SUMMARY OF SAFETY AND EFFECTIVENESS DATA

1.0 GENERAL INFORMATION

Device Generic Name:	Intravascular Stent with Delivery System
Device Trade Names:	ACCULINK™ Carotid Stent System RX ACCULINK™ Carotid Stent System
Applicant's Name and Address:	Guidant Corporation 3200 Lakeside Drive Santa Clara, CA 95054
PMA Number:	P040012
Date of Panel Recommendation:	None
Date of Notice of Approval to the Applicant:	August 30, 2004

2.0 INDICATIONS FOR USE

The ACCULINK™ Carotid Stent System and the RX ACCULINK™ Carotid Stent System, used in conjunction with Guidant carotid embolic protection systems, is indicated for the 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 and ≥50% stenosis of the common or internal carotid artery by ultrasound or angiogram **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 4.0 mm and 9.0 mm at the target lesion.

3.0 CONTRAINDICATIONS

The ACCULINK™ and RX ACCULINK™ Carotid Stent Systems are contraindicated for use in:

Patients in whom anti-coagulant and / or anti-platelet therapy is contraindicated.

Patients with severe vascular tortuosity or anatomy that would preclude the safe introduction of a guide catheter, sheath, embolic protection system, or stent system.

Patients with known hypersensitivity to nickel-titanium.

Patients with uncorrected bleeding disorders.

Lesions in the ostium of the common carotid artery.

4.0 WARNINGS AND PRECAUTIONS

See additional *Warnings* and *Precautions* in the Instructions for Use for the ACCULINK™ and RX ACCULINK™ Carotid Stent Systems.

5.0 DEVICE DESCRIPTION

5.1 ACCULINK™ Carotid Stent

The ACCULINK™ Carotid Stent is a nickel-titanium, self-expanding stent that is superelastic at body temperature. The stent design is based upon a series of serpentine rings that are connected at 3 locations around the circumference. The connections are aligned along the length of the stent and are positioned 120 degrees from each other. The serpentine rings are designed to nest within adjacent rings. The same ACCULINK™ Carotid Stent is used for both the ACCULINK™ and RX ACCULINK™ Carotid Stent Systems. Table 1 identifies available diameters and lengths of straight and tapered ACCULINK™ Carotid Stents.

5.2 ACCULINK™ and RX ACCULINK™ Carotid Stent Systems

The ACCULINK™ Carotid Stent System is a single-use device that uses a sheath to mechanically constrain the ACCULINK™ Carotid Stent at a small diameter for delivery to the treatment site. The system is inserted through a guide catheter or sheath and tracked over a 0.014” guide wire in a coaxial, over-the-wire configuration. Radiopaque markers, located on the delivery system at the proximal and distal ends of the stent, aid in accurate placement of the stent in the lesion. With the handle in the unlocked position, retracting the pullback handle withdraws the sheath and deploys the ACCULINK™ Stent. The stent expands at body temperature, from the distal to the proximal end as the sheath is retracted.

The RX ACCULINK™ Carotid Stent System, a rapid-exchange version of the ACCULINK™ System, also uses a sheath to mechanically constrain the same ACCULINK™ Stent. The system is inserted through a guide catheter or sheath, and is tracked over a 0.014” guide wire that passes through the coaxial, distal 22cm of the system. All other features of the System are the same as the ACCULINK™ Carotid Stent System. Table 1 lists the available sizes and part numbers.

Table 1. ACCULINK™ System and RX ACCULINK™ System Model Numbers

ACCULINK™ System Model Numbers	RX ACCULINK™ System Model Numbers	Stent Diameter (mm)	Stent Length (mm)
Straight Configurations			
1011345-20	1011337-20	5.0	20
1011346-20	1011338-20	6.0	20
1011347-20	1011339-20	7.0	20
1011348-20	1011340-20	8.0	20
1011349-20	1011341-20	9.0	20
1011350-20	1011342-20	10.0	20
1011345-30	1011337-30	5.0	30
1011346-30	1011338-30	6.0	30
1011347-30	1011339-30	7.0	30
1011348-30	1011340-30	8.0	30
1011349-30	1011341-30	9.0	30
1011350-30	1011342-30	10.0	30
1011345-40	1011337-40	5.0	40
1011346-40	1011338-40	6.0	40
1011347-40	1011339-40	7.0	40
1011348-40	1011340-40	8.0	40
1011349-40	1011341-40	9.0	40
1011350-40	1011342-40	10.0	40
Tapered Configurations			
1011351-30	1011343-30	6.0 - 8.0	30
1011352-30	1011344-30	7.0 - 10.0	30
1011351-40	1011343-40	6.0 - 8.0	40
1011352-40	1011344-40	7.0 - 10.0	40

6.0 ALTERNATIVE PRACTICES AND PROCEDURES

Treatment of carotid artery disease (CAD) currently includes surgery, medical therapy, or a combination of both. The primary treatment used to prevent stroke in patients with significant CAD is surgery to remove plaque from the affected artery (endarterectomy). Medical therapy includes use of antiplatelet and / or anticoagulant medicine, as well as antihypertensive and antilipidemic drugs as indicated. Antiplatelet drugs include aspirin, Plavix® (clopidogrel), or Ticlid® (ticlopidine). Anticoagulants include Coumadin® (warfarin). Medical therapy can also include modification of lifestyle risk factors for stroke, such as cigarette smoking and alcohol use.

