SUMMARY OF SAFETY AND EFFECTIVENESS DATA

1.0 GENERAL INFORMATION

Device Generic Name:	Intravascular Carotid Stent with Delivery System
Device Trade Names:	NexStent® Carotid Stent and Delivery System NexStent® Carotid Stent and Monorail Delivery System
Applicant's Name and Address:	EndoTex Interventional Systems 10231 Bubb Road Cupertino, CA 95014
PMA Number:	P050025
Date of Panel Recommendation:	None

Date of Notice of Approval to the Applicant: October 27, 2006

2.0 INDICATIONS FOR USE

The NexStent System used in conjunction with Boston Scientific FilterWire EZ embolic protection system, is indicated for treatment of patients at high risk for adverse events from carotid endarterectomy who require carotid revascularization and meet the criteria outlined below:

1. Patients with neurological symptoms associated with ≥50% stenosis of the common or internal carotid artery OR patients without neurological symptoms and ≥80% stenosis of the common or internal carotid artery by ultrasound or angiogram, AND
2. Patients must have a reference vessel diameter within the range of 4mm and 9mm at the target lesion and a stenosis less than 30mm in length.

3.0 CONTRAINDICATIONS

The NexStent System is contraindicated for use in:

- Patients in whom anti-coagulant and/or anti-platelet therapy in contraindicated.
- Patients with severe vascular tortuosity or anatomy that would preclude the safe introduction of a guiding catheter/sheath, embolic protection system, delivery catheter and/or retrieval catheter.
- Patients with a known hypersensitivity to nickel or titanium.
- Patients with uncorrected bleeding disorders.
- Lesions in the ostium of the common carotid artery.

4.0 WARNINGS AND PRECAUTIONS

Warnings and Precautions can be found in the Instructions for Use for the NexStent Carotid Stent and Delivery System and the NexStent Carotid Stent and Monorail Delivery System.

5.0 DEVICE DESCRIPTION

NexStent Carotid Stent

The EndoTex NexStent is a nickel-titanium alloy (Nitinol), flexible, self-expanding stent. The stent design is a fine mesh Nitinol flat sheet, laser-etched to form a specific geometric design. The stent geometry is a variable multi-cellular design with adaptive cells capable of differential expansion. As the stent is deployed, it undergoes both uncoiling and cellular expansion due to the mesh design and the properties inherent in the superelastic nature of Nitinol. One stent size is used for treating vessel sizes ranging from 4mm to 9mm in diameter. The length of the stent is 33mm in the delivery system and is approximately 30mm at a fully deployed diameter of 9mm.

NexStent Carotid Stent and Delivery System (Over-the-Wire)

The NexStent Carotid Stent and Delivery System is a single-use system designed to deliver a self-expanding stent to the extracranial carotid arteries via a sheathed percutaneous delivery system. The NexStent delivery system is an over-the-wire device compatible with standard 0.014" guidewires. The stent is contained within the distal end of a 135cm, 5 French (0.066" O.D.) percutaneous delivery sheath. The stent is positioned in the distal end of the delivery system against an inner coil assembly adjacent to a proximal radiopaque marker. The delivery handle controls the relative position of the inner coil assembly, sheath, and stent during stent delivery.

The stent is deployed by rotating the control knob counter-clockwise, thus retracting the sheath. The distal end of the sheath opens as it is withdrawn over the stent and the stent gradually expands to meet the vessel wall. The stent releases from the delivery system and fully expands against the vessel wall when the sheath is retracted beyond the proximal edge of the stent.

NexStent Carotid Stent and Monorail Delivery System

The NexStent Carotid Stent and Monorail Delivery System is a single-use system designed to deliver a self-expanding stent to the extracranial carotid arteries via a sheathed percutaneous Monorail delivery system. The delivery system has a radiopaque tracking tip to facilitate delivery system tracking through the carotid arterial vasculature. The stent is located at the distal end of the delivery system catheter between two radiopaque markers. The delivery system is a monorail system compatible with standard 0.014" (0.36mm) or smaller guidewires. The delivery handle functions in the same manner as the over-the-wire version, rotating the control knob of the delivery handle retracts the sheath during stent delivery.

6.0 ALTERNATIVE PRACTICES AND PROCEDURES

Treatment of carotid artery disease currently includes surgery, medical therapy, or a combination of both. The primary alternative treatment used to prevent stroke in patients with significant carotid artery disease is surgery to remove plaque from the affected artery (endarterectomy). Medical therapy may be used alone, or in conjuction with surgery and includes use of antiplatelet and/or anticoagulant medicine, as well as antihypertensive and antilipidemic drugs as indicated.

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Antiplatelet drugs include aspirin, Plavix® (clopidogrel), or Ticlid® (ticlopidine). Anticoagulants include Coumadin® (warfarin). Conservative treatment in the form of medical therapy can also include modification of lifestyle risk factors for stroke, such as cigarette smoking and alcohol use.

7.0 MARKETING HISTORY

The NexStent Carotid Stent and Delivery System and NexStent Carotid Stent and Monorail Delivery System are approved for commercial sale in the European Economic Area (EEA) and in additional countries. These devices have not been withdrawn in any country due to reasons related to safety and effectiveness of the device.

8.0 POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

8.1 Observed Adverse Events

In the CABERNET trial, the NexStent Carotid Stent and Delivery System (OTW) was evaluated for the treatment of patients with significant extracranial carotid artery stenosis who required carotid revascularization and were at high risk for adverse events from carotid endarterectomy. A total of 454 patients were enrolled in the main registry of the trial. The majority of the population had a strong cardiovascular history where 63.7% had an anatomical high-risk factor, 19.6% had a comorbid high-risk factor and 16.7% had both an anatomical and comorbid risk factors.

The primary endpoints of the trial were as follows:

1. Major clinical events at one-year defined as any death, stroke or myocardial infarction (MI).
2. Thirty day event rate defined as any death, stroke or MI ≤30-days post-procedure; plus the 31-day to12-month event rate defined as any ipsilateral stroke including any death as a result of an ipsilateral stroke.

The primary objective of the trial was to demonstrate that the major adverse event (MAE) rates for both primary endpoints were not inferior to the MAE rate historically associated with carotid endarterectomy (CEA).

Tables 1 and 2 present the MAE and the serious adverse events (SAE) reported for the enrolled patients through 1 year. Table 3 presents the patient deaths by causation. The major adverse events table summarizes all deaths, strokes and MIs.

Table 1. Major Adverse Events

Major Adverse Events	≤30 days (n=438) [1]		31-365 days (n=421) [2]		Cumulative 0-365 Days (n=421) [2]	
Primary Endpoints	# Patients	%	# Patients	%	# Patients	%
All Death Stroke and MI at 1 Yr.	17	3.9	33	7.8	50	11.9 [4]UCL=14.8 %
	# Patients	%Patients (N=438)	# Patients	% Patients (N=404)[3]	# Patients	% Patients (N=404)[3]
All Death Stroke and MI ≤ 30 days; plus the 31-day to12-month event rate defined as any ipsilateral stroke including any death as a result of an ipsilateral stroke	17	3.9	3	0.7	19	4.7 UCL=6.8%
Major Adverse Events by Classification	≤30 days (n = 438)		31-365 days (n = 421) [2]		Cumulative 0-365 Days (n = 421) [2]	
	# Patients	%	# Patients	%	# Patients	%
Death	2	0.5	17	4.0	19	4.5
Stroke	15	3.4	8	1.9	21	5.0
Ipsilateral Stroke	12	2.7	3	0.7	14	3.3
Major	5	1.1	1	0.2	5	1.2
Minor	7	1.6	2	0.5	9	2.1
Non-Ipsilateral Stroke	3	0.7	6	1.4	8	1.9
Major	1	0.2	3	0.7	4	1.0
Minor	2	0.5	3	0.7	4	1.0
Myocardial Infarction (MI)	1	0.2	16	3.8	17	4.0

[1] N= Patients enrolled in main trial registry (N=454) less patients not stented (N= 11), patients lost to follow-up at 30-day evaluation period (N=3) and patients who had a missed visit by 30-day timepoint (N=2)

[2] N=421 for the 31-365 and 0-365 time periods. This includes 398 patients evaluated at 1 year, 19 deaths, and 4 patients that did not have a 1-year visit but experienced an adverse event (398+19+4 = 421).

[3] In an effort to present the most conservative analysis for the MAE rate concerning the composite Primary Endpoint N=404 was used. Seventeen patient deaths that occurred during the 31-365 day time period were not due to ipsilateral stroke and were excluded from this analysis. Therefore N = 404 (421-17=404).

