over the embolic protection device wire. Radiopaque markers on the 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.

The Protégé® RX Carotid Stent System, a rapid exchange version of the Protégé® GPS™ Carotid Stent System, also uses a sheath to mechanically constrain the same Protégé® GPS™ Stent. The delivery system is inserted through a guide catheter or sheath and is tracked over the embolic protection device wire that passes through the distal 27.5 cm of the delivery system. Stent deployment is achieved by pulling the manifold y-connector proximally. The delivery system radiopaque stent retainer holds the stent stationary until the outer sheath is fully retracted to facilitate accurate placement.

Table 1 provides the available Protégé® GPS™ and Protégé® RX Carotid Stent System configurations.

Table 1: Protégé® GPS™ and Protégé® RX Carotid Stent System Model Numbers

Protégé® GPS™ Carotid Stent System Model Numbers	Protégé® RX Carotid Stent System Model Numbers	Nominal Stent Diameter (mm)	Stent Length (mm)
Straight Configurations			
SERC-6-20-135	SECX-6-20-135	6.0	20
SERC-6-30-135	SECX-6-30-135	6.0	30
SERC-6-40-135	SECX-6-40-135	6.0	40
SERC-6-60-135	SECX-6-60-135	6.0	60
SERC-7-20-135	SECX-7-20-135	7.0	20
SERC-7-30-135	SECX-7-30-135	7.0	30
SERC-7-40-135	SECX-7-40-135	7.0	40
SERC-7-60-135	SECX-7-60-135	7.0	60
SERC-8-20-135	SECX-8-20-135	8.0	20
SERC-8-30-135	SECX-8-30-135	8.0	30
SERC-8-40-135	SECX-8-40-135	8.0	40
SERC-8-60-135	SECX-8-60-135	8.0	60
SERC-9-20-135	SECX-9-20-135	9.0	20
SERC-9-30-135	SECX-9-30-135	9.0	30
SERC-9-40-135	SECX-9-40-135	9.0	40
SERC-9-60-135	SECX-9-60-135	9.0	60
SERC-10-20-135	SECX-10-20-135	10.0	20
SERC-10-30-135	SECX-10-30-135	10.0	30
SERC-10-40-135	SECX-10-40-135	10.0	40
SERC-10-60-135	SECX-10-60-135	10.0	60
Tapered Configurations			
SERC-8-6-30-135	SECX-8-6-30-135	8.0 - 6.0	30
SERC-8-6-40-135	SECX-8-6-40-135	8.0 - 6.0	40
SERC-10-7-30-135	SECX-10-7-30-135	10.0 - 7.0	30
SERC-10-7-40-135	SECX-10-7-40-135	10.0 - 7.0	40

6. Alternative Practices and Procedures

Alternative practices and procedures for treatment of atherosclerotic disease of the carotid arteries currently include lifestyle modifications, endovascular intervention using other FDA-approved carotid stents and embolic protection systems, carotid endarterectomy, medical therapy, or a combination of these treatments. Lifestyle modifications include measures such as cessation of smoking and changes to diet and alcohol usage. Medical therapy includes use of antiplatelet and/or anticoagulant medicine (aspirin, clopidogrel or ticlopidine) as well as pharmaceutical treatment for hypertension and hyperlipidemia. The primary treatment used to prevent stroke in patients with carotid artery disease is surgical removal of the plaque from the stenotic artery by means of an endarterectomy.

7. Marketing History

The Protégé® GPS™ and Protégé® RX Carotid Stent Systems are approved for commercial use in the European Union (EU), Australia, New Zealand, Canada and in many additional countries across Asia, Latin America and the Middle East. The Protégé® GPS™ and Protégé® RX Carotid Stent Systems have not been withdrawn from marketing for any reason relating to the safety or effectiveness of the device.

8. Potential Adverse Effects of the Device on Health

8.1. Observed Adverse Events

The Protégé® GPS™ Carotid Stent System was evaluated for the treatment of internal and/or common carotid artery stenoses in patients at high risk for surgical revascularization via the Carotid Revascularization with ev3 Inc. Arterial Technology Evolution (CREATE) Trial. A total of 419 patients were enrolled in the CREATE Pivotal Trial. The primary objective of the study was to demonstrate the safety and effectiveness of the Protégé® GPS™ Carotid Stent System and SPIDER™ Embolic Protection Device in the treatment of common and/or internal carotid artery stenoses for subjects that are at high risk for carotid endarterectomy. The primary endpoint for the study was the 30-day composite of myocardial infarction (MI), ipsilateral stroke, procedure-related contralateral stroke or death and the ipsilateral stroke rate from 31 to 365 days post-implantation

Table 2 presents the serious adverse events that were reported within the first 30 and 365 days for registry patients enrolled in the CREATE Pivotal Trial. **Table 3** presents the cause of all patient deaths.

The numbers and types of adverse events observed were anticipated given the high co-morbid state of these patients.

Table 2: Serious Adverse Event Summary (≤ 30 Days, ≤ 365 Days)

Description of Event	≤ 30 Days (N = 417)		≤ 365 Days (N = 395)*	
	n	%	n	%
All Death, Stroke and MI	26 / 417	6.2%	37 / 395	9.4%
Death (study-defined)[1]	8 / 417	1.9%	21 / 395	5.3%
Stroke-Related	5 / 417	1.2%	9 / 395	2.3%
Not Stroke-Related	3 / 417	0.7%	12 / 395	3.0%
All-cause Death	8 / 417	1.9%	35 / 395	8.7%
Ipsilateral Stroke	16 / 417	3.8%	19 / 395	4.8%
Major	14 / 417	3.4%	16 / 395	4.1%
Minor	3 / 417	0.7%	4 / 395	1.0%
Non-ipsilateral Stroke	4 / 417	1.0%	4 / 395	1.0%
Non-stroke Neurological[2]	8 / 417	1.9%	8 / 395	2.0%
Restenosis (≥ 70% stenosis as measured by ultrasound)[3]	0 /417	0.0%	1 / 395	0.3%
Restenosis (≥ 50% stenosis as measured by ultrasound)[4]	14 /417	3.4%	27 / 395	6.8%
Target Lesion Revascularization (TLR)[5]	0 / 417	0.0%	1 / 395	0.3%