7.0 MARKETING HISTORY

The ACCULINK™ and RX ACCULINK™ Carotid Stent Systems 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

The ACCULINK™ Carotid Stent System and ACCUNET™ EPS were evaluated for the treatment of high-risk surgical patients and non-surgical patients with lesions in the internal carotid artery (ICA) in three separate clinical trials. Indicative of the poor health status of these patients, 42% had two or more medical / surgical risk factors on enrollment. A total of 581 registry patients were enrolled in the trials as follows:

ARCHeR 1: evaluated the over-the-wire (OTW) ACCULINK™ Carotid Stent System only and included 158 registry patients. The primary objective of the study was to determine if the occurrence rate of the composite primary endpoint of stroke, death, and myocardial infarction (MI) at 30 days and ipsilateral stroke at one year for carotid stenting is not inferior to the occurrence rate of carotid endarterectomy (CEA) in the population under evaluation

ARCHeR 2: evaluated the OTW ACCULINK™ Carotid Stent System and OTW ACCUNET™ Embolic Protection System and included 278 registry patients. The primary objective of the study was the same are ARCHeR 1. The second primary endpoint for this study was ACCUNET™ device success.

ARCHeR 3: evaluated the rapid exchange (RX) ACCULINK™ Carotid Stent System and RX ACCUNET™ Embolic Protection System and included 145 patients. The primary objective of the study was to establish equivalence (Non-inferiority) to the ARCHeR 2 results with respect to 30-day death, stroke, and MI as a means of establishing equivalency between the OTW and RX devices.

Tables 2 and 3 present the adverse events reported for registry patients enrolled in each trial. P values are given for the comparison of rates observed in the ARCHeR 2 and ARCHeR 3 trials. Because the ARCHeR 1 trial did not use embolic protection, it is not compared statistically to the other trials. Table 4 details the cause of any patient deaths. Events are categorized by body system and are defined as follows:

- Non-stroke neurological includes events such as visual / speech disturbances, confusion, seizure, weakness, and TIA.
- TLR is defined as 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. To be considered clinically indicated, the patient must be symptomatic with ≥50% stenosis or asymptomatic with ≥80% stenosis.
- Access site complications include events such as bruising, hematoma, and bleeding.
- Vascular includes events such as peripheral arterial disease, and deep vein thrombosis (DVT).
- Hemodynamic includes events such as hypo- and hypertension, syncope, and dizziness.
- Bleeding includes events such as non-access site bleeding, anemia up to 30 days, and GI bleed up to 30 days.
- Blood dyscrasia includes events such as anemia later than 30 days, and thrombocytopenia.
- Respiratory includes events such as pneumonia, embolism, chronic obstructive pulmonary disease (COPD), and respiratory failure.
- Gastrointestinal (GI) includes events such as nausea, ulcer, bowel obstruction, and GI bleed later than 30 days.
- Genitourinary includes events such as urinary tract infection, and prostatic hyperplasia.
- Infection includes events such as laryngitis, sepsis, and endocarditis.
- Metabolic includes events such as diabetes, electrolyte imbalance, and renal failure.
- Musculoskeletal includes events such as pain, fractures, and joint replacements.

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

Table 2. Serious Adverse Events Summary, ≤ 30 days

Event Categories[1,2]	ARCHeR 2 (N=278)		ARCHeR 3 (N=145)		P value[3]	ARCHeR 1 (N=158)	
	n	%	n	%		n	%
All Death, Stroke, and MI[4]	23	8.27	11	7.59	0.824	12	7.59
Death	6	2.16	2	1.38	0.625	4	2.53
Stroke-Related	2	0.72	0	0.00	0.406	1	0.63
Not Stroke-Related	4	1.44	2	1.38	0.965	3	1.90
Ipsilateral Stroke	14	5.04	7	4.83	0.933	6	3.80
Major	3	1.08	2	1.38	0.802	2	1.27
Minor[4]	11	3.96	5	3.45	0.816	4	2.53
Non-ipsilateral Stroke	1	0.36	1	0.69	0.653	1	0.63
Non-stroke Neurological	6	2.16	1	0.69	0.341	3	1.90
Target Lesion Revascularization (TLR), Clinically Indicated	0	0.00	0	0.00	1.000	0	0.00
Cardiac	23	8.27	13	8.97	0.826	22	13.92
MI	8	2.88	2	1.38	0.406	4	2.53
Arrhythmia	3	1.08	3	2.07	0.433	4	2.53
Angina	3	1.08	3	2.07	0.433	1	0.63
Congestive Heart Failure (CHF)	5	1.80	4	2.76	0.542	4	2.53
Coronary Artery Disease (CAD)	0	0.00	1	0.69	0.087	3	1.90
Procedural Complication	27	9.71	8	5.52	0.194	11	6.96
Hypotension	15	5.40	2	1.38	0.092	6	3.80
Arrhythmia	11	3.96	0	0.00	0.048	5	3.16
Vasospasm	4	1.44	0	0.00	0.238	0	0.00
Dissection[5]	2	0.72	3	2.07	0.223	0	0.00
In-stent Thrombosis	1	0.36	1	0.69	0.653	0	0.00
Emergent CEA[6]	2	0.72	0	0.00	0.406	0	0.00
Emergent Intervention[7]	1	0.36	1	0.69	0.653	0	0.00
Access Site Complication	13	4.68	4	2.76	0.405	9	5.70
Requiring Repair / Transfusion	8	2.88	2	1.38	0.406	6	3.80
Vascular	3	1.08	0	0.00	0.308	2	1.27
Hemodynamic	6	2.16	4	2.76	0.722	3	1.90
Bleeding	7	2.52	6	4.14	0.387	11	6.96
Requiring transfusion	5	1.80	5	3.45	0.310	9	5.70
GI bleeding	0	0.00	2	1.38	0.015	2	1.27
Blood Dyscrasia	5	1.80	2	1.38	0.776	0	0.00
Respiratory	5	1.80	0	0.00	0.186	2	1.27
Gastrointestinal	2	0.72	0	0.00	0.406	0	0.00
Genitourinary	1	0.36	1	0.69	0.653	1	0.63
Infection	4	1.44	0	0.00	0.238	1	0.63
Metabolic	5	1.80	0	0.00	0.186	1	0.63
Musculoskeletal	0	0.00	0	0.00	1.000	1	0.63
Miscellaneous[8]	0	0.00	0	0.00	1.000	3	1.90