[4] Upper confidence Limit

Table 2. Serious Adverse Events

Event Categories[1]	≤ 30 days (N = 454)		31-365 days (N =443)		0-365 Days (N =454)	
	# Patients	% Patients	# Patients	% Patients	# Patients	% Patients
Procedure Related						
Angina	3	0.7	0	0.0	3	0.7
Bleeding/Anemia[2]	16	3.5	1	0.0	17	3.7
Cardiac Dysrrhythmia	14	3.1	0	0.0	14	3.1
Cardiogenic Shock	1	0.2	0	0.0	1	0.2
Ischemia/ ↑ Enzymes	4	0.9	0	0.0	4	0.9
Syncope	4	0.9	0	0.0	4	0.9
Cerebrovascular	3	0.7	0	0.0	3	0.7
Emergent CEA	1	0.2	0	0.0	1	0.2
Genitourinary	1	0.2	0	0.0	1	0.2
Hypotension	19	4.2	0	0.0	19	4.2

Event Categories[1]	≤ 30 days (N = 454)		31-365 days (N =443)		0-365 Days (N =454)	
	# Patients	% Patients	# Patients	% Patients	# Patients	% Patients
Hypertension	1	0.2	0	0.0	1	0.2
Infection	3	0.7	0	0.0	3	0.7
Metabolic	5	1.1	0	0.0	5	1.1
Musculoskeletal	2	0.4	0	0.0	2	0.4
Neurological	11	2.4	0	0.0	11	2.4
Prolonged Hospitalization	1	0.2	0	0.0	1	0.2
Respiratory	2	0.4	0	0.0	2	0.4
Vascular	7	1.5	5	1.1	12	2.6
Other	2	0.4	0	0.0	2	0.4
Access Site Complications[3]						
Bleeding and Hematoma	9	2.0	0	0.0	9	2.0
Ecchymosis	1	0.2	0	0.0	1	0.2
Pseudoaneurysm	3	0.7	1	0.2	4	0.9
Poss. Femoral Artery Thrombosis	1	0.2	0	0.0	1	0.2
Wound Infection	2	0.4	0	0.0	2	0.4
Total Procedure related	80	17.6	7	1.6	85	18.7
Non-Procedure Related						
Cardiac						
Angina	2	0.4	20	4.5	22	4.8
Cardiogenic Shock	0	0.0	1	0.2	1	0.2
Congestive Heart Failure (CHF)	3	0.7	16	3.6	19	4.2
Coronary Artery Disease	2	0.4	26	5.9	28	6.2
Dysrrhythmia	2	0.4	12	2.7	14	3.1
Ischemia/ ↑ Enzymes	3	0.7	3	0.7	5	1.1
Syncope	1	0.2	1	0.2	1	0.2
Valvular Disease	0	0.0	5	1.1	5	1.1
Other	1	0.2	2	1.1	3	0.7
Neurological						
TIA	0	0.0	8	1.8	8	1.8
Altered Mental Status	1	0.2	2	0.5	3	0.7
Organic Brain Syndrome/Memory Loss	0	0.0	2	0.5	2	0.4
Seizure	1	0.2	2	0.5	3	0.7
Syncope/Dizziness	1	0.2	11	2.5	12	2.6
Visual Disturbance	0	0.0	2	0.5	2	0.4
Other	0	0.0	1	0.2	1	0.2
Other Systems						
Bleeding	2	0.4	8	1.8	10	2.2
Blood Dyscrasia	9	2.0	9	2.0	17	3.7
Carcinoma	1	0.2	9	2.0	10	2.2
Cerebrovascular	0	0.0	5	1.1	5	1.1
Gastrointestinal	6	1.3	30	6.8	35	7.7

Event Categories[1]	≤ 30 days (N = 454)		31-365 days (N =443)		0-365 Days (N =454)	
	# Patients	% Patients	# Patients	% Patients	# Patients	% Patients
Genitourinary	3	0.7	1	0.2	4	0.9
Hemodynamic	2	0.4	7	1.6	9	2.0
Infection	2	0.4	10	2.3	12	2.6
Metabolic	2	0.4	10	2.3	12	2.6
Musculoskeletal	1	0.2	13	2.9	14	3.1
Other Hospitalization	0	0.0	22	5.0	22	4.8
Respiratory	2	0.4	18	4.1	19	4.2
Vascular[4]	4	0.9	42	9.5	45	9.9
Other	6	1.3	7	1.6	11	2.4
Total Non-Procedure Related	46	10.1	186	42.0	206	45.4

[1] Patients may have had multiple events and therefore can be counted in more than one category/subcategory of event. Counts represent the number of patients who have experienced one or more events.
[2] Twenty patients that had procedure related bleeding (non-access site) required a blood transfusion; 14 of the 20 events were procedure related
[3] Six access site complications required blood transfusions.
[4] Three of the 9 patients reported as having restenosis are not included in the "Vascular" event category secondary to AE forms which were pending for "target lesion restenosis"; however the 3 patients are reported in the secondary endpoint for restenosis.

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

- Access site includes such events as aneurysm, bleeding, bruising or ecchymosis, hematoma, pseudo-aneurysm, pain and arterial thrombosis.
- Bleeding includes such non access-site bleeding, nose bleed, surgical or incisional bleeding and retroperitoneal bleed.
- Blood Dyscrasia includes events such as anemia, thrombocytopenia, and leucopenia.
- Carcinoma includes such events as lung cancer, breast cancer, leukemia, brain tumor, rectal cancer.
- Cardiac includes such events as angina, coronary artery disease, cardiac dysrrhythmia, congestive heart failure cardiac-related syncope and valvular disease (aortic and mitral).
- Cerebrovascular includes such events as headache and brain hemorrhage.
- Gastrointestinal includes events such as dysphagia, indigestion, nausea, vomiting, esophageal stenosis or varicies, ulcer, bowel obstruction, GI Bleed, colitis, cholecystitis, pancreatitis, hepatic disorders, diverticulitis, melena and rectal prolapse.
- Genitourinary includes events such as urinary retention, hematuria, nocturia related to prostatic hyperplasia and lower abdominal pain related to the bladder or prostate.
- Hemodynamic includes events such as hypotension and hypertension
- Metabolic includes events such as diabetes, dehydration, electrolyte imbalance and renal failure.
- Musculoskeletal includes events such as bone, muscle or joint pain, fractures and arthritis injury, and inguinal hernia.

- Infection includes events such as conjunctivitis, cellulitis, parotitis, abscess, system infection, sepsis, fungal infection, urinary tract infection, wound infection and non-specified infection.
- Neurological includes all non-stroke related events such as altered mental status/confusion/dementia/organic brain syndrome, seizure, sensory deficits (peripheral numbness or weakness), visual/speech disturbances, neurologic-related syncope or dizziness, and TIA.
- Respiratory includes events such as pneumonia, hemoptysis, respiratory. failure and chronic obstructive lung disease.
- Vascular includes such as events as carotid restenosis (target and non-target lesion), peripheral arterial disease, and peripheral arterial or venous thrombosis.
- Other Hospitalizations include hospitalizations for other medical/surgical treatment.
- Other is a miscellaneous category that includes such events as agitation, drug hypersensitivity, patient fall (non-neurologic) rash, general weakness, gout, peripheral edema, fatigue etc.

Table 3. Patient Deaths

Event Categories	Total (n=421)	
	Deaths	%
0-30 days		
Cardiac	1	0.2
Sepsis	1	0.2
31-365 days		
Cardiac	9	2.1
Carcinoma	2	0.5
Respiratory	2	0.5
Gastrointestinal	1	0.2
Renal Failure	1	0.2
Liver Failure	1	0.2
Unknown	1	0.2
Total Deaths (0-365 days)	19	4.5

Note: There were no neurologic related deaths

8.2 Potential Adverse Events

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

- Allergic reactions to anti-platelet agents/contrast medium
- Aneurysm
- Angina/coronary ischemia
- Arrhythmia
- Arterial occlusion/thrombosis at puncture site or remote site
- Ateriovenous fistula
- Bacteremia or septicemia

- Bleeding from anticoagulant or antiplatelet medications
- Cerebral edema
- Cerebral hemorrhage
- Cerebral ischemia/transient ischemia attack (TIA)
- Congestive heart failure (CHF)
- Death
- Detachment and/or implantation of a component of the system
- Emboli, distal (air, tissue or thrombotic emboli)
- Emergent or urgent endarterectomy surgery (CEA)
- Fever
- Filter thrombosis/occlusion
- Groin hematoma, with or without surgical repair
- Hemorrhage, with or without transfusion
- Hyperperfusion syndrome
- Hypotension/hypertension
- Infection and pain at insertion site
- Ischemia/infarction of tissue/organ
- Myocardial infarction (MI)
- Pain (head, neck)
- Pseudoaneurysm, femoral
- Renal failure/insufficiency
- Restenosis of stented segment
- Seizure
- Severe unilateral headache
- Stent/filter entanglement/damage
- Stent embolization
- Stent malposition
- Stent migration
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident (CVA)
- Total occlusion of carotid artery
- Vessel dissection, perforation, or rupture
- Vessel spasm or recoil

9.0 SUMMARY OF PRE-CLINICAL STUDIES

Preclinical studies related to the NexStent Carotid Stent and Delivery System, the NexStent Carotid Stent and Monorail Delivery System are presented below for in vitro and in vivo product testing, biocompatibility, sterilization, packaging and shelf life.

9.1 In Vitro Testing

EndoTex Interventional Systems has conducted a complete battery of in vitro tests to verify that the design of the NexStent Carotid Stent and Delivery System and the NexStent Carotid Stent and Monorail Delivery System fully meet performance specifications. The bench testing conducted covered all aspects of delivery system and stent performance and is consistent with Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices: Intravascular Stents US FDA May 1995.

The stent materials and design were subjected to a complete mechanical, chemical, dimensional, analytical and fatigue evaluation. The in vitro device bench testing and analytical analysis are summarized in Table 4.