Description of Event	≤ 30 Days (N = 417)		≤ 365 Days (N = 395)*	
Cardiac	14 / 417	3.4%	16 / 395	4.1%
MI	4 / 417	1.0%	4 / 395	1.0%
Arrhythmia	2 / 417	0.5%	3 / 395	0.8%
Angina	0 / 417	0.0%	0 / 395	0.0%
Congestive Heart Failure (CHF)	7 / 417	1.7%	8 / 395	2.0%
Coronary Artery Disease (CAD)	1 / 417	0.2%	1 / 395	0.3%
Procedural Complication	81 / 417	19.4%	81 / 395	20.5%
Hypotension	71 / 417	17.0%	71 / 395	18.0%
Arrhythmia	12 / 417	2.9%	12 / 395	3.0%
Vasospasm	0 / 417	0.0%	0 / 395	0.0%
Dissection	5 / 417	1.2%	5 / 395	1.3%
In-stent Thrombosis	0 / 417	0.0%	0 / 395	0.0%
Emergent Carotid Endarterectomy (CEA)	0 / 417	0.0%	0 / 395	0.0%
Emergent Intervention	3 / 417	0.7%	3 / 395	0.8%
Access Site Complication[6]	11 / 417	2.6%	11 / 395	2.8%
Requiring Repair/Transfusion	8 / 417	1.9%	8 / 395	2.0%
Vascular[7]	3 / 417	0.7%	4 / 395	1.0%
Hemodynamic[8]	4 / 417	1.0%	4 / 395	1.0%
Bleeding[9]	22 / 417	5.3%	25 / 395	6.3%
Requiring transfusion	20 / 417	4.8%	22 / 395	5.6%
GI bleeding	7 / 417	1.7%	12 / 395	3.0%
Blood Dyscrasia[10]	0 / 417	0.0%	0 / 395	0.0%
Respiratory[11]	5 / 417	1.2%	5 / 395	1.3%
Gastrointestinal[12]	0 / 417	0.0%	5 / 395	1.3%
Genitourinary[13]	3 / 417	0.7%	5 / 395	1.3%
Infection[14]	3 / 417	0.7%	3 / 395	0.8%
Metabolic[15]	7 / 417	1.7%	7 / 395	1.8%
Musculoskeletal[16]	0 / 417	0.0%	0 / 395	0.0%
Other[17]	4 / 417	1.0%	6 / 395	1.5%

* Patients were excluded if they missed the one-year visit, withdrew or were lost to follow up and did not have any reported adverse events.

Patients may have had multiple events and therefore can be counted in more than one category / subcategory of event. Counts in **Table 2** represent the number of patients who have experienced one or more events.

Events are categorized by body system and are defined as follows:

[1]**Death (study-defined):** The Clinical Events Committee (CEC) adjudicated all deaths to determine if the death was considered a study adverse event (i.e., device-related, procedure related, and/or a study endpoint). Study-defined deaths do not include 14 deaths adjudicated as non-study related by the CEC including accident, cancer, respiratory failure, renal failure, cardiac death, and unknown death.

[2]**Non-stroke neurological:** includes visual/speech disturbances, confusion, seizure, weakness and transient ischemic attack (TIA).

[3]**Restenosis:** re-narrowing of lesion as defined in the protocol by a ≥ 70% stenosis as determined via duplex ultrasound scan

[4]**Restenosis rates** representing ≥ 50% stenosis in the target lesion as determined by duplex ultrasound are also reported, as this definition is commonly employed for surgical revascularization outcomes.

[5]**Target Lesion Revascularization (TLR):** any repeat invasive procedure, including angioplasty, stenting, endarterectomy, or thrombolysis, performed to open or increase the luminal diameter inside or within 10 mm of the previously treated lesion.

[6]**Access site complications**: bruising, hematoma and bleeding.

[7]**Vascular:** peripheral arterial disease, artery perforation and deep vein thrombosis.

[8]**Hemodynamic**: includes hypotension and hypertension (that are not procedural complications), syncope and dizziness.

[9]**Bleeding:** includes non-access site bleeding, anemia up to 30 days, GI bleed up to 30 days and subarachnoid hemorrhage.

[10]**Blood dyscrasia**: includes anemia later than 30 days and thrombocytopenia.

[11]**Respiratory**: includes pneumonia, embolism, chronic obstructive pulmonary disease (COPD) and respiratory failure.

[12]**Gastrointestinal**: includes nausea, ulcer, bowel obstruction and GI bleed later than 30 days.

[13]**Genitourinary**: includes urinary tract infection, hematuria, urosepsis and prostatic hyperplasia.

[14]**Infection**: includes laryngitis, puncture site infection, sepsis, endocarditis and bacteremia from IV site.

[15]**Metabolic**: includes diabetes, electrolyte imbalance, metabolic acidosis, renal insufficiency and renal failure.

[16]**Musculoskeletal:** includes pain, fractures and joint replacements.

[17]**Other:** Subconjunctival hemorrhage and clot in left eye secondary to fall (n=1), stent misplacement (n=1), filter perforation through delivery catheter (n=1), psychiatric admission for major depression (n=1), drug side effect (n=2).