[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]Three of the reported adverse events were related to device failures / malfunctions. The three are described below in footnotes 5 – 7.

[3]Because of the multiple tests of significance performed, the individual test level for significance was set conservatively at $p < 0.01$ after a Bonferroni adjustment. Therefore, none of the AE rates were deemed significantly different statistically between ARCHeR 2 and ARCHeR 3.

[4]Two patients suffered strokes that were determined to be non-serious adverse events. Patient 249-3715 (ARCHeR 2) suffered blurred vision that was subsequently diagnosed by an ophthalmologist as "central retinal artery occlusion with multiple refractile emboli and macular edema". Patient 074-4804 had mild facial weakness that was subsequently diagnosed by MRI as an acute lacunar infarct. Both events resolved without treatment. The Clinical Events Adjudication Committee adjudicated both of these events as strokes. However, because the events did not meet the criteria for a serious adverse event (no intervention to prevent permanent impairment, no persistent or significant disability), they are not included in this table. The events are included as strokes in the composite endpoints.

[5]One dissection in the ARCHeR 2 study was attributed by the physician to the OTW ACCUNET™ System. The physician was not able to cross the lesion with the device.

[6]One CEA in the ARCHeR 2 study resulted when the OTW ACCUNET™ System became entangled with the deployed stent and could not be retrieved by the physician.

[7]The emergent intervention in the ARCHeR 3 study resulted when the RX ACCUNET™ Filter Basket became entangled with the deployed stent and detached from the guidewire during the retrieval attempt. The physician opted to stent the basket in place in the artery. No additional adverse events related to this device malfunction were reported as of the last patient follow-up (9 months post-procedure).

[8]The 3 miscellaneous adverse events reported in the ARCHeR 1 study were bladder tumor, headache, and rash.

Table 3. Serious Adverse Events Summary, Up to 365 Days1

Event Categories[2,3]	31 – 365 Days				0 – 365 Days			
	ARCHeR 1 N = 154		ARCHeR 2 N = 272		ARCHeR 1 N = 158		ARCHeR 2 N = 278	
	n	%	n	%	n	%	n	%
Death	10	6.49	18	6.62	14	8.86	24	8.63
Stroke-Related	0	0.00	1	0.37	1	0.63	3	1.08
Not Stroke-Related	8	5.19	16	5.88	11	6.96	20	7.19
Unknown	2	1.30	1	0.37	2	1.27	1	0.36
Ipsilateral Stroke	1	0.65	3	1.10	7	4.43	17	6.12
Major	0	0.00	0	0.00	2	1.27	3	1.08
Minor	1	0.65	3	1.10	5	3.16	14	5.04
Non-ipsilateral Stroke	1	0.65	3	1.10	2	1.27	4	1.44
Non-stroke Neurological	1	0.65	3	1.10	4	2.53	9	3.24
Target Lesion Revascularization (TLR), Clinically Indicated	7	4.55	6	2.21	7	4.43	6	2.16
Cardiac	26	16.88	50	18.38	46	29.11	69	24.82
MI	1	0.65	8	2.94	4	2.53	16	5.76
Arrhythmia	6	3.90	4	1.47	10	6.33	7	2.52
Angina	6	3.90	13	4.78	7	4.43	16	5.76
Congestive Heart Failure (CHF)	5	3.25	7	2.57	8	5.06	11	3.96
Coronary Artery Disease (CAD)	6	3.90	6	2.21	9	5.70	6	2.16
Procedural Complication	0	0.00	0	0.00	11	6.96	27	9.71
Hypotension	0	0.00	0	0.00	6	3.80	15	5.40
Arrhythmia	0	0.00	0	0.00	5	3.16	11	3.96
Vasospasm	0	0.00	0	0.00	0	0.00	4	1.44
Dissection	0	0.00	0	0.00	0	0.00	2	0.72
In-stent Thrombosis	0	0.00	0	0.00	0	0.00	1	0.36
Emergent CEA	0	0.00	0	0.00	0	0.00	2	0.72
Emergent Intervention	0	0.00	0	0.00	0	0.00	1	0.36
Access Site Complication	0	0.00	1	0.37	9	5.70	14	5.04
Requiring Repair / Transfus.	0	0.00	0	0.00	6	3.80	8	2.88
Vascular	14	9.09	25	9.19	15	9.49	27	9.71
Hemodynamic	4	2.60	4	1.47	7	4.43	10	3.60
Bleeding	0	0.00	3	1.10	11	6.96	10	3.60
Requiring transfusion	0	0.00	2	0.74	9	5.70	7	2.52
GI bleeding	0	0.00	0	0.00	2	1.27	0	0.00
Blood Dyscrasia	2	1.30	1	0.37	2	1.27	6	2.16
Respiratory	5	3.25	5	1.84	7	4.43	10	3.60
Gastrointestinal	10	6.49	5	1.84	10	6.33	6	2.16
Genitourinary	0	0.00	1	0.37	1	0.63	2	0.72
Infection	2	1.30	4	1.47	4	2.53	8	2.88
Metabolic	2	1.30	3	1.10	3	1.90	8	2.88
Musculoskeletal	1	0.65	5	1.84	2	1.27	5	1.80
Miscellaneous[4]	5	3.25	9	3.31	8	5.06	9	3.24