Table 4. Summary of in vitro bench test for the stent

Test	Requirement	Results Summary
Stent Material Elemental Composition and Surface Characterization	Material characterization	Elemental composition analyses of the base Nickel Titanium material comprising the EndoTex stent were conducted. In addition, various means including Scanning Electron Microscopy (SEM), Energy Dispersive X-ray Spectroscopy (EDS), Electron Spectroscopy for Chemical Analysis (ESCA) and Auger Spectroscopy were employed to analyze the electro-polished surface of the finished stent. The results from these analyses were acceptable.
Tensile Properties	Material characterization	The mechanical, superelastic properties of the Nitinol alloy comprising the EndoTex stent were evaluated using temperature-controlled tensile and compressive tests. The results from these tests were acceptable.
Corrosion	Durability and integrity of the implanted device	A comparison of the NexStent was made to an FDA approved small implant device made from 316L Stainless Steel. The NexStent Nitinol Stent demonstrated corrosion resistance performance that is equivalent or slightly better than a conventional stainless steel stent.
Stent Dimensional Verification	Appropriate sizing and accurate deployment of the implant	The dimensional properties of the stent mesh following final electropolishing were evaluated using an automated optical dimensional inspection system. The results obtained from stent dimensional testing were acceptable and consistent with specifications.
Stent Dimensional Changes and Free-Area Percentage	Deployment accuracy and patency of the implant	Stent length was directly measured by deploying the stent into plastic tubes of known diameters from 4-9mm. The percent length change ranged from 0.6% at 4 mm to 9.4% at 9mm. The stent metal area was calculated using computer aided design software. The free area of the stent ranged from 75.9% at 4mm to 88.3% at 9mm.
Finite Element Analysis	Analytical validation of stent design to ensure durability and integrity of the implanted device	The stresses induced in the stent mesh during loading into the delivery system and the advance of the delivery system through tortuous human anatomy were analytically determined using FEA. The analysis was conducted under simulated worst-case loading conditions and accounted for stent manufacturing and delivery system tolerances. The FEA analysis demonstrated analytically that the NexStent design has adequate design safety margin relative to expected design loads.
Stent Pulsatile Fatigue Testing	Durability and integrity of implanted device in a pulsatile environment over the implant life	EndoTex conducted accelerated radial pulsatile fatigue testing on the NexStent implant at a deployment diameter of 4mm and the results were acceptable. The stent remained intact and maintained patency through 400 million cycles, the equivalent of 10 years of fatigue loading.
Stent Flexural Fatigue Testing	Durability and integrity of implanted device as it relates to neck bending and head turning over the implant life	EndoTex examined the flexural fatigue of the stent to evaluate the stents' durability in neck bending and head turning over the implant life. A custom built flexure fatigue machine simulated representative flexing of stent. The machine flexed the stent through a 20 degree end-to-end deflection. EndoTex assumed that a 20 degree flexure of the neck every 5 minutes, 24 hours a day, for 10 years was sufficiently tortuous. This results in a cycle count objective of 1.052 million cycles. The results for the flexural loading fatigue test were acceptable in that the stent remained intact and maintained patency through 1.052 million cycles.

Test	Requirement	Results Summary
Stent Radial Strength	Durability, integrity and patency of the implanted device	The radial strength of the stent was evaluated at the minimum and maximum specification diameters. The test was conducted by deploying and post-dilating the stent into a latex tube and then subjecting the latex to a crushing load to a deformation level of 50%. All radial strength testing was conducted with a 50% geometric deformation rather than a defined external load given the possibility of large externally applied crushing forces on the stent. All of the results for radial strength testing were acceptable.
Kink Resistance	Durability, integrity and patency of the implanted device	The bending and kink properties were evaluated using sample stents deployed into latex tubes at the minimum and maximum target vessel diameters. The latex tubes were then subjected to three point loading under temperature and force-controlled conditions to bend the vessel until 50% intrusion of the tube was achieved. All of the results for vessel bending were acceptable.
Recoverability	Durability, integrity and patency of the implanted device	Recoverability of the stent following either bending/kink or crush was evaluated immediately following the bending/kink testing and the radial strength testing. In all cases the stent/vessel successfully recovered. The results for recoverability were acceptable.
Magnetic Resonance Imaging	MRI Compatibility	Magnetic Resonance (MR) Safety for the NexStent Carotid Stent considered the NexStent "MR safe" up to a field strength of 3 tesla under testing conditions of the ASTM F2052-00 [1]. acceptance criteria for deflection angle and MRI related heating in a static magnetic field.

1. ASTM F2052-00 Standard Test Method for Measurement of Magnetically Induced Displacement Force on Passive Implants in the Magnetic Resonance Environment

The overall stent and delivery system design were subjected to a complete battery of bench tests to verify that the design fully met performance specifications. The bench testing conducted covered all aspects of delivery system and stent performance. The in vitro device bench testing is summarized in Table 5.

Table 5. In Vitro Bench Testing for Complete Stent and Delivery Systems (OTW/Monorail)

Test	Requirement	Results Summary
Product Integrity, Visual Examination & Dimensional Verification	System integrity and usability including access to intended location and deployment of implant	The key dimensions of the delivery systems were inspected using conventional dimensional inspection techniques. This testing included visual examination of the samples for product integrity and configuration. All dimensions were within specifications. The results of the inspections were acceptable.
Catheter Preparation	System integrity, usability and compatibility with other devices including access to intended location, deployment and retrieval of catheter	Clinical preparation of the catheters was evaluated during the in vitro bench testing. All of the normal catheter preparation steps including guidewire lumen flushing, sheath flushing, stent advance, guiding catheter compatibility, and guidewire compatibility were evaluated. All of the results were acceptable.
Deployment Force and Accuracy	Ability to access intended location in a tortuous anatomy and accurately deploy the implant	Stent deployment was evaluated in a simulated worst-case condition of guide catheter tortuosity. The stent was deployed into simulated worst-case tortuous carotid anatomy, a glass model simulating both severe stenosis and vessel tortuosity. The ability of the delivery system to provide for accurate deployment of the stent within ±1.5mm was also evaluated. All results were acceptable.
Bond Strength	System integrity and usability including access to intended location, deployment and retrieval of catheter	The joints of the delivery catheters were destructively tested in tension to verify adequate strength and compliance to specifications. All results were acceptable.

Test	Requirement	Results Summary
PTCA Balloon Compatibility	Compatibility with commercially available dilatation balloons	Six commercially available balloons, two 4 mm diameter, two 7 mm diameter and two 9 mm diameter, were employed to post-dilate the EndoTex stent in the simulated tortuous carotid model and both minimum and maximum anatomical diameters of latex tubing. A total of 100 dilatations were performed for the test with no damage to the balloons and no difficulty recrossing the stent areas. Post-stent deployment balloon dilatation was also conducted for all of the stents deployed during the chronic in-vivo testing. All results of balloon compatibility were acceptable.
FilterWire EZ Compatibility	Compatibility with distal protection device	The NexStent was evaluated in vitro for compatibility with the Boston Scientific EZ System. The testing confirmed the ability to advance and deploy the NexStent over the FilterWire, the ability of the FilterWire retrieval sheath to cross the deployed NexStent, and the ability to retrieve a FilterWire containing simulated debris without damaging the filter, sheath, stent, or disturbing the stent position. Additionally, the NexStent/FilterWire systems were evaluated to ensure that, should the guidewire lumen of the NexStent delivery catheter engage the proximal marker of the FilterWire, the lumen could be disengaged without damage and the stent could be successfully deployed. All results of FilterWire compatibility were acceptable.
Air Embolization	Must not introduce air emboli during use	EndoTex developed and validated an in vitro simulated-use test to evaluate the potential for the device to introduce air emboli into a system. The Monorail system was evaluated both with and without bleed-back during catheter insertion in simulated worse case conditions. The results demonstrated that the NexStent Monorail Delivery System performs comparable to or better than the OTW System in air embolization testing.