Table 3: Cause Of All Death (≤ 30 Days, ≤ 365 Days)

	≤ 30 Days		≤ 365 Days	
Cause of Death	**Pivotal N= 8**	**%**	**Pivotal N = 35**	**%**
Stroke	5/417	1.2%	9/395	2.3%
Cardiac	3/417	0.7%	14/395	3.5%
Cancer	NA	NA	4/395	1.0%
Infection	NA	NA	2/395	0.5%
Accidental	NA	NA	2/395	0.5%
Other	NA	NA	2/395	0.5%
Unknown	NA	NA	2/395	0.5%

8.2. Potential Adverse Events

Based on the literature and on clinical and commercial experience with carotid stents and embolic protection devices the following alphabetic list includes possible adverse events associated with the use of these devices.

- Abrupt closure
- Allergic reactions to procedural medications, contrast dye or device materials
- Amaurosis fugax
- Aneurysm
- Angina/coronary ischemia
- Arrhythmia
- Arterial occlusion or thrombosis at puncture site or remote site
- Arteriovenous fistula
- Bacteremia or septicemia
- Bleeding from anticoagulant or antiplatelet medications
- Bleeding, with or without transfusion
- Cerebral edema
- Cerebral hemorrhage
- Cerebral ischemia or transient ischemic attack
- Congestive heart failure
- Death
- Detachment of a component of the device system
- Embolism (air, tissue, thrombus)
- Emergent or urgent endarterectomy surgery (CEA)
- Fever
- Filter thrombosis or occlusion
- Fluid overload
- Groin hematoma, with or without surgical repair
- Hemorrhage, with or without transfusion
- Hyperperfusion syndrome
- Hypotension or hypertension
- Infection and/or pain at the puncture site
- Ischemia or infarction of tissue/organ
- Myocardial infarction (MI)
- Pain (head, neck)
- Pseudoaneurysm, femoral
- Renal failure/insufficiency (new or worsening)
- Restenosis of stented segment
- Seizure
- Severe unilateral headache
- Slow/no flow during procedure
- Stent/filter collapse or fracture
- Stent/filter entanglement or damage
- Stent/filter failure to deploy
- Stent embolization, migration or misplacement
- Stent or vessel thrombosis/occlusion
- Stroke/cerebrovascular accident (CVA)
- Total occlusion of carotid artery
- Vessel dissection, flap, perforation, or rupture
- Vessel spasm or recoil

9. Summary of Pre-Clinical Studies

Pre-clinical studies related to the Protégé® GPS™ and Protégé® RX Carotid Stent Systems are presented in Sections 9.1 through 9.4 for *in vitro* product testing and *in vivo* product testing, biocompatibility, sterilization, packaging and shelf life testing.

9.1. *In Vitro* Product Testing

In vitro bench testing to support the Protégé® GPS™ and Protégé® RX Carotid Stent Systems was developed based on the device risk assessment and is consistent with both the *Guideline for the Submission of Research and Marketing Applications for Interventional Cardiology Devices*, May 1995, and *Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems*, January 13, 2005. A summary of the tests performed and associated results is provided in Table 4 (stent component) and Table 5 (delivery systems).

Because the Protégé® GPS™ stent is self-expanding, the tests recommended specifically for balloon-expandable stents were not conducted.

Table 4: *In Vitro* Summary For The Protégé® GPS™ Carotid Stent

Test	Objective	Summary of Methods and Results
Material Analysis/ Mechanical Properties	Ensure that the stent material properties are sufficiently well-characterized. Provide a baseline for the evaluation of the effects of future changes in materials.	The stent material composition was chemically analyzed and quantified, and the stent material tensile strength and percent elongation were determined. Certificates of conformance are provided by the vendor for each lot of material. The stent material properties are appropriately characterized and verified.
Austenitic Finish Temperature (A_f)	Determine the shape memory profile of the stent.	The austenitic finish temperature for the stents was measured by chilling samples and observing their shape recovery as a function of temperature. The results met the established device specifications, indicating that the stent displays adequate shape recovery properties.
Corrosion Testing	Establish compatibility of stent material with vascular environment. Determine extent of stent corrosion, which can result in premature stent failure or generation of toxic by-products.	Stent samples were subjected to accelerated corrosion conditions intended to simulate ten years of exposure to the *in vivo* environment. Stents were then inspected for signs of pitting corrosion using light and scanning electron microscopy. There were no signs of stent corrosion, indicating that the stent is sufficiently resistant to corrosion.
Percent Stent Surface Area	Determine the amount of vessel area in contact with the stent, as this property may affect tissue ingrowth or prolapse.	Percent stent surface area was calculated for each implanted diameter. The stented area ranged from 14.0% to 29.4%, which does not raise any concerns.
Dimensional Verification	Ensure that finished devices meet established specifications. Ensure that the stent dimensions do not vary along the length or circumference of the stent.	Stent diameters and lengths were measured at multiple locations after deployment. The stent surface was also examined at 20X – 50X for evidence of defects after expansion. The results confirm that the stent uniformly self-expands to its nominal diameter and length without visible defects.