[1]Data >30 days for ARCHeR 3 is not available because not all subjects have completed 1-year follow-up.
[2]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.
[3]None of the adverse events reported in the period 31 – 365 days were related to device failures / malfunctions.
[4]The 5 miscellaneous adverse events reported in the ARCHeR 1 during the 31 – 365 day period study include hospitalization for planned surgery (1), bladder cancer (1), biopsy (1), non-responsive episode adjudicated as chronic subdural hematoma (1), and a fall (1). The additional 3 events in the 0 – 365-day period were bladder tumor (1), headache (1), and rash (1).
The 9 miscellaneous adverse events reported in the ARCHeR 2 study during the 31 – 365-day period included cancer (4), weakness accompanying a GI bleed (1), glaucoma (1), cataract surgery (1), post-thoracotomy syndrome (1), and hospitalization for elective surgery (1)

Table 4. Cause of Death[1]

Events					ARCHeR 3	
	n	%	n	%	n	%
0 – 30 days[2]	**N=158**		**N=278**		**N=145**	
Stroke	1	0.63	2	0.72	0	0.00
Cardiac	3	1.90	4	1.44	1	0.69
Bleeding (GI)	0	0.00	0	0.00	1	0.69
31 – 365 days[3]	**N=154**		**N=272**		**N/A[4]**	
Stroke	0	0.00	1	0.36		
Cardiac	3	1.94	9	3.31		
Cancer	1	0.65	2	0.74		
Bleeding (GI)	0	0.00	0	0.00		
Respiratory	2	1.30	2	0.74		
Gastrointestinal	0	0.00	1	0.36		
Genitourinary	1	0.65	0	0.00		
Infection	1	0.65	2	0.74		
Unknown	2	1.30	1	0.36		
Total Deaths (0 – 365 days)	14	8.90	24	8.63		

[1]None of the reported deaths were due to a device malfunction or failure.
[2]Of the deaths 0 – 30 days, 5 were considered device or procedure related: 3 strokes, 2 cardiac.
[3]Of the deaths 31 – 365 days, 1 was considered device or procedure related: 1 stroke.
[4] Data >30 days for ARCHeR 3 is not available because not all subjects have completed 1-year follow-up.

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 ACCULINK™ and RX ACCULINK™ Carotid Stent Systems are presented below 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 ACCULINK™ and RX ACCULINK™ Carotid Stent Systems was developed based on the device risk assessment and is consistent with *Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices: Intravascular Stents* US FDA May 1995, and the applicable ASTM Standards. The relevant tests outlined in the guidance were conducted to demonstrate the *in vitro* safety and effectiveness of these devices. All test units were sterilized by E-Beam radiation prior to testing.

ACCULINK™ Carotid Stent Material Specification Conformance Testing

The ACCULINK™ Carotid Stent is fabricated from superelastic nickel-titanium tubing. The ACCULINK™ Carotid Stent was analyzed and found to conform to *ASTM F2063-00, Standard Specification for Wrought Nickel-Titanium Shape Memory Alloys for Medical Devices and Surgical Implants* and additional Guidant standards for chemical content and impurities.

The austenite transformation temperature, A_f, is measured by the bend and free recovery tangent method. Tensile strength and elongation testing was performed on the stent raw material to determine the tensile strength and breaking elongation. Corrosion testing conducted on the ACCULINK™ Self-Expanding Stent, a precursor of the ACCULINK™ Carotid Stent, composed of the same material, and demonstrated corrosion resistance of the nickel-titanium alloy. Additional *in vitro* testing performed on the ACCULINK™ Carotid Stent is summarized in Table 5.