9.2 Animal Studies

EndoTex Interventional Systems, Inc. has established an in vivo animal testing regimen aimed to collect acute and chronic data in animal models for the NexStent Carotid Stent and Delivery System and the NexStent Carotid Stent and Monorail Delivery System. The intent of the studies was to demonstrate the acute and chronic performance of the devices in vivo and to evaluate any biological response related to the devices. The porcine model was selected since the cardiovascular system in this animal species is well suited and understood for the study of implantable intravascular stents. The availability of this species is adequate and the size of the vascular structures (arteries) is similar to that of humans. All animal studies were conducted under Good Laboratory Practices in compliance with the requirements of the Food and Drug Administration's Good Laboratory Practices for non-clinical laboratory study regulations as set forth by CFR 21 Part 58. Table 7 summarizes the results of the in vivo studies:

Table 7. Summary of NexStent System In Vivo Studies

Study	Number of Animals Timepoints Device(s) Tested	Study Summary
Chronic In-vivo Evaluation of EndoTex Carotid Stent System (OTW) (IAC-434)	11 Animals 2 days, 1 & 6 months 22 stents/delivery systems (over-the-wire)	Chronic in vivo studies were performed using the NexStent Carotid Stent and Delivery System (over-the-wire). Subjective evaluations of the EndoTex delivery systems by physicians revealed adequate to excellent performance. Vessel patency was achieved immediately post implantation and maintained throughout the 48 hour, 1-month and 6-month implant duration. IVUS revealed patent lumen with essentially no change in lumen diameter over time. Angiographic, hemodynamic and histological results revealed no abnormalities or trauma to the vessels induced as a result of EndoTex stent implantations.
Chronic In-vivo Evaluation of EndoTex Coiled Sheet Stent System Manufactured at Different Sites	1 Animal 1 month 2 stents	This animal study was done as a confirmatory test to assess and understand any differences between the endothelial responses of the tissues to stents manufactured at two different sites. This was done to reflect a laser-cutting supplier change that occurred during the course of the previous animal studies. Gross inspection of the explanted stented vessels revealed widely patent stents and no significant gross lesions. Histopathologic evaluation concluded that there were no significant differences between the biological responses elicited in the arteries by the two stents.
NexStent MR Acute Animal Study	2 Animals 20 stents w/ monorail delivery system 2 stents w/ over-the-wire delivery system	This study was intended to provide a comparison of the acute performance of the Monorail delivery system to the EndoTex NexStent Carotid Stent and Delivery System (OTW) used in the clinical trial and previous animal studies. Both systems successfully accessed and treated up to 5 porcine peripheral arteries of two animals. Catheter tip and marker radiopacity was rated "very good" for all devices. The NexStent Carotid Stent and Monorail Delivery System was able to access tortuous anatomy and performed well in comparison to the NexStent Carotid Stent and Delivery System. Deployment accuracy was rated "excellent" in most of the vessels and "very good" in the most tortuous vessels for both systems. No air embolization was observed during deployment of the stents. No angiographic irregularities were noted during deployment procedures. The NexStent Carotid Stent and Monorail Delivery Systems were all rated "very good" to "exceptional", for all the parameters observed. Similarly, the NexStent Carotid Stent and Delivery Systems (OTW) were rated at or above "acceptable" except in one animal where it failed to access the left subclavian artery due to its very tortuous nature.

9.3 Biocompatibility

The materials comprising the NexStent Carotid Stent and Delivery System and the NexStent Carotid Stent and Monorail Delivery System were verified for biocompatibility and toxicity in accordance with ISO 10993 and the FDA G95-1 guideline.[2,3] The stent and delivery systems together were evaluated as externally communicating devices with circulating blood contact for a limited duration (<24 hours). The stent materials were tested for biocompatibility and toxicity as a permanent implant with blood contact. The device materials have been shown to be biocompatible and non-toxic. Table 9 summarizes the tests performed on the finished device with all current materials.

2. ISO 10993-1 Biological Evaluation of Medical Devices Part-1: Evaluation and Testing, July 1, 1995
3. General Program Memorandum BlueBook G95-1 http://www.fda.gov/cdrh/g951.html

Table 9. NexStent Carotid Stent System Biocompatibility

Biocompatibility Test	Test Subject
Sensitization Assay- Murine Local Lymph Node Assay	Stent & Delivery Systems
Irritation Test - ISO Intracutaneous Study	Stent & Delivery Systems
Cytotoxicity - ISO Elution Method	Stent & Delivery Systems
Systemic Toxicity (Acute) - USP and ISO Systemic Toxicity Study	Stent & Delivery Systems
Hemocompatibility/Hemolysis Study - In Vitro Procedure	Stent & Delivery Systems
Plasma Recalcification Time Coagulation	Stent & Delivery Systems
Pyrogenicity - USP Pyrogen Study Material Mediated	Stent & Delivery Systems
In Vivo Thromboresistance Study – Carotid Artery	Stent & Delivery Systems
Subchronic Intravenous Toxicity - Systemic Injection Test Method	Stent only
Implantation - 48 hour, 1 month and 6 month implantation in porcine arteries	Stent only
Bacterial Reverse Mutation	Stent only
Chromosomal Aberrations, Genotoxicity Assay	Stent only
Mouse Bone Marrow Micronucleus	Stent only
C3a Complement Activation Assay	Stent only

9.4 Sterilization

The sterilization process for the EndoTex NexStent Carotid Stent and Delivery System was validated using the *"half-cycle"* method in accordance with the ANSI/AAMI/ISO 11135 and EN 550 standards to provide a minimum Sterility Assurance Level (SAL) of 10^{-6}. Residual testing demonstrated that device residuals were at acceptable levels per ISO 10993-7 [4] after 12 hours of aeration. The EndoTex NexStent Carotid Stent and Monorail Delivery System was adopted into the current validated sterilization cycle for the OTW device.

4. "Biological Evaluation of Medical Devices—Part 7: Ethylene Oxide (EtO) Sterilization Residuals,"

9.5 Packaging and Shelf-life

Product stability testing of the EndoTex NexStent Carotid Stent and Delivery System was performed. The packaging and packaged product were evaluated to provide assurance that it will withstand hazards of the distribution environment. Testing indicated that the stent and delivery catheter performed within product specification, and that the sterility is maintained for up to two years. Based upon these results, an expiration date of 2 years has been established.

The shelf-life of the NexStent Carotid Stent and Monorail Delivery System was qualified according to a test regimen conducted after 1 year accelerated aging. The packaging and packaged product were evaluated to provide assurance that it will withstand hazards of the distribution environment. Testing indicated that the stent and delivery catheter performed within product specification and that the sterility is maintained for at least one year. Based upon the results of accelerated aging studies, an expiration date of one year has been established for the device.

10.0 SUMMARY OF CLINICAL STUDIES

The Carotid Artery Revascularization Using the Boston Scientific EPI FilterWire EZ or EX System and the EndoTex NexStent (CABERNET Trial) was a prospective, non-randomized multicenter clinical trial evaluating the safety and efficacy of the NexStent Carotid Stent and Delivery System (NexStent) in conjunction with the Boston Scientific FilterWire EZ (FilterWire). The CABERNET study protocol included implantation of the NexStent for the treatment of patients with significant extracranial carotid artery stenosis who required carotid revascularization and are at high risk for adverse events from carotid endarterectomy.

An overview of the clinical trial is provided in Table 11.

Table 11. CABERNET Trial Overview

Title:	Carotid Artery Revascularization Using the Boston Scientific FilterWire EZ System and the EndoTex NexStent.
Products Evaluated	EndoTex NexStent in conjunction with Boston Scientific FilterWire EX or EZ System.
Study Design:	A prospective, non-randomized, multicenter clinical trial.
Clinical Sites:	A total of 21 Sites participated in the trial. At two sites the study was transitioned to other institutions. Of the remaining 19 sites, there were 15 US sites and 4 OUS sites.
Primary Endpoints[6]:	**Safety** 1) Major clinical events at one-year defined as any death, stroke or myocardial infarction 2) 30-day event rate defined as any death, stroke or MI ≤ 30-days post-procedure; plus the 31-day to12-month event rate defined as any ipsilateral stroke including any death as a result of an ipsilateral stroke.
Secondary Endpoints:	**Safety and Efficacy** NexStent Technical Success[1] FilterWire Technical Success[1] Overall System Technical Success[1] Angiographic Success[2] Procedure Success[3] Restenosis [4] Target Vessel Revascularization[5]
Study Hypothesis	Non-Inferiority compared to a historical control for patients at high risk for CEA.
Patient Follow-up	Follow-up Visits: Hospital Discharge, 1-Month, 6-Month, 12-Month, 2-Year, 3-Year.

[1]Technical Success rates were based on the devices being placed and retrieved as described in the study protocol.
[2]Angiographic Success was achievement of ≤50% residual stenosis based on the original diameter of the target lesion.
[3]Procedural Success was defined as patients who had angiographic success, overall system success and MAE free within 24 hours of the index procedure.
[4]Restenosis was defined >80% narrowing of the target lesion based on the Strandness criteria that occurred >1 month post procedure.
[5]Target Vessel Revascularization was defined as any narrowing of the target lesion or vessel >1 month post procedure, requiring revascularization.
[6]The primary endpoints of the trial were evaluated at 1 year.

The primary endpoints of the trial were:

1. Major clinical events at one-year defined as any death, stroke or myocardial infarction (MI).
2. Thirty day event rate defined as any death, stroke or MI ≤30-days post-procedure; plus the 31-day to12-month event rate defined as any ipsilateral stroke including any death as a result of an ipsilateral stroke.

The primary objective of the trial was to demonstrate that the major adverse event (MAE) rates for both primary endpoints were not greater than the objective performance criterion (OPC) of 12.1% plus an additional delta of 4% (margin to establish non-inferiority) established for this study (16.1%).

The OPC is based on the review of current literature related to outcomes from high-risk carotid endarterectomy, representing the standard of care. The MAE rates occurring in high-risk patients undergoing carotid endarterectomy are 11% for anatomical risk factors and 14% for comorbidity risk factors. Because the MAE rate differed depending on the nature of a patient's risk factors, a weighted OPC was used. The weighting factors were determined by the observed case mix in the CABERNET trial of anatomical high-risk patients versus co-morbid high-risk patients.

The null hypothesis of study device system inferiority to OPC was tested against the alternative hypothesis of equivalence (non-inferiority) to OPC.