Test	Objective	Summary of Methods and Results
Compression Force	Ensure that the stent can adequately resist radially applied compressive loads.	The stent compression force was measured after deployment and expansion by compressing the stent between two flat plates. The results demonstrate that the stent offers sufficient resistance to radial compression.
Expansion Force	Ensure that the stent can provide sufficient radial outward force to the vessel walls to maintain patency.	The stent expansion force was measured by compressing the stent between two flat plates and measuring the radial force exerted by the stent as it expands. The results demonstrate that the stent offers sufficient radial outward force.
Magnetic Resonance Imaging (MRI) Compatibility	Ensure that the stented area can be imaged with MRI without risks to patient safety.	Testing was conducted to evaluate the force, torque, and RF heating induced by a 3 Tesla MRI system on the stent. The resulting force was 0.158 mN, with a deflection angle of 3°. The induced torque ranged from 0.4 μNm to 1.0 μNm. The maximum observed temperature rise was 0.54°C with a SAR of 3.0 W/kg. The results suggest that the stent is sufficiently MRI-compatible.
Stress and Fatigue Analysis	Along with accelerated durability testing, ensure that the stent can withstand anticipated static and dynamic mechanical loads.	Stress characteristics under worst-case anticipated radial and bending loads were calculated using finite element analysis (FEA) modeling. Based on a Goodman analyses of the calculated stresses, the straight and tapered stents exhibited safety factors in excess of 1.0, indicating sufficient durability under anticipated clinical conditions.
Accelerated Durability	Determine whether stent fractures occur when subject to physiologically relevant radial fatigue loads.	Stents were subjected to a total of 400 million pulsatile cycles at a frequency of 50 Hz in latex tubes with a 2 – 4% diameter change to simulate more than 10 years of implant life at the indicated implant location. Test samples were then inspected at 20X magnification using light microscopy. No cracks or other material defects were observed, suggesting satisfactory durability under simulated pulsatile radial loads.

Table 5: *In Vitro* Summary For The Protégé® GPS™ and Protégé® RX Carotid Stent Systems

Test	Objective	Summary of Methods and Results
Delivery System Dimensions	Ensure that the catheter dimensions meet established specifications	Catheter lengths and diameters were measured. The measured dimension fell within the device specifications.
Crossing Profile	Ensure that the maximum stent system diameter is sufficient to permit lesion crossing without complication.	The crossing profile of complete stent systems was measured using a calibrated gauge. The results indicate that stent systems can pass through lesions without significant interaction between the mounted stent and the lesion.
Tensile Strength	Ensure that the delivery system bonds will not fail during clinical use.	Longitudinal tensile strength of all key delivery system bonds was assessed using an axial tensile tester. The results demonstrate adequate tensile strength for the delivery systems.

Test	Objective	Summary of Methods and Results
Burst Pressure	Determine the maximum pressure the stent system can withstand before leakage occurs.	To measure the maximum injection pressure, delivery systems were pressurized until leakage was observed. The burst rate for each sample was above the maximum specified injection pressure. These results indicate satisfactory burst pressure.
Catheter Priming	Ensure that the space between the inner and outer catheter can be easily primed with saline or contrast.	Saline was manually injected into the annular space, and the time for the saline to reach the distal end of the catheter was recorded. The catheters were also examined for signs of leakage. The results suggest that the catheter can be easily primed during clinical use without significant leakage.
Catheter/Stent Kink Resistance	Ensure that stent delivery does not result in kinking of the delivery catheter, which may affect stent deployability, or the stent, which may affect vessel patency.	Mounted stent systems were tracked along a 0.014" guide wire, through a 6 Fr sheath, and around a 1.5" bend to simulate worst-case anticipated patient anatomy. No kinks were observed on the delivery system or stent, indicating that passage through tortuous anatomy does not permanently affect the structure of the device.
Deployment Force	Ensure that the force required by the operator to deploy the stent does not adversely affect stent deployability.	The force required to deploy the stent using the delivery system handle was measured using a force gauge. The results met the established specification and demonstrate that the deployment force is acceptable.
Deployment Accuracy	Ensure that the stent can be deployed in the intended implant location.	Stents were deployed into tubing sized to represent the nominal recommended vessel diameter. The location of the deployed stents was measured in reference to two markers, which indicated the target implant location. The results suggest accurate and reproducible stent deployment.
SpideRX Compatibility	Ensure that the stent systems can be safely used with the ev3 SpideRX® Embolic Protection Device without device entanglement or damage.	Partially full SpideRX® filter baskets were retrieved through tubing arranged in a tortuous configuration, in which overlapping Protégé® stents had been deployed. No device dmagae or complications were observed. The Protégé® and SpideRX® devices were also used successfully together in an acute animal study, in which SpideRX® devices were successfully retrieved without complication in porcine carotid arteries. The test results demonstrate that the two devices are compatible.

9.2. Animal Testing

Two *in vivo* studies were performed to demonstrate device performance and short- and long-term safety. Both studies were conducted in accordance with Good Laboratory Practices (GLP) per 21 CFR § 58. Table 6 provides a summary of the *in vivo* animal testing performed with the Protégé® GPS™ and Protégé® RX Carotid Stent Systems.

Table 6: *In Vivo* Summary For The Protégé® GPS™ and Protégé® RX Carotid Stent Systems

Study	Number of Animals, Timepoints, Devices Tested, Implant Sites	Relevant Findings
Performance and Long Term Evaluation of Protégé Stents in the Carotid and Iliac Arteries	10 animals (canine) Acute, 1, 3, and 6 months 30 devices Carotid and iliac arteries (15 stents each)	All stent delivery and deployment procedures were uneventful with good stent apposition and accurate stent delivery. At explant, all devices were widely patent with no areas of stenosis. Histology results indicated that no perforations, hemorrhages or significant inflammation were present at each time interval.
Performance of the Protégé® RX Carotid Stent Delivery System	3 animals (porcine) Acute 18 devices Subclavian (9 stents), carotid (6 stents) and iliac (3 stents) arteries	The Protégé® RX Carotid Stent Delivery System performed satisfactorily in all cases. Successful tracking and deployment was achieved with all devices. There were no safety issues associated with the delivery system.

The *in vivo* study results support the safety of delivery and implantation of the Protégé® GPS™ Carotid Stent.

9.3. Biocompatibility

The biocompatibility of the materials found in the delivery system and stent was evaluated according to ISO 10993-1, "Biological Evaluation of Medical Devices Part 1: Evaluation of Testing" and FDA's Blue Book Memorandum dated May 1, 1995. All testing was conducted on sterile, finished devices in accordance with the FDA Good Laboratory Practices (GLP) outlined in 21 CFR, Part 58. The stent is considered an implant with permanent blood contact (> 30 days). The delivery system is categorized as an external communicating device that contacts circulating blood for less than 24 hours (limited exposure). The biocompatibility test regimen is outlined in Table 7.