Table 5. Summary of ACCULINK™ Carotid Stent *In Vitro* Testing

In Vitro Test	Relevant Functional Requirement	Summary of Test Result
Finite Element Analysis	• Durability and integrity of the implanted device	The structural integrity of the ACCULINK™ Carotid Stent was evaluated utilizing finite element analysis (FEA) modeling. The FEA modeling simulated the arterial environment using the conservative assumption of unstented arterial contraction, which is higher than in a stented vessel. The strain and extension analysis and the Goodman analysis showed that the local deformation did not exceed the breakage strain specification, and the stent survived 380 million cycles, equivalent to 10 years fatigue loading.
Accelerated Fatigue Testing	• Durability and integrity of the implanted device	Accelerated *in vitro* fatigue testing of approximately 10 years equivalent real time was conducted on the largest diameter (10 mm) and shortest length (20 mm) stents the to ensure that the ACCULINK™ Carotid Stent, when expanded to its largest intended diameter, will not show fatigue failure during a 10-year use period.
Magnetic Resonance Imaging	• MRI compatibility	Testing has shown that the ACCULINK™ Carotid Stent to be MRI safe at field strengths of 3.0 Tesla or less, a maximum spatial gradient of 3.3 Tesla/meter and a maximum whole body averaged specific absorption rate (SAR) of 2.0W/kg for 15 min of MRI. The ACCULINK™ Carotid Stent should not migrate in this MRI environment.
Stent-Free Area	• Patency of the implant	Stent-free area percentage was calculated for all diameters of the ACCULINK™ Carotid Stent and ranged from 80% to 90% for the smallest (5mm) and largest (10mm) diameters, respectively.
Length Change During Expansion from Delivery System to Vessel	• Ability to accurately deploy	Percent length change was measured for the all lengths of the largest diameter stent (10mm) and ranged from 1.87% for the longest (40 mm) to 3.8% for the shortest (20 mm) stent.
Stent Diameter and Length Specifications	• Ability to accurately deploy • Appropriate sizing of the implant	Testing was performed on a range of stent sizes to verify the outside diameter, length, and mass of the ACCULINK™ Carotid Stent. All stents met acceptance criteria.
Stent Radial Force	• Expansion effectiveness of the implant • Appropriate sizing of the implant • Patency of the implant	Testing was conducted on the largest diameter stent to determine the radial resistance of the ACCULINK™ Carotid Stent. All stents met acceptance criteria.
Permanent Deformation Test (Crush Resistance)	• Expansion effectiveness of the implant • Appropriate sizing of the implant • Patency of the implant	Testing was conducted on the largest diameter stent to evaluate the deformation resistance of the ACCULINK™ Carotid Stent when exposed to external forces. All stents met acceptance criteria, demonstrating functional ability for a minimum of 2 years.

ACCULINK™ and RX ACCULINK™ Carotid Stent System Functional Testing

The *in vitro* bench test plan was developed as a result of the device risk assessment and the use of guidance documents for similar devices: *Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices: Intravascular Stents* US FDA May 1995. Testing was conducted on test units that were manufactured in accordance with prespecified procedures, sterilized by E-beam radiation and then extreme conditioned (temperature and transportation). Testing was conducted at zero time and following 2 year accelerated aging. Tensile testing was conducted on device samples that had been pre-conditioned in a Carotid Tortuosity Model. Table 6 lists the tests performed and results obtained for the ACCULINK™ Carotid Stent System and RX ACCULINK™ Carotid Stent System.

Table 6. Summary of ACCULINK™ and RX ACCULINK™ Carotid Stent Systems *In Vitro* Testing

In Vitro Test	Relevant Functional Requirement	Summary of Test Result
Delivery System Dimensional Inspection	• Ability to access the intended location • Ability to deploy the implant	Dimensional testing was conducted on eight important system dimensions related to system length and cross sectional diameter. All systems tested met product specification.
System Preparation and Flush	• Ability to access the intended location • Ability to deploy the implant	Samples were tested to determine the ease and ability to evacuate air from the stent system. All systems tested met product specification.
Device Compatibility (Catheter Bend Integrity)	• Ability to access the intended location	The bend integrity of the delivery systems and compatibility of the OTW and RX ACCULINK™ Carotid Stent Systems with standard 6F introducer sheaths and 8F guide catheters was evaluated. All systems tested met product specification
Stent Deployment Force	• Ability to deploy the implant	The amount of force required to deploy the stent was evaluated for the ACCULINK™ and RX ACCULINK™ Carotid Stent Systems. All systems tested met product specification with measured forces at 2 years ranging from 3.45 - 8.00N (OTW) and 2.22 – 4.00N (RX).
Stent Deployment Accuracy*	• Ability to deploy the implant	The deployment accuracy of the delivery system was determined for the OTW and RX ACCULINK™ Carotid Stent Systems. All systems tested met product specification with measured distances ranging from 0.0 - 2.5mm (OTW) and 0.0 -2.0mm (RX). The integrity of the proximal marker band post-deployment of the stent was also assessed* and all deployed systems met product specification.
Post Deployment Sheath Replacement	• Ability to deploy the implant • Ability to withdraw the delivery system	The ability to resheath the delivery system post-deployment of the stent was assessed for the OTW and RX ACCULINK™ Carotid Stent Systems. All systems tested met product specification.
Tensile / Bond Strength	• Ability to access the intended locations • Ability to deploy the implant • Ability to withdraw the delivery system	The tensile strengths of nine critical bonds / joints of the OTW and RX ACCULINK™ Carotid Stent Systems were determined. All test results passed the established acceptance criteria.

*Testing conducted on aged samples only for OTW ACCULINK™ System

9.2 Animal Testing

The ACCULINK™ and RX ACCULINK™ Carotid Stent Systems were subjected to a series of acute and chronic animal studies. The intent of the studies was to demonstrate acceptable functional performance of the subject devices in an *in vivo* setting and to ensure that the devices do not cause untoward hemodynamic vascular or other biological (e.g. thrombotic events, etc.) responses. Studies of the 20mm and 30mm ACCULINK™ Carotid Stents were performed in the non-atherosclerotic swine model in accordance with the FDA Guidance for the *Submission of Research and Marketing Applications for Interventional Cardiology Devices dated May 1994;* the results of these studies is summarized in Table 7. The non-atherosclerotic swine model was selected as the test model because the swine model is anatomically similar to the human with regard to the carotid anatomy and has similar pathological changes in response to vascular interventions. All studies were conducted in accordance with Good Laboratory Practices (GLP) per 21 CFR § 58. In vivo animal studies of the 40mm ACCULINK™ Carotid Stent was not performed as data from the ARCHeR studies provides sufficient long term implant data.