H_0: $P \geq OPC + 0.04$
H_a: $P < OPC + 0.04$

The hypotheses were tested by calculating a normal approximation to the binomial test statistic, Z. If $Z > Z_{0.05} = 1.645$ (the weighted OPC plus equivalence threshold) then the null hypothesis of inferiority will be rejected and the study device system was considered equivalent to CEA.

Patients were followed at hospital discharge, 1-Month, 6-Months, and 1-Year. Additionally, registry patients will be followed annually through 3 years from the date of the index procedure. Patients were seen in follow-up by the treating physician as well as independent neurologist (neurological assessments). Core laboratories were utilized for the analysis of angiographic, ultrasound, ECG and CT/MRI (only for evaluation of neurological events or symptomology) data. To ensure patient safety, medical monitors reviewed safety data to ensure appropriate reporting of adverse events.

A Clinical Events Committee (CEC) reviewed all reported major adverse events for the primary endpoint and a Data Safety Monitoring Board (DSMB) reviewed the summary of these events to ensure patient safety.

10.1 Patient Eligibility Criteria

Patients were required to be high-risk candidates for CEA and meet all general inclusion criteria as well as the high-risk inclusion criteria (as specified) and none of the exclusion criteria to be considered eligible for study participation in the CABERNET trial.

General Inclusion Criteria

1. Patient is ≥18 years of age.
2. Anticipated patient life expectancy of at least one year from the date of the index procedure.
3. Lesion is located in the common carotid artery (CCA) and/or the internal carotid artery (ICA) or the carotid (ICA/CCA) bifurcation.
4. Target vessel is the only vessel being treated at this intervention and the lesion is ≤30 mm and can be treated with a single stent.
5. Vessel to be treated is between 4.0mm and 9.0mm in diameter.
6. Distal vessel "landing zone" for placement of the FilterWire must be between 3.5mm and 5.5mm in diameter and have available the following artery lengths:
   - A minimum of 2.0cm distal to the target lesion.
   - A minimum of 2.0cm straight vessel segment for placement of the filter.
   - A minimum of 1.0cm from a major vessel curve.
7. Patient must meet **one** of the following criteria:
   - **Symptomatic:** Stenosis must be ≥50% as determined by duplex ultrasound and angiogram; and the patient has a history of stroke, TIA and/or amaurosis fugax in the hemisphere supplied by the target vessel within 180 days of the procedure.

     OR
   - **Asymptomatic:** Stenosis must be ≥80% as determined by duplex ultrasound and ≥60% as determined by angiogram without any neurological symptoms.
8. Distal vessel "landing zone" for placement of the FilterWire must be between 3.5mm and 5.5mm in diameter with visual angiographic recommendations as described in the Instructions for Use (IFU).
9. Female patients with no childbearing potential or a documented negative pregnancy test (urine or blood) within 10 days of the index procedure.
10. Patient (or their legal guardian) understands the nature of the procedure and has provided a signed informed consent using a form that has been reviewed and approved by the Investigational Review Board/Ethics Committee of the respective clinical site prior to the procedure. This will be obtained prior to participation in the study.
11. Patient is willing to comply with the protocol requirements and return to the treatment center for all required clinical evaluations.

High-Risk Inclusion Criteria

Patients enrolled in the trial were at high risk for carotid endarterectomy (CEA). Eligible patients were required to meet at least one of the following high risk anatomical conditions, one of the Class I high risk comorbid conditions or two of the Class II high risk comorbid conditions criteria in order to be eligible to participate in the study:

Anatomical High-Risk Conditions

1. Previous carotid endarterectomy with significant restenosis (as defined above for symptomatic or asymptomatic patients).
2. Total occlusion of the contralateral carotid artery.
3. Previous radiation treatment to the neck or radical neck dissection.
4. Target lesion is at or above the second vertebral body (C2) or below the clavicle.
5. Inability to extend the head due to cervical arthritis or other cervical disorders.
6. Tracheostomy or tracheal stoma.
7. Presence of laryngeal nerve palsy.
8. Bilateral carotid artery stenosis as determined by angiography in which both carotid arteries require treatment, as defined as;
   - Bilateral asymptomatic stenosis ≥60% or
   - Bilateral symptomatic stenosis ≥50% or
   - Bilateral stenosis, one side with a symptomatic stenosis ≥50% and the other side asymptomatic with a stenosis ≥60%

Comorbid High-Risk Conditions

<u>CLASS I</u>

1. Unstable angina (chest pain at rest with ECG changes).
2. Known severe left ventricular dysfunction, LVEF <30%.
3. Congestive heart failure (CHF) - New York Heart Association (NYHA) Functional Class III or IV.
4. Dialysis dependent renal failure.
5. Severe pulmonary disease (COPD) with either:
   - Forced Expiratory Volume in 1 Second (FEV_1) <50% predicted or
   - chronic oxygen therapy or
   - resting Partial Oxygen Tension (PO2) of ≤60 mmHg or
   - baseline Hematocrit ≥50%
6. Requirement for staged Coronary artery bypass graft (CABG) or valve replacement post carotid index procedure.

<u>CLASS II</u>

1. Patient is ≥75 years of age.
2. Myocardial infarction within previous 6 weeks.
3. Requires staged peripheral vascular surgery (i.e. abdominal aortic aneurysm repair) or other major surgery post carotid index procedure.
4. Two or more proximal or major diseased coronary arteries with ≥70% stenosis that have not or cannot be revascularized.

Exclusion Criteria

A patient with any of the following criteria was not considered eligible for treatment in the trial.

1. Previously placed stent in target vessel.
2. Total occlusion of target vessel (Internal Carotid Artery;ICA or Common Carotid Artery;CCA).
3. Angiographically visible thrombus.
4. Carotid string sign (a tiny, long segment of contrast in the true lumen of the artery, aneurysmal pouch formation, and the distal location of the arteriopathy) with poor visualization of the distal vessel.
5. Vertebrobasilar insufficiency symptoms only, without clearly identifiable symptoms referable to the targeted carotid artery.
6. Vessel anatomy precluding use of stent system or distal protection system.
7. Presence of carotid artery dissection.
8. Requirement for staged CABG, valve replacement or abdominal aortic aneurysm procedure ±30 days of the index procedure.
9. Evidence of a major disabling stroke within the previous 30 days.
10. Patient has an evolving stroke or has experienced a major stroke as determined by the National Institutes of Health Stroke Scale (NIHSS ≥15) within 3 months.
11. History of intracranial hemorrhage within the past 12 months.
12. Any condition that precludes proper angiographic assessment or makes percutaneous arterial access unsafe, e.g. morbid obesity, history of chronic hypertension that is not controlled by medical therapy.
13. Contraindication to heparin, aspirin, clopidogrel (Plavix®), X-ray contrast or ticlopidine (Ticlid®) in cases of intolerance to clopidogrel.
14. History of liver failure with elevated prothrombin time.
15. History or current indication of bleeding diathesis or coagulopathy.
16. Hgb <8gm/dl (unless on dialysis), platelet count <50,000, WBC >15,000, INR >1.5 (irreversible) or heparin-associated thrombocytopenia.
17. Known cardiac sources of emboli not under treatment with anticoagulant therapy.
18. Atherosclerotic disease involving adjoining vessels precluding safe placement of the guiding catheter or sheath.
19. Planned treatment of non-target lesion within 30 days.
20. Other abnormal angiographic findings that indicate the patient is at risk of a stroke due to a problem other that the target lesion, such as: ipsilateral arterial stenosis greater in severity than the target lesion, cerebral aneurysm, or arteriovenous malformation (AVM) of the cerebral vasculature.
21. Dementia or confusion.
22. The patient is enrolled in another study protocol.
23. Patient may not participate in another investigational trial up to 12 months post-index procedure.

10.2 Description of Patient Population

The first patient was enrolled on February 20, 2002. Enrollment was completed on March 10, 2004. A total of 488 patients enrolled in the CABERNET trial at 21 participating centers worldwide. Forty-one of the 488 patients also underwent a contralateral procedure (>30 days following initial index procedure). Thirty-four of the 488 patients were enrolled with "Roll-In" status at 16 centers, yielding a total of 454 (488-34) patients enrolled in the main registry of the trial. Eleven patients did not receive a NexStent at the time of implant and were terminated from the study per protocol, but seen in follow-up by their physician at 30 days post procedure for the purpose of capturing any peri-procedural adverse events, yielding a total of 443 evaluable patients at the time of discharge. Three patients were lost to follow-up (LTF) and 2 patients expired after hospital discharge, with 438 patients available for their 1-month follow-up visit. There were 17 patients that were LTF and 17 patients that expired between the 30-day and 1 year follow-up. There were 6 missed visits at 1 year yielding 398 patients whom completed their 1-year follow-up.

Table 12 summarizes an overview of patient enrollment at each participating center.

Table 12.