Table 7: Protégé® GPS™ Stent and Delivery Systems Biocompatibility Testing

Test Performed	Results
Cytotoxicity (MEM Elution)	Pass
Acute Systemic Toxicity	Pass
Intracutaneous Reactivity	Pass
In Vitro Hemocompatibility	Pass
ASTM Hemolysis Assay	Pass
Lee and White Coagulation	Pass
Sensitization (Kligman Maximization)	Pass
AMES Mutagenicity Assay	Pass
Material–Mediated Pyrogenicity	Pass
1- and 4-Week Intramuscular Implantation Test (Stent Only)	Pass

Evaluation of chronic toxicity and carcinogenicity was not necessary due to the extensive clinical history of the device materials and their well-characterized long-term safety profile. Device thrombogenicity was evaluated as part of the other *in vivo* studies conducted to evaluate device safety and performance.

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

9.4. Sterility and Shelf Life Testing

Sterility
The Protégé® GPS™ and Protégé® RX Carotid Stent Systems are ethylene oxide sterilized per the requirements of ANSI/AAMI/ISO 11135:1994, "Medical devices—Validation and routine control of ethylene oxide sterilization." The validation results demonstrated that the sterilization process achieves a minimum sterility assurance level of 10^{-6}, and that residual levels were within the acceptable ranges for an implant according to ISO 10993-7 and AAMI TIR No. 19.

Pyrogenicity testing of finished lots is conducted regularly using the Limulus Amebocyte Lysate (LAL) method.

Shelf Life Tests
A two-year shelf life has been substantiated for both the Protégé® GPS™ Carotid Stent System and the Protégé® RX Carotid Stent System. Product and packaging specifications, quality, functionality, and safety requirements were demonstrated after sterilization and accelerated aging.

10. Summary of Clinical Studies

The Carotid Revascularization with ev3 Inc. Arterial Technology Evolution (CREATE) Pivotal Trial was a prospective, non-randomized, multi-center, single-arm clinical trial. The trial was performed to demonstrate the safety and efficacy of the Protégé® GPS™ Carotid Stent System and the SPIDER™ Embolic Protection Device when used to treat internal and/or common carotid artery stenoses in symptomatic (≥ 50% stenosis) and asymptomatic (≥ 70% stenosis) patients at high risk for adverse events from surgical revascularization. A total of 419 patients were enrolled at 31 clinical sites in the United States. Of these 419, twenty-five underwent staged stenting of both carotid arteries. For these subjects, both lesions were enrolled into the CREATE Pivotal Trial, bringing the total lesion count to 444.

An overview of the CREATE Trial is presented in Table 8:

Table 8: Overview of CREATE Pivotal Trial

Products Evaluated	Over-the-wire Protégé® GPS™ Carotid Stent System and over-the- wire SPIDER™ Embolic Protection Device
Study Design	Non-randomized, multi-center, single-arm, prospective clinical trials
Patients Enrolled	419
Number of Sites	31
Primary Endpoint	30-day composite of myocardial infarction (MI), ipsilateral stroke, procedure-related contralateral stroke, or death AND ipsilateral stroke from 31 to 365 days post-implantation
Secondary Endpoints	-Ipsilateral stroke, procedure-related contralateral stroke, or death within 30 days of implantation; and ipsilateral stroke from 31 to 365 days post-implantation. -Target lesion revascularization through 1 year -Target vessel revascularization through 1 year -Primary patency at 1 year (defined as < 70% stenosis as measured by duplex scan) -Technical Success (defined as successful delivery and retrieval of the filter and stent deployment with final residual stenosis < 50%)
Study Hypothesis	The primary endpoint rate for the treatment is significantly less than the upper limit of an objective performance criterion (uOPC) of 16%.
Patient Follow-up	25 - 45 days post procedure: neurological evaluation by neurologist or NIH-approved surrogate, adverse event assessment, ultrasound
	150 - 240 days post procedure: Telephone follow-up including evaluation of Barthel Index and Rankin Score, adverse event reporting, current anticoagulation/antiplatelet regimen
	335 - 425 days post procedure: neurological evaluation by neurologist or NIH-approved surrogate, adverse event assessment, ultrasound

Core laboratories provided independent assessments of angiographic and ultrasound data. Monitors reviewed all data to ensure appropriate reporting of adverse events and adherence to the study protocol. A Clinical Events Committee (CEC) consisting of non-investigators adjudicated adverse events reports for study subjects. A Data Safety Monitoring Board (DSMB) monitored study progress and adverse events to ensure patient safety.

Statistical Methods

The statistical analysis of the CREATE Pivotal Trial was designed to show that the ev3 Inc. carotid artery stent system primary endpoint is significantly less than an objective performance criterion (uOPC). The uOPC was derived from a review of the current literature related to outcomes at one year from carotid endarterectomy and medical therapy, which represented the standard of care at the time of study initiation.

The upper bound of the confidence interval around the primary endpoint observed was expected to be less than the uOPC of 16%. ev3 Inc. estimated the rate for the carotid artery stent system would be similar to the rate observed in the SAPPHIRE study at one year of 9.8% (*N Engl J Med* 351:1493-1501). Conservatively, an 11% rate was estimated for the primary endpoint. The sample size estimation was determined by assuming an

exact confidence interval for this primary endpoint. The following assumptions were made to determine the study sample size:

- Although the estimated endpoint rate for the ev3 Inc. carotid stent is 9.8%, a conservative estimate for sample size assumed a rate of 11%.
- The Type I error rate $\alpha = 0.05$
- This Type I error is one-sided
- The Type II error rate $\beta = 0.20$, which is equivalent to 80% power
- uOPC of 16%

The study hypotheses are presented below:

H_0: $p \geq 16\%$
H_A: $p < 16\%$

where *p* is the observed primary endpoint rate for the Protégé GPS™ Carotid Stent System. A one-sided upper 95% confidence bound that is less than 16% is equivalent to rejecting H_0 at the 0.05 level of significance and concluding the primary endpoint rate is significantly less than the uOPC of 16% ($p < 0.0001$). Exact methods were used to form the confidence bound.