Table 7. Summary of ACCULINK™ Carotid Stent *In Vivo* Testing

Study	Number of Animals Timepoints Device(s) Tested	Relevant Findings
Acute Performance Evaluation and Characterization of the Chronic Vascular Response to Implantation of the ACCULINK™ Self-Expanding Stent	• 8 animals • 7, 14, 168 days • CS65 Design • (29) 20mm stents/ delivery systems	Long-term implant studies (168 days) were performed with the 20mm ACCULINK™ Self-Expanding Carotid Stent System. Results of the longer-term implantation studies demonstrated results similar to those noted for the 28-day time point. Additional long-term studies with the improved CS73 design were performed at 3, 14,28, and 84 days. Angiographic evaluation revealed patent lumens, no evidence of stent tapering, TIMI3 flow characteristics and no intraluminal filling defects.
	• 8 animals • 3, 14, 28, 84 days • CS73 Design • (28) 20mm Stents / delivery systems	
ACCULINK™ Self-Expanding Stent: Acute Performance Evaluation and Characterization of the Chronic Vascular Response to Implantation of the 30mm length	• 4 animals • 31, 84, 168 days • CS73 Design • (16) 30mm Stents/ delivery systems	Long-term implant studies were performed with the 30mm ACCULINK™ Self-Expanding Carotid Stent System. Stent performance during clinical use was good; no stent movement was observed during delivery or deployment. All stents deployed within 1mm of target. Delivery System usage was rated as above average. No incidence of vessel injury or luminal narrowing was noted after deployment, however, in one animal with two stents, 100% narrowing occurred. Overall, long-term performance was equivalent to the 20mm stent.
Characterization of Vascular Response to Implantation of the ACCULINK™ Stent	• 5 animals • 3, 14, 28 days • 12 stents / delivery Systems	Stents were implanted in the carotid artery. All stents were successfully and accurately delivered and deployed with acceptable performance characteristics. Animals remained hemodynamically stable during delivery and deployment. Implanted stents did not elicit acute or chronic thrombosis, adverse inflammatory reactions or excessive neointimal proliferation. There were no stent migrations, luminal protrusions or filling defects. A patent lumen was maintained immediately after deployment and at all re-look time points.

Study	Number of Animals Timepoints Device(s) Tested	Relevant Findings
In Vivo Acute Evaluation of the ACCULINK™ Carotid Stent Delivery System	• 1 animal • 5 stents / delivery systems	The ACCULINK™ Carotid Stent Delivery System demonstrated clinically acceptable acute performance. No issues were noted during system preparation, stent / system delivery, and stent deployment. All stent deployments were accurate. Post-deployment angiography demonstrated good stent apposition and no compromise of vessel integrity.

9.3 Biocompatibility

The ACCULINK™ Carotid Stent System was tested for biocompatibility in accordance with ISO 10993-1, *Biological evaluation of medical devices*, the *US Pharmacopeia*, the *Tripartite Biocompatibility Guidance for Medical Devices* dated September 1986, and with the Federal Good Laboratory Practices Regulation (21 CFR § 58). The samples for all biocompatibility testing conducted were prepared from the entire final device and with recommended solvent to surface ratios. Tests considered for the ACCULINK™ and RX ACCULINK™ Carotid Stent Systems were appropriate for an externally communicating device having contact with circulating blood for a limited (<24 hours) exposure (the delivery system), and for an implant device with permanent (>30 days) blood contact (the ACCULINK™ Carotid Stent). Tests performed, listed in Table 8; all yielded acceptable results. Ninety-day implantation testing was carried out *in situ* and Chronic Toxicity, Carcinogenicity, and Immunotoxicity were not carried out due to the vast experience with nickel-titanium as an implant material.

Table 8. ACCULINK™ and RX ACCULINK™ Biocompatability Tests

Biocompatibility Tests Performed	ACCULINK™ and RX ACCULINK™ Carotid Stent System
Cytotoxicity	Stent and Delivery System
Hemolysis	Stent and Delivery System
Coagulation [Prothrombin Time (PT), Unactivated Thromboplastin Time (UPTT)]	Stent and Delivery System
Systemic Injection	Stent and Delivery System
Intracutaneous Toxicity	Stent and Delivery System
Sensitization (polar and non-polar fluids)	Stent and Delivery System
Pyrogenicity (Rabbit)	Stent and Delivery System
Pyrogen, LAL	Stent and Delivery System
Mutagenicity (Ames)	Stent and Delivery System
Intramuscular Implantion (7 day)	Stent only
Subchronic Toxicity	Stent only

9.4 Sterilization

E-Beam radiation Sterilization was validated in accordance with "*Sterilization of health care products – Requirements for validation and routine control – Radiation sterilization"*, ANSI/AAMI/ISO 11137 – 1994 and "*Sterilization of medical devices – Validation and routine control sterilization by irradiation",* EN552.

9.5 Packaging and Shelf Life

Packaging shelf life for the ACCULINK™ Carotid Stent System, the RX ACCULINK™ Carotid Stent System is based on qualification testing performed using the MULTI-LINK RX DUET ™ Coronary Stent System packaging (P970020). A 2-year packaging shelf life was established based on real time aging studies.