Patient Population	Index Procedure	30-days	1 Year
Total Number of Patients Enrolled	488		
Roll-In Patients	34		
Patients Enrolled in Main Trial Registry	454		
Patients Without a NexStent Implanted	11		
Evaluable Patients [1]	443	443	443
Patients lost to Follow-Up or Withdrawals (Cumulative)	0	3	20
Deaths (Cumulative)	0	2	19
Evaluable Patients Available for Follow-up	443	438	404
Total number of planned visits among evaluable patients			
Total missed visits among evaluable patients		2	6
Clinical Assessments performed		428 (97.7%)	377 (93.3%)
Neurologic Assessments Performed		412 (94.1%)	365 (90.3%)
12 Lead ECG (30-Day FU Only) Performed		335 (76.5%)	
Duplex Ultrasound Exams performed		387 (88.3%)	331 (81.9%)
Stroke Scales Performed		412 (93.6%)	354 (87.6%)
Total Patient Follow-Up Rate		436(99%)	398 (98.5%)

{1} Evaluable patients only include those that have a NexStent implant

The majority of the patients enrolled in the trial were asymptomatic, Caucasian males with an average age of 72.5 years. Of the 454 patients enrolled in the main registry 63.7% had an anatomical high risk factor, 19.6% had a comorbid high risk factor and 16.7% had both. In terms of baseline lesion characteristics, the majority of the patients

had a de novo target lesion located in the internal carotid artery. The mean baseline lesion stenosis was 71.9% with an average length of 13.9mm and average diameter of 1.3mm. Baseline demographics and lesion characteristics for the patient population are provided in Tables 7, 8, and 9. Baseline lesion characteristics were analyzed by a centralized angiographic core laboratory.

Required patient study intervals for the CABERNET trial included hospital discharge, 1-month, 6-month, 1-year, 2-year and 3-year follow up visits. The data analyses for the primary endpoint includes follow-up through one year as pre-specified in the study protocol.

Baseline Demographics

Baseline demographics, lesion characteristics and measurements and high risk inclusion criteria for the patient population are provided in Tables 13, 14, 15 and 16. Baseline lesion measurements were analyzed by a centralized angiographic core laboratory.

Table 13. Baseline Demographics

Patient Characteristic		Patients (N = 454)	% (except as noted)
Age (years)	Mean ± SD		72.5 ± 8.6 yrs
	Minimum to Maximum		46 to 94 yrs
Age by Decade of Life	40-49	6	1.3
	50-59	29	6.4
	60-69	124	27.3
	70-79	194	42.7
	80-89	97	21.4
	>90	4	0.9
Gender	Male	297	65.4
	Female	157	34.6
Ethnicity	Caucasian	414	91.2
	African American	21	4.6
	Hispanic	10	2.2
	Asian	5	1.1
	Other	4	0.9
Patient Classification	Symptomatic	110	24.2
	Asymptomatic	344	75.8
Medical History	Diabetes Mellitus	150	33.0
	Liver Failure	0	0.0
	Dyslipidemia	315	69.4
	GI Bleeding/peptic ulcer disease (PUD)	29	6.4
	Hypertension	377	83.0
	Uncontrolled Hypertension	6	1.3
	Cigarette Smoker	320	70.5
	Current Cigarette Smoker	83	18.3
	Family Hx Premature atrial septal defect (ASD)	74	16.3
	Significant Aortic Arch Atherosclerosis	5	1.1
	Cardiac Arrhythmia	81	17.8
	Valvular Disease	26	5.7
	Coronary artery disease	283	62.3
	Pulmonary Vein Disease	178	39.2
	Prior Percutaneous Transluminal	119	26.2

Patient Characteristic	Patients (N = 454)	% (except as noted)
Angioplasty (PTA)		
Prior Valve Replacement	21	4.6
Prior Coronary Artery Bypass Graft	161	35.5
Prior Carotid PTA	13	2.9
Prior Carotid Stenting	12	2.6
Hx of Transient Ischemic Attack (TIA)	124	27.3
Hx of Stroke	96	21.1
Family Hx of Stroke	52	11.5
Hx of Seizures	11	2.4
Hx of Other Neuro	30	6.6
Prior Vertebrobasilar Intervention	1	0.2
Other	73	16.1

Table 14. Baseline Lesion Characteristics

Parameter	Patients (N=454)	%
Lesion Type		
de novo	360	79.3
Restenotic	94	20.7
Lesion Location in Carotid Artery		
Common	34	7.5
Internal	411	90.5
Bifurcation	49	10.8
Lesion Morphology		
Eccentric	327	72.0
Ulceration	169	37.2
Calcification	190	41.9

Table 15. Baseline Lesion Measurements (Pre-Procedure)

Angiographic Data (Core Laboratory Assessment)		Results
Target Lesion Length (mm)		
Mean ± SD	n=441[1]	13.9 ± 5.9
Minimum Lumen Diameter (MLD)(mm)		
Mean ± SD	n=443[1]	1.3 ±0.6
Baseline Percent Diameter Stenosis (%)		
Mean ± SD	n=443[1]	71.9 ± 11.0

[1] Lesion length was not available in 13 patients; MLD and Percent Diameter Stenosis were not available in 11 patients.

Table 16.0 Baseline High Risk Inclusion Criteria

Inclusion Criteria	Patients (N=454)	%
High Risk Category		
Anatomical Only	289	63.7
Comorbid Only	89	19.6
Both Anatomic and Comorbid	76	16.7
Class I - Comorbid	139	30.6
Class II - Comorbid	53	11.7
Anatomical High Risk Inclusion Criteria (A)		
Previous CEA	95	20.9
Total Occlusion of Contralateral Carotid Artery	85	18.7
Previous Radial Neck Dissection or Radiation Therapy to Neck Region	30	6.6
Target Lesion at or above C2 or below Clavicle	25	5.5
Spinal Immobility of Neck (cervical arthritis or other)	54	11.9
Tracheostomy or tracheal stoma	3	0.7
Presence of laryngeal nerve palsy	8	1.8
Bilateral Carotid Artery Stenosis	143	31.5
Class I: Comorbid High Risk Inclusion Criteria (CI)		
Unstable Angina	26	5.7
Severe LV Dysfunction	42	9.3
CHF (NYHA Class III/IV)	40	8.8
Renal Failure (Dialysis Dependent)	5	1.1
Severe COPD	38	8.4
Requires Staged CABG or Valve Surgery	21	4.6
Class II: Comorbid High Risk Inclusion Criteria (CII)		
Patient is ≥75 years of Age	199	43.8
MI within 6 weeks	5	1.1
Requires Staged Peripheral Vascular Surgery	34	7.5
Major CAD (≥70 Stenosis that have not or cannot be revascularized)	64	14.1

10.3 Trial Results

The primary and secondary endpoints evaluating the safety and efficacy of the NexStent in the CABERNET trial are presented in Table 17 and 18 respectively. The 30-day primary endpoint MAE rate (all death, stroke and MI within 30 days) was 3.9%. The 1-year endpoint MAE rate for all death, stroke and MI was 11.9%. The rate for the composite 1-year endpoint that includes the 30-day MAEs plus ipsilateral stroke or death from ipsilateral stroke within 31-365 days was 4.7%.

Angiographic success was attained in 97.7% (423/433) of evaluable patients, with an overall system technical success 93.0% (422/454). The mean post-procedure residual stenosis was 20.5% as assessed by the core laboratory and 6.45% as per the visual inspection performed by the treating physician at the completion of the procedure. Acute procedure success, defined as the composite of angiographic success and overall technical success, was demonstrated in 395 patients (87.0%).

Secondly, the primary endpoints of the trial were met. The upper confidence limits for both primary endpoint MAE rates fall below the reference OPC plus the non-inferiority margin of 4% established for this study, demonstrating that carotid stenting using the

NexStent Carotid Stent and Delivery System with the Boston Scientific FilterWire EZ is non-inferior to carotid endarterectomy in the studied high-risk population.

Table 17. Primary Endpoints (Major Adverse Events)

Primary Endpoints	≤ 30 Days		31-365 Days		0-365 Days	
	# Patients[1]	% Patients (N=438)	# Patients[1]	% Patients (N=421)[2]	# Patients[1]	% Patients (N=421)[2]
All Death, Stroke and MI at 1-Year	17	3.9	33	7.8	50	11.9 UCL=14.8 %
	# Patients[1]	%Patients (N=438)	# Patients[1]	% Patients (N=404)[3]	# Patients[1]	% Patients (N=404)[3]
All Death, Stroke and MI ≤ 30 days; plus the event rate defined as any ipsilateral stroke including any death as a result of an ipsilateral stroke within 31-365 days.	17	3.9	3	0.7	19	4.7 UCL=6.8%
Major Adverse Events	≤ 30 Days		31-365 Days		0-365 Days	
	# Patients[1]	% Patients (N=438)	# Patients[1]	% Patients (N=421)[2]	# Patients[1]	% Patients (N=421)[2]
Death	2	0.5	17	4.0	19	4.5
Stroke-Related	0	0.0	0	0.0	0	0.0
Non Stroke-Related	2	0.5	17	4.0	19	4.5
Stroke	15	3.4	8	1.9	21	5.0
Ipsilateral Stroke	12	2.7	3	0.7	14	3.3
Major	5	1.1	1	0.2	5	1.2
Minor	7	1.6	2	0.5	9	2.1
Non-Ipsilateral Stroke	3	0.7	6	1.4	8	1.9
Major	1	0.2	3	0.7	4	1.0
Minor	2	0.5	3	0.7	4	1.0
Myocardial Infarction (MI)	1	0.2	16	3.8	17	4.0

[1] Patients may have had multiple events, counts represent the number of patients who have experienced one or more events.
[2] N=421 for the 31-365 and 0-365 time periods. This includes 398 patients evaluated at 1 year, 19 deaths, and 4 patients that did not have a 1-year visit but experienced an adverse event (398+19+4 = 421).
[3] In an effort to present the most conservative analysis for the MAE rate concerning the composite Primary Endpoint N=404 was used. Seventeen patient deaths that occurred during the 31-365 day time period were not due to ipsilateral stroke and were excluded from this analysis. Therefore N = 404 (421-17=404).