Eligibility Criteria Summary
Male and female patients who presented for percutaneous treatment of an internal and/or common carotid artery intervention were considered for enrollment. To be included, the patients were required to be at least 18 years old and considered to be at high risk for carotid endarterectomy.

Patients were considered symptomatic if their target stenosis was associated with ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral ischemic stroke within 6 months prior to enrollment. Patients who were characterized as symptomatic were also required to have a target lesion stenosis ≥ 50%, based on the results of the North American Symptomatic Carotid Endarterectomy Trial (NASCET; *N Engl J Med* 339:1415-25). Asymptomatic patients were required to have a target lesion stenosis ≥ 70%.

High-risk criteria are included in Table 9. The subjects were required to meet at least one or more high-risk criterion in either column.

Table 9: High Surgical Risk Criteria

Clinical Criteria	Anatomic Criteria
1. Age > 75 yrs	1. Contralateral carotid artery occlusion
2. Canadian Cardiovascular Society (CCS) angina class 3 – 4 or unstable angina	2. High cervical lesion (above the angle of the jaw)
3. Congestive heart failure (CHF) class III – IV	3. Infraclavicular lesion
4. Left ventricular ejection fraction (LVEF) < 35%	4. Tandem lesions > 70%
5. Myocardial infarction < 6 weeks pre-procedure	5. Previous cervical radiation treatment, tracheostomy/stoma, or radical neck dissection
6. Coronary artery disease with > two-vessel disease in major vessel and history of angina	6. Restenosis from previous carotid endarterectomy
7. Severe pulmonary disease: home oxygen, resting pO_2 < 60 or forced expiration volume (FEV_1) < 50%	7. Cervical immobility due to fusion or arthritis
8. Permanent contralateral cranial nerve injury	8. Bilateral carotid stenoses, both requiring treatment

Description of Patients Evaluated

Table 10 summarizes patient follow-up compliance in the CREATE Pivotal Trial.

Table 10: CREATE Pivotal Patient Follow-up

Time	Compliance
Procedure	419 / 419 (100%)
Discharge	417 / 419 (99.5%)
30 Days	405 / 419 (96.7%)
6 Months	386 / 419 (92.1%)
12 Months	353 / 419 (84.2%)
Primary Endpoint	370 / 419 (88.3%)

Baseline demographics and lesion characteristics are presented in Table 11.

Table 11: Baseline Demographics and Lesion Characteristics (All Patients Treated)

Patient Characteristics	Pivotal (N = 419)
Age (yrs.)	
Mean	73.6
Standard deviation (SD) (N)	9.1 (419)
Range (min, max)	48 (46, 94)
Male	(255 / 419) 60.9%
Diabetes Mellitus	(131 / 419) 31.3%
Hypertension	(377 / 419) 90.0%
Hyperlipidemia	(367 / 419) 87.6%
Renal Insufficiency	(80 / 419) 19.1%
Smoking	
Never	(96 / 419) 22.9%
Current	(69 / 419) 16.5%
Former > 1 Year	(254 / 419) 60.6%
History of Arrhythmia	(84 / 419) 20.0%
History of Myocardial Infarction	(126 / 419) 30.1%
History of Previous Percutaneous Transcatheter Coronary Angioplasty (PTCA)/Coronary Artery Bypass Grafting (CABG)	(219 / 419) 52.3%
History of CEA	(123 / 419) 29.4%
History of Other Treatment to Target Artery	(3 / 419) 0.7%
History of TIA	(97 / 419) 23.2%
History of Stroke	(85 / 419) 20.3%
Current Carotid Bruit	(318 / 411) 77.4%
Lesion Location	
Common	(25 / 444) 5.6%
Internal	(334 / 444) 75.2%
Both	(85 / 444) 19.1%
Lesion Length	17.5
Eccentric Lesion	(337 / 442) 76.2%
Calcified Lesion	(222 / 442) 50.2%
Ulcerated Lesion	(173 / 442) 39.1%
Symptomatic	(73 / 419) 17.4%
Pre-procedure % Stenosis	82.2
Pre Reference Vessel Diameter	5.5
Pre Vessel Diameter (minimum lumen diameter)	
Mean	1.9
SD (N)	0.8 (377)
Range (min, max)	7.3 (0.4, 7.7)
Post Vessel Diameter	
Mean	4.4

Patient Characteristics	Pivotal (N = 419)
SD (N)	0.83 (365)
Range (min, max)	4.8 (2.4, 7.2)
High Risk Factors	
Anatomical	(100 / 419) 23.9%
Clinical	(196 / 419) 46.8%
Both	(123 / 419) 29.4%
Clinical Risk Factors	
Age > 75	(209 / 419) 49.9%
CCS Angina 3-4	(17 / 419) 4.1%
CHF NYHA III-IV	(28 / 419) 6.7%
Coronary Artery Disease	(146 / 419) 34.8%
LVEF < 35%	(41 / 419) 9.8%
MI < 6 weeks	(3 / 419) 0.7%
Perm. Contralateral Injury	(0 / 419) 0.0%
Severe Pulmonary Disease	(16 / 419) 3.8%
Anatomical Risk Factors	
Bilateral Carotid Stenosis	(43 / 419) 10.3%
CEA Restenosis	(100 / 419) 23.9%
Cervical Immobility	(11 / 419) 2.6%
High Cervical Lesion	(26 / 419) 6.2%
Contralateral Occlusion	(40 / 419) 9.5%
Hostile Neck	(29 / 419) 6.9%
Infraclavicular Lesion	(1 / 419) 0.20%
Tandem Lesions >70%	(3 / 419) 0.70%

Clinical Results Summary

The primary endpoint of the CREATE Pivotal Trial was a composite of MI, ipsilateral stroke, procedure-related contralateral stroke or death within 30 days of implantation plus the ipsilateral stroke rate within one year of implantation (also referred to as MACCE). The incidence rates for each primary and secondary endpoint component are provided in **Table 12**.