10.0 SUMMARY OF CLINICAL STUDIES

The ACCULINK for Revascularization of Carotids in High Risk Patients (ARCHeR) Clinical Trials were a series of prospective, non-randomized, multi-center, single-arm clinical trials. These trials were performed to demonstrate the safety and efficacy of the ACCULINK™ and RX ACCULINK™ Carotid Stent Systems with embolic protection to treat high-risk, surgical and non-surgical symptomatic (≥50% stenosis) and asymptomatic (≥80% stenosis) subjects with disease in the internal carotid artery. A total of 581 patients were enrolled at 45 clinical sites in the United States and five sites outside of the United States. These trials are summarized Table 9.

Table 9. An Overview of the ARCHeR Trials

			ARCHeR 3
Products Evaluated	Over-the-wire ACCULINK™ Carotid Stent System	Over-the-wire ACCULINK™ and Over-the-wire ACCUNET™ Systems	Rapid Exchange ACCULINK™ and Rapid Exchange ACCUNET™ Systems
Study Design	Non-randomized, multi-center, single-arm, prospective clinical trials		
Sample Size	158 (plus 51 lead-in patients)[5]	278 (plus 25 lead-in patients)[5]	145 patients
Number of Sites	25 Sites in the U.S.	37 Sites in the U.S. and 1 Site in South America	19 Sites in the U.S., 4 Sites in Europe, and 1 Site in South America
Primary Endpoint	30-day death, stroke, MI and ipsilateral stroke at 31-365 days	30-day death, stroke, and MI and ipsilateral stroke at 31-365 days; ACCUNET™ device success[2]	30-day death, stroke, and MI
Secondary Endpoints-All Trials	-Device Success [1,2] -Clinical Success [3] -Target Lesion Revascularization -Access Site complications requiring treatment		
Specific Secondary Endpoints	-Six and 12 month ultrasound (annually thereafter)	-Six and 12 month ultrasound (annually thereafter) -Medical Resource Utilization	-Six and 12 month ultrasound -Ipsilateral stroke between 31 and 365 days[4]
Study Hypothesis	Non-inferiority to historical control	Non-inferiority to historical control	Non-inferiority to ARCHeR 2 results at 30 days
Patient Follow-up	-Neurologic evaluation by an independent neurologist and patient assessment at 24 hours, 30 days, 6 months, 12 months (every 6 months thereafter for ARCHeR 1and 2 only) -TIA / Stroke Questionnaire and adverse event assessment at 30 days and 3, 6, 9 and 12 months. -ECG at 30 days -Ultrasound at 30 days, 6 and 12 months (annually thereafter for ARCHeR 1 and 2only)		

[1]Attainment of final result, <50% residual stenosis covering an area no longer than the original lesion, using the ACCULINK™ System as described in the protocol.
[2]Device delivered, placed, and retrieved as described in the protocol.
[3]ACCULINK™ device / procedure success without death, emergency endarterectomy, repeat PTA / thrombolysis of the target vessel, stroke, or MI within seven days of the procedure.
[4]Data collection for the ARCHeR 3 study is not complete beyond 30 days. Secondary endpoints have not been evaluated.
[5]The ARCHeR 1 and 2 trials each had a lead-in phase for initial clinical experience. An additional 76 patients were enrolled in this phase of the clinical study, 51 in ARCHeR 1 and 25 in ARCHeR 2. The natures and frequencies of endpoints and adverse events reported in lead-in patients were consistent with those reported in the pivotal trials, and thus are not reported here.

The study hypothesis of the ARCHeR 1 and ARCHeR 2 trials was to show equivalence (non-inferiority) between carotid stenting and an historical control, based on the standard of care. The historical control was established based on a review of the current literature on carotid endarterectomy and medical therapy. From this review, the rate of 30-day death, stroke, MI and ipsilateral stroke at 31 – 365 days was estimated at 15% for patients with medical co-morbidities, and estimated at 11% for patients with anatomy unfavorable for CEA. A weighted historical control (WHC) was calculated based on the proportion of each of these patient groups enrolled in the study.

$$WHC = pc * 15\% + pa * 11\%$$

Where: pc = the proportion of patients with medical co-morbidities, and

pa = the proportion of patients with unfavorable anatomy.

Using this equation, the WHC rate at one year was calculated for both ARCHeR 1 and ARCHeR 2 to be 14.5%. The ARCHeR 3 trial was designed to demonstrate equivalence (non-inferiority) of the safety and performance of the rapid exchange RX ACCULINK™ and RX ACCUNET™ Systems to results observed in the ARCHeR 2 trial for the OTW ACCULINK™ and ACCUNET™ Systems based on 30-day results.

As shown in Table 9, the protocol required regular patient follow-up by the treating physician and follow-up neurological assessments by an independent neurologist. Core laboratories provided independent assessments for angiographic, ultrasound, ECG, and pathologic evaluation of captured debris (ACCUNET™ only). Medical monitors reviewed all safety data to ensure appropriate reporting of adverse events. A Clinical Events Adjudication Committee adjudicated suspected primary endpoint events. A Data Safety Monitoring Board monitored adverse events to ensure patient safety.

10.1 Eligibility Criteria Summary

The study population consisted of male and female patients, at least 18 years of age, with discrete lesions in the internal carotid artery. Patients had to be high-risk candidates for surgery or non-surgical candidates; both symptomatic and asymptomatic patients were eligible.