Table18. Secondary Endpoints

Endpoint	Results		95% Confidence Limit (LCL= lower confidence limit; UCL= upper confidence limit) (%)
	n/N	%	
FilterWire Technical Success	454/477	95.2	LCL=93.2
NexStent Technical Success	443/470	94.3	LCL=92.2
Overall System Technical Success	422/454	93.0	LCL=90.7
Angiographic Success	423/433	97.7	LCL=96.1
Procedure Success (Acute)	395/454	87.0	LCL=84.1
Restenosis 50-79%			
(Cumulative 0-6 Month)	55/343[1]	16.0%	UCL=19.7
(Cumulative 0-12 Month)	65/347[2]	18.7%	UCL=22.5
Restenosis >80%			
(Cumulative 0-6-Month)	3/340[3]	0.9	UCL=2.3
(Cumulative 0-12-Month)	9/333[4]	2.7	UCL=4.7
Target Vessel Revascularization (6-Month)	4/443	0.9	UCL=2.1
(1-Year)	9/443	2.0	UCL=3.5

[1] N=343 includes all patients with duplex ultrasound data available at 6 months plus any patient without a 6 month evaluation that had 50-79% restenosis at an earlier evaluation (339+4=343).
[2] N=347 includes all patients with duplex ultrasound data available at 12 months, any patient without a 6 month evaluation that had 50-79% restenosis at an earlier evaluation, (331+16=347).
[3] N=340 includes all patients with duplex ultrasound data available at 6 months plus any patient without a 6 month evaluation that had >80% restenosis at an earlier evaluation (339+1=340).
[4] N=333 includes all patients with duplex ultrasound data available at 12 months, any patient without a 12 month evaluation that had >80% restenosis at an earlier evaluation and 1 patient that had a late 1 year follow-up who had >80% restenosis (331+2=333).

Finally, the secondary endpoints of the study specifications were also met. The study protocol defined restenosis as stenosis of the stent of 80% or greater. This occurred in 3.6% of vessels. Similar studies of carotid stenting have reported this rate as ≥ 50% stenosis of the stent. Restenosis of 50% or more occurred in 21.4% of vessels. Target Vessel Revascularization occurred in 2.0% of vessels.

Additional safety data were presented previously in Table 2 for other serious adverse events and Table 3 for patient deaths by causation.

10. 4 Additional Analyses

The primary endpoints in this study were further explored through a time-to-event analysis using a Kaplan-Meier (KM) estimator for the survival function. Life table estimates were obtained for:

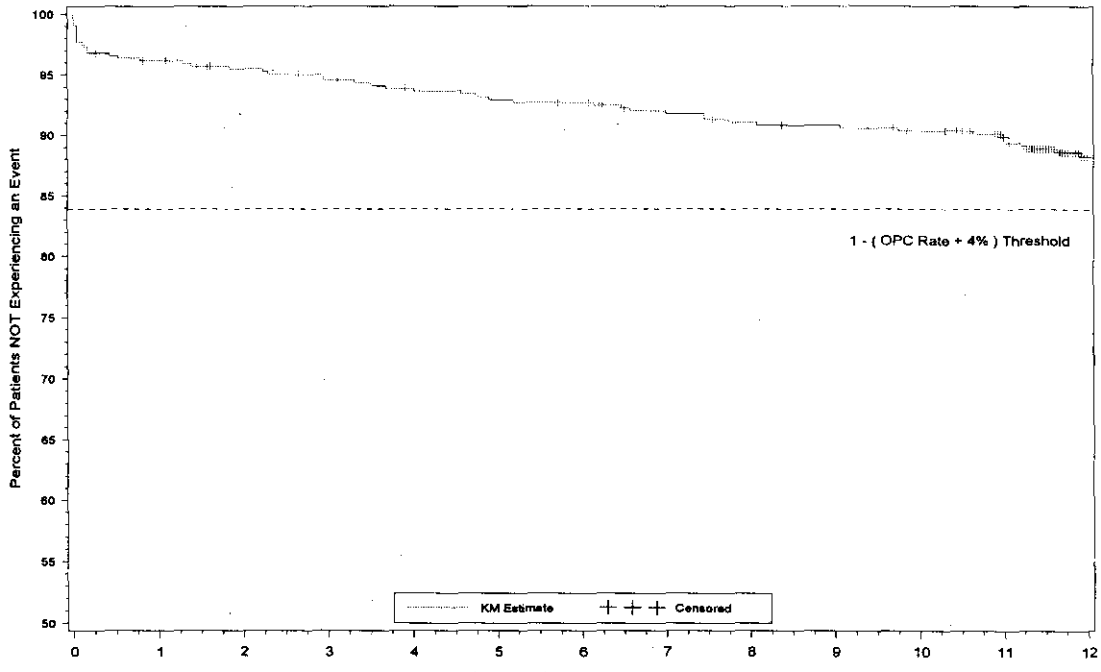
a. Freedom from major adverse events (All Deaths, Strokes and MIs) at 1-Year

b. Freedom from major adverse events (All Deaths, Strokes and MIs) at 30-Days; plus ipsilateral stroke or death related to ipsilateral stroke at 1-Year.

Patients were included in these analyses if they had a successful NexStent implant. The survival time for patients who experienced a major adverse event was calculated as the number of days from the index procedure to the date the adverse event was first identified. For patients who withdrew from the study before the time of analysis, the survival time was calculated as the number of days from the index procedure to the date of their withdrawal. For the composite endpoint, for patients who died of causes unrelated to an ipsilateral stroke, the survival time for the composite endpoint analysis was calculated as the number of days from the index procedure to the date of their death. Patients who were terminated early from the study are considered censored in the analyses performed.

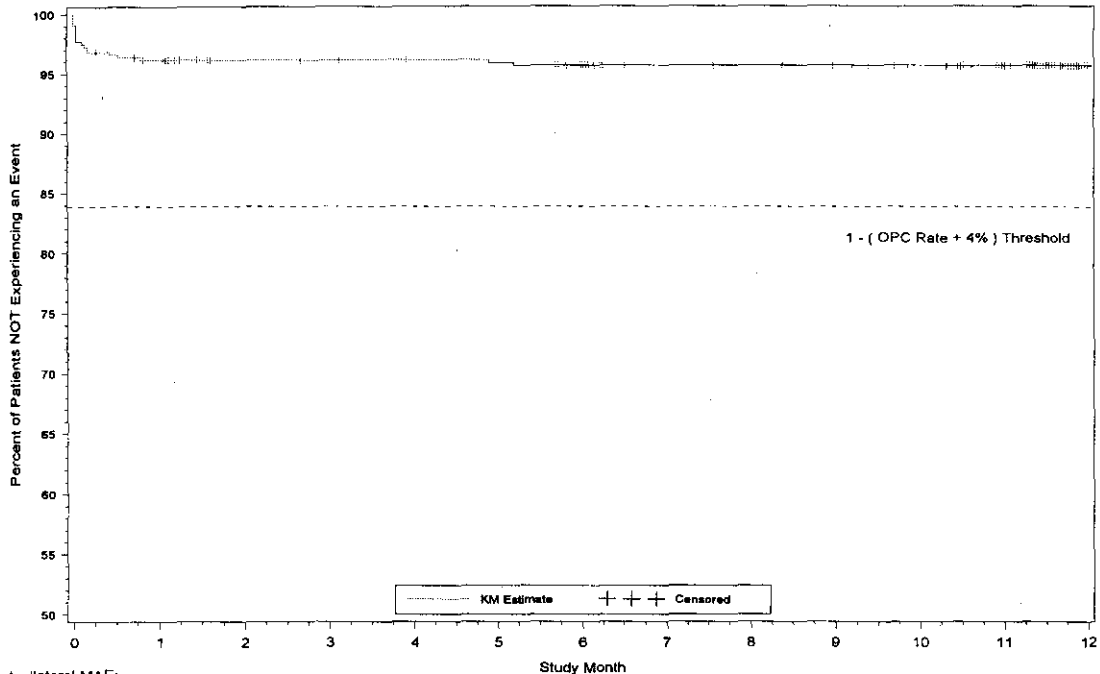
Figure 1 and 2 present the KM analysis for each endpoint. Figures 3 through 6 present the KM analysis for asymptomatic and symptomatic patients for each endpoint. The event rate estimate of 11.7% obtained for all death, strokes, and MIs at 12 months from the life table is consistent with the estimate of 11.9% obtained according to the analysis performed per protocol. Similarly, the estimate obtained from the life table of 4.3% for the event rate for the composite endpoint of major adverse events (All Deaths, Strokes and MIs) at 30 Days; plus ipsilateral stroke or death related to ipsilateral stroke at 1-Year is consistent with the obtained estimate of 4.7% according to the analysis performed per protocol.