Table 12: Safety And Efficacy Measures (All Patients Treated)

Safety and Efficacy Measures	(N = 419)
Primary Endpoint	29 / 370 (7.8%)
30-Day MACCE*	26 / 414 (6.3%)
Myocardial Infarction	4 / 414 (1.0%)
Ipsilateral CVA - Major - Minor	16 / 414 (3.9%) 14 / 414 (3.4%) 3 / 414 (0.7%)
Procedure-Related Contralateral CVA	3 / 414 (0.7%)
Death	8 / 414 (1.9%)
1 year Ipsilateral CVA	3 / 370 (0.8%)
Secondary Endpoints	
MANE**	26 / 370 (7.0%)
TLR	1 / 370 (0.2%)
TVR	1 / 370 (0.2%)
Primary Patency at 1 year	286 / 304 (94.1%)
Technical Success	408 / 419 (97.4%)
Acute Procedure Success (Angiographic)	397 / 397 (100.0%)
Acute Procedure Success (Site)	437 / 444 (98.4%)

* 30-day MACCE is done via a hierarchical calculation. Only the worst event that occurred in any subject is counted. The individual components of MACCE are counted per occurrence.

** Major Adverse Neurological Events (MANE) includes 11 elements of the primary endpoint **except** myocardial infarction

In the CREATE Pivotal Trial, 29 of the 370 subjects followed to one year were observed to have at least one primary endpoint. This leads to an overall primary endpoint rate of 7.8% (29/370 = 7.8%). This estimate of the primary endpoint rate was performed only on subjects with recorded endpoints, excluding subjects with missing endpoint information. Using exact confidence methods, the upper 95% confidence limit for the primary endpoint rate was 11.3%. The corresponding p-value for the above null hypothesis is less than 0.0001. Thus the null hypothesis that the primary efficacy of the carotid stent system is equal to or greater than 16% is rejected and the primary endpoint event rate is significantly less than 16% (p-value < 0.0001).

Figures 1 and 2 contain primary endpoint Kaplan-Meier Survival Estimates overall and by symptom group. When the overall 30-day MACCE number was calculated, it was done in a hierarchical fashion and only the worst event that occurred in any subject was counted. The individual components of MACCE were actually counted per occurrence.

Kaplan-Meier Analysis of Time-to-Primary-Endpoint for All Patients

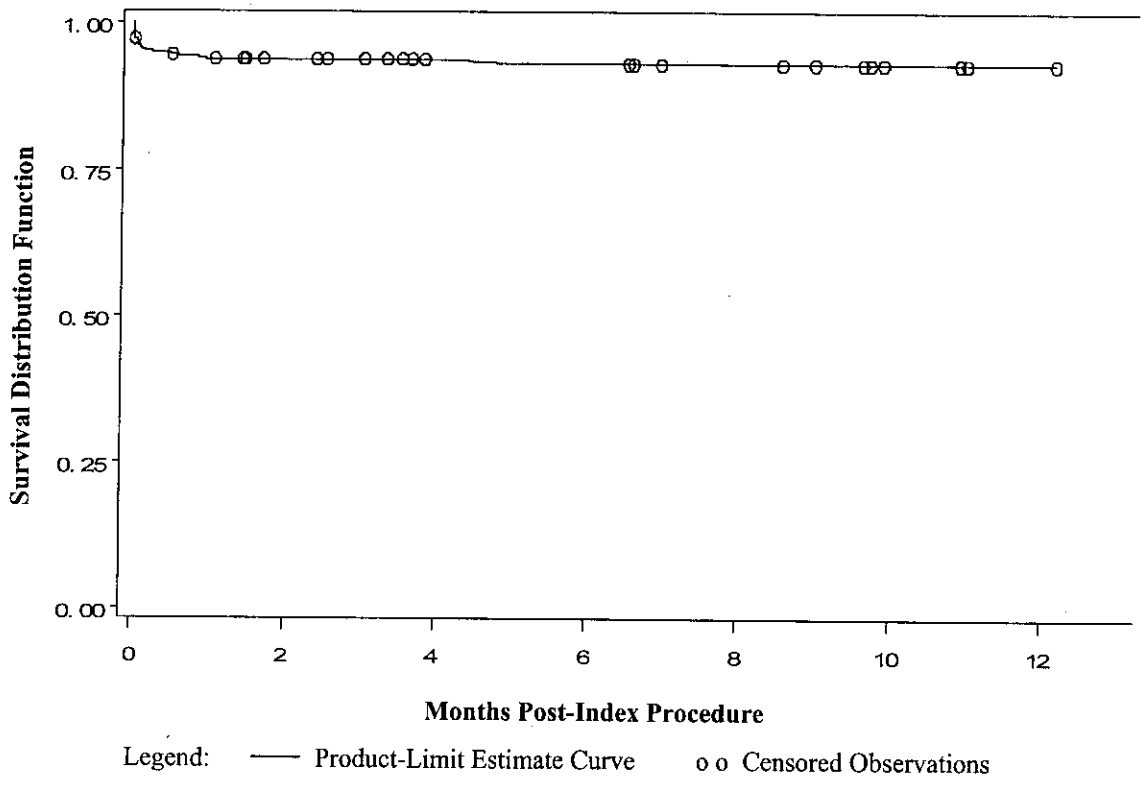

Figure 1. Primary Endpoint Overall Pivotal Cohort
All Patients

Months After Index Procedure	0	1	3	6	12
Number At Risk	419	391	384	376	366
Number Censored	0	2	9	14	24
Number of Events	0	26	26	29	29
Percent Event Free	100%	93.8%	93.8%	93.0%	93.0%