Figure 1. Survival from major adverse events (All Deaths, Strokes and MIs) through 1-Year



Any MAE:												
At Risk:441	422	414	409	404	400	398	389	385	383	378	369	239
Events: 0	17	20	24	27	31	32	36	39	40	42	43	50
Event %:00	3.86	4.54	5.47	6.16	7.09	7.32	8.26	8.97	9.21	9.68	9.93	11.74

Figure 2. Survival from major adverse events (All Deaths, Strokes and MIs) at 30-Days; plus ipsilateral stroke or death related to ipsilateral stroke through 1-Year.



ipsilateral MAE:												
At Risk:	441	421	409	408	406	405	399	390	389	387	383	374	244
Events:	0	17	17	17	17	18	19	19	19	19	19	19	19
Event %	0.00	3.86	3.86	3.86	3.86	4.09	4.33	4.33	4.33	4.33	4.33	4.33	4.33

Figure 3. Survival from Major Adverse Events (All Deaths, Stokes and MIs) at One Year
Symptomatic Patient Group

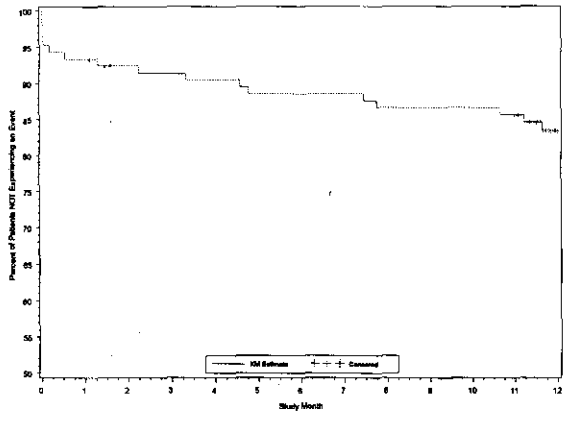
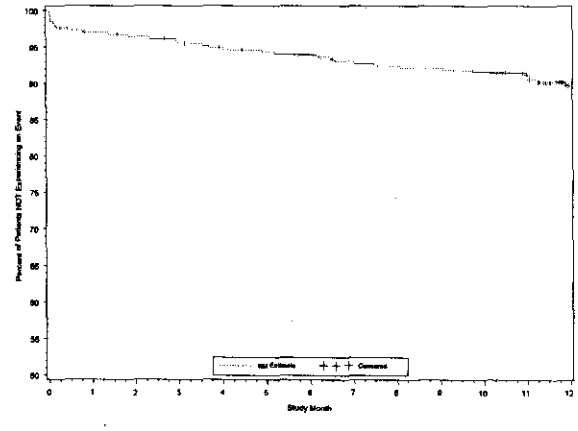


Figure 4. Survival from Major Adverse Events (All Deaths, Stokes and MIs) at One Year
Asymptomatic Patient Group



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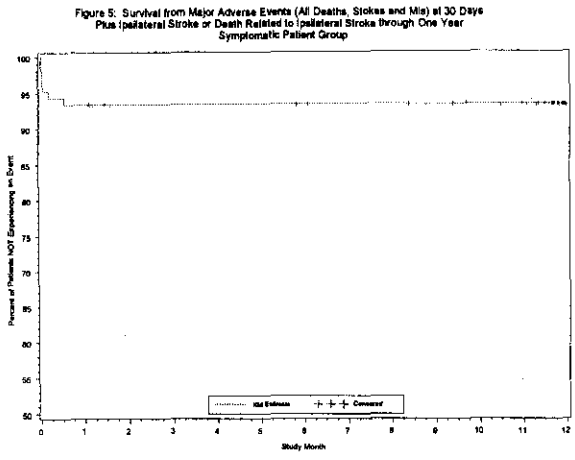

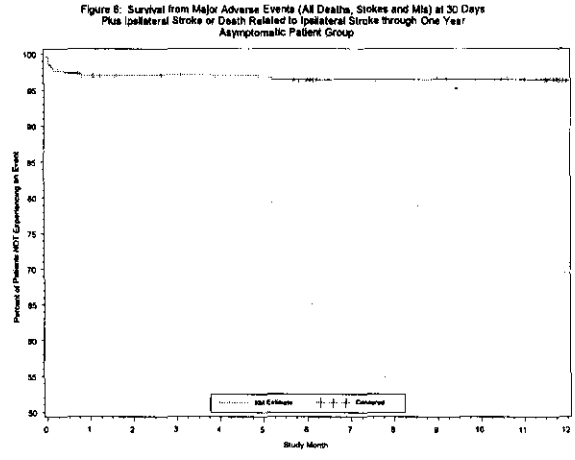

10.5 Study Conclusions

The upper confidence limits for both primary endpoint MAE rates fell below the Reference OPC plus the Non-Inferiority Margin of 4% established for this study and both null hypotheses were rejected. The primary endpoints of the trial were met.

The results of the secondary endpoints were comparable to current clinical practice and experience. The results of the CABERNET trial demonstrate that the NexStent® Carotid Stent and Delivery System used with the FilterWire EZ™ Embolic Protection System were found to be safe and effective as treatment for carotid artery disease in the population indicated. Results from the pre-clinical and clinical evaluations provide valid scientific evidence and reasonable assurance that the devices were safe and effective when used in accordance with the instructions for use.

10.6 NexStent® Carotid Stent and Monorail® Delivery Catheter

The CABERNET Trial utilized an "over-the-wire" (OTW) stent delivery system (SDS) for the NexStent®. EndoTex subsequently developed a Monorail SDS as an extension to the NexStent product family. The implant, a carotid stent (NexStent), is the same for both catheters. The primary difference between the two products is that the revised product uses a Monorail (single operator exchange) SDS with a modified tip. The modified tip on the Monorail SDS is soft and trackable. The mechanics of the delivery systems are similar and the systems have many components in common.

EndoTex elected to conduct a prospective validation study to confirm the acute performance of the monorail delivery system in a clinical setting. Between October 18th and 23rd, 2004, 11 patients were treated at Sankt Katharinen Hospital, Frankfurt, Germany. The treating physician was Professor Horst Sievert, MD. The study protocol and informed consent were approved by Freiberg Ethics Committee prior to initiation of the study.

The primary objective of this study was acute NexStent Monorail technical success defined as delivery of the NexStent implant at the intended location (based on the investigator's judgment) and to evaluate lesion access, deployment of the NexStent and successful retrieval of the delivery catheter after stent placement. Due to the small number of patients treated, formal sample size calculations or analyses were not performed. Prior to the beginning of the study, it was determined that in the case of a

technical failure, the cause of the failure was to be evaluated with input from the physician for their interpretation of the failure (i.e. extreme tortuosity of the patient's vascular anatomy, extreme calcification of the target lesion or device failure/malfunction).

Pre-procedure assessment included determination of stenting eligibility criteria, carotid ultrasound screening and baseline neurological evaluation. Stenosis was determined by ultrasound and confirmed by angiography prior to each procedure. Stent placement occurred in each subject with distal protection in place prior to stenting. Patients were observed until release from the catheterization laboratory.

Eleven patients were enrolled into the evaluation and signed an informed consent. All 11 were treated successfully with the NexStent Carotid Stent and Monorail Delivery System. Subjects ranged in age from 59 to 77 years (mean 67 years). The cohort gender was fairly equally distributed for this sample size with 5 female and 6 male participants. Six of the patients presented as asymptomatic and 5 patients were symptomatic exhibiting evidence of neurological events within the past 180 days. The patients presented with a variety of vasculature in order to properly assess the limits of the NexStent Monorail System. Stenosis of the lesions ranged from approximately 62%-95% with a mean stenosis of approximately 81%.

Each catheter performed as anticipated and without incident. For each case there was successful tracking of the device to the intended location, successful deployment of the stent and successful retrieval of the delivery catheter. As expected, the physician was able to employ shorter guidewires to facilitate single-operator use and optimal control of the devices during the procedure. No adverse events were experienced by the patients during the procedure and all patients were discharged from the hospital per standard care following carotid stenting.

11.0 CONCLUSIONS DRAWN FROM THE STUDIES

The preclinical studies, and testing of the NexStent Carotid Stent and Monorail delivery system (Section 10.4) indicate that the NexStent Carotid Stent and Delivery System should behave similarly in clinical use. Multicenter clinical data have demonstrated that the NexStent Carotid Stent and Delivery System used with the Boston Scientific FilterWire EZ is safe and effective as a treatment for carotid artery disease when used according to the indications, including use in vessels with minimum reference diameters of 4mm. 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.

12.0 PANEL RECOMMENDATION

In accordance with the provisions of section 515 (c)(2) of the act as amended by Safe Medical Devices Act of 1990, the 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 the panel.

13.0 CDRH DECISION

FDA issued an approval order on October 27, 2006. The conditions of approval require a post-approval study of 1,500 new patients to be assessed at 30 days and one year, as well as continued follow-up of the existing cohort of patients from the CABERNET study for total of three years. The results of these studies will be evaluated to determine whether any changes should be made to the labeling to ensure that the information available to physicians is complete, appropriate and up-to-date.

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

14.0 APPROVAL SPECIFICATIONS

Directions for Use: See product labeling for Over-the-Wire (OTW) and Monorail (MR) versions.

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

Post-approval Requirements and Restrictions: See approval order.