Kaplan-Meier Analysis of Time-to-Primary-Endpoint for Symptomatic and Asymptomatic Patients

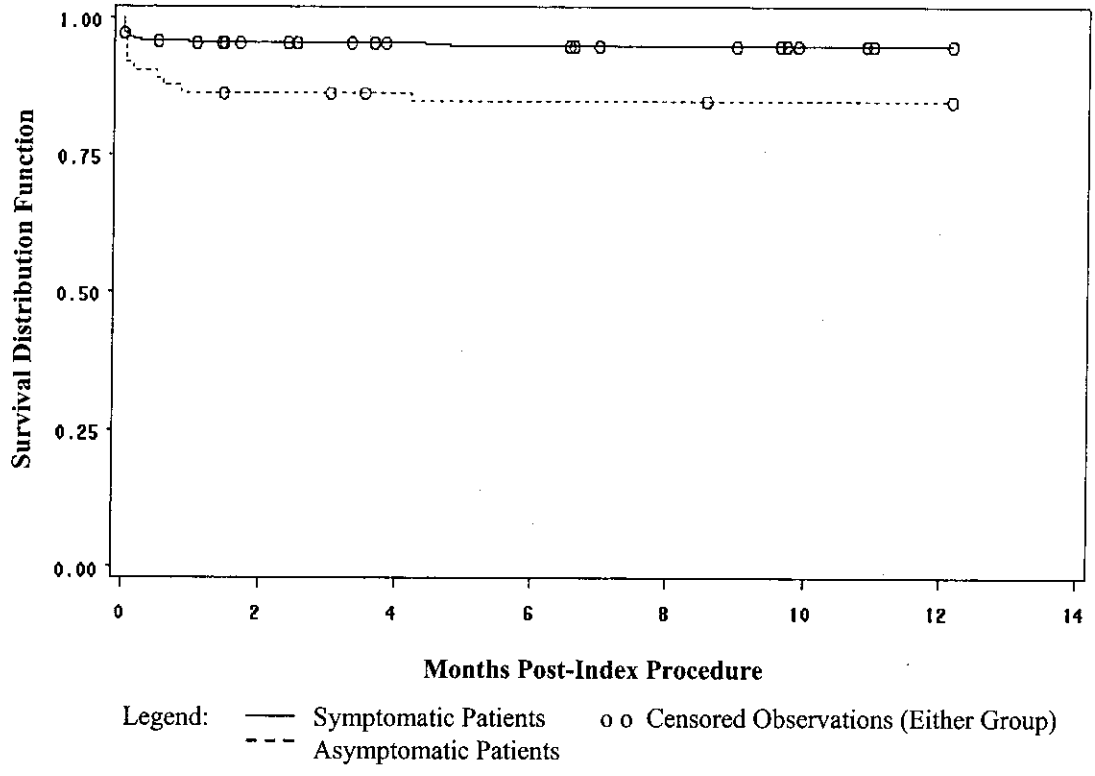

Figure 2. Primary Endpoint by Symptom Group

Asymptomatic Patients

Months After Index Procedure	0	1	3	6	12
Number At Risk	346	328	322	317	308
Number Censored	0	2	8	11	20
Number of Events	0	16	16	18	18
Percent Event Free	100%	95.4%	95.4%	94.8%	94.8%

Symptomatic Patients

Months After Index Procedure	0	1	3	6	12
# At Risk	73	63	62	59	58
# Censored	0	0	1	3	4
# Events	0	10	10	11	11
% Event Free	100%	86.3%	86.3%	84.9%	84.9%

11. Conclusions Drawn from Clinical Studies

The preclinical studies indicate that the Protégé® GPS™ and Protégé® RX Carotid Stent Systems used with embolic protection meet or exceed safety and performance specifications as a treatment for carotid artery disease in the population indicated.

The multicenter clinical studies indicate that the Protégé® GPS™ Carotid Stent System used with embolic protection is safe and effective as a treatment for carotid artery disease in the population indicated. The Protégé® RX Carotid Stent System is expected to perform similarly to the Protégé® GPS™ Carotid Stent System in clinical use based on similarities in design and non-clinical performance between the two systems.

While asymptomatic patients with 70 – 79% carotid artery stenosis were enrolled in the CREATE Pivotal Trial, these patients are not included in the approved indications because of a lack of demonstrated clinical benefit from revascularization for this patient population (*N Engl J Med* 315:860 – 865; *Stroke* 22:1485- 1490). The indications for this device may be expanded to include these patients once additional evidence of clinical benefit becomes available.

Results from the preclinical and clinical evaluations provide valid scientific evidence and reasonable assurance that the devices are safe and effective when used in accordance with the labeling.

12. Panel Recommendation

In accordance with 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.

13. CDRH Decision

FDA issued an approval order on January 24, 2007. The conditions of approval require a post-approval study of 1,500 new patients to be evaluated at 30 days and 365 days post-procedure, as well as the continued follow-up of the existing cohort of patients from the CREATE Pivotal Trial for a total of three years. The results of these studies will be evaluated to determine whether any changes should be made to the device labeling to ensure that the information available to physicians is complete, appropriate, and up-to-date.

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

14. Approval Specifications

Instructions for Use: See labeling

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

Postapproval Requirements and Restrictions: See approval order.