The inclusion criteria for ARCHeR 1, 2, and 3 were essentially identical. Key inclusion criteria included the following:

- Symptomatic patient: Transient ischemic attack (TIA), amaurosis fugax, or minor / non-disabling stroke (in the hemisphere supplied by the target vessel) within 180 days of enrollment; carotid stenosis had to be ≥50% by angiography, using NASCET[a] methodology to determine degree of stenosis.
- Asymptomatic patient: meets angiographic and clinical inclusion criteria; carotid stenosis had to be ≥80% by angiography, using NASCET methodology to determine degree of stenosis.

[a] NASCET, North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. Stroke, 1991. 22(6): p. 711-20.

- Patient had to meet **two** or more of the criteria listed in a-e **OR one** or more of the criteria listed in f-q to qualify as a high-risk or non-surgical candidate:
  a) Knowledge of two or more proximal or major diseased coronary arteries with ≥70% stenosis that have not, or cannot be revascularized;
  b) Unstable angina defined as rest angina with ECG changes;
  c) MI within the previous 30 days and current need for carotid artery revascularization.
  d) Concurrent requirement for aortocoronary bypass or cardiac valve surgery within 30 days;
  e) Contralateral occlusion of the ICA.
  f) Currently on a list for major organ transplantation (i.e. heart, lung, liver, kidney) or is being evaluated for such;
  g) Ejection fraction <30% or New York Heart Association (NYHA) Functional Class III or higher;
  h) FEV_1 <30% (Predicted);
  i) Dialysis-dependent renal failure;
  j) Uncontrolled diabetes defined as fasting glucose >400 mg/dl and ketones >2+;
  k) Restenosis after previous CEA;
  l) Patient is status / post radiation treatment to the neck;
  m) Patient is status / post radical neck surgery;
  n) Surgically inaccessible lesions (e.g. lesions above the level of C2 or below the clavicle, lesions obstructed by tumors in the neck);
  o) Spinal immobility – inability to flex neck beyond neutral or kyphotic deformity;
  p) Presence of tracheostomy stoma;
  q) Contralateral laryngeal nerve paralysis.
- Patient had a discrete lesion located in the ICA (with or without involvement of the contiguous CCA)
- Target ICA vessel reference diameter had to be ≥4.0 mm and ≤9.0 mm by angiography.

Specific Inclusion Criteria for the ACCUNET System (ARCHeR 2 and 3 only)

The vessel distal to the lesion had to have an absence of excessive tortuosity and an available straight or mildly angulated segment ≥ 4 cm, by angiography, in the distal ICA (prior to the petrous portion of the vessel) in which to place the embolic protection device.

The diameter of the straight or mildly angulated segment, in the distal ICA prior to the petrous portion of the vessel, had to be ≥ 3.25 mm and ≤ 7.5 mm (ARCHeR 2) or ≥ 3.25 mm and ≤ 7.0 mm (ARCHeR 3) by angiography.

10.2 Description of Patients Evaluated

Table 10 summarizes patient follow-up at the endpoint evaluation time points of 30 days and 365 days. Patients were considered to have been evaluated if they had physician contact including one or more of the following at the given time point: office visit, neurologic evaluation, TIA / Stoke questionnaire, hospital admission, or lab tests including ultrasound, angiogram, or ECG.

Table 10. Patient Follow-up

	ARCHeR 1	ARCHeR 2	ARCHeR 3
30 Days			
Patients Enrolled	158	278	145
Cumulative Death	4	4	2
Cumulative Withdrawn or LTF	2	1	1
Patients evaluable	152	273	142
Patients evaluated[1]	152	272	141
Neurological Evaluation	128	256	130
Ultrasound Evaluation	133	256	136
Other Clinical Evaluation only[2]	14	10	5
365 Days			
Cumulative Death	12	21	
Cumulative Withdrawn / LTF	14	11	
Patients evaluable	132	246	
Patients evaluated[1]	131	239	
Neurological Evaluation	116	207	
Ultrasound Evaluation	121	213	
Other Clinical Evaluation only[2]	9	19	

[1]Patients evaluated may have one or more of the evaluations listed: neurological, ultrasound, or clinical
[2]Other Clinical Evaluation includes: Office visit, telephone conversation with site, TIA / Stroke Questionnaire, Hospitalization

Baseline demographics and lesion characteristics for the three studies are presented in Table 11. All reported angiographic data on the treated lesions are based on measurements obtained by a centralized angiographic core laboratory.

Table 11. Baseline Patient Demographics

Demographics and Medical History	ARCHeR 2 N=278	ARCHeR 3 N=145	P value[1]	ARCHeR 1 N=158
Age				
Mean ± SD	70.48± 9.38 (278)	71.13± 9.40 (145)	0.499	69.21± 9.65 (158)
Range (min, max)	(45.29, 92.67)	(38.94, 88.78)		(40.28, 90.14)
Age ≥ 80 year	15.5% (43/ 278)	17.9% (26/145)	0.579	13.3% (21 / 158)
Gender				
Male	68.3% (190/278)	68.3% (99/145)	1.000	63.9% (101 / 158)
Medical History				
Diabetes	39.9% (111/ 278)	34.5% (50/145)	0.293	37.3% (59 / 158)
Hypertension	84.2% (234/ 278)	83.3% (120/144)	0.889	83.5% (132/ 158)
Hypercholesterolemia	71.9% (200/ 278)	82.4% (117/142)	0.022	64.7% (101/ 156)
Current Smoker	17.7% (49/ 277)	17.7% (25/141)	1.000	23.7% (37 / 156)
Number of Symptomatic Patients (TIA, Stroke or Amaurosis Fugax Within 180 Days)	24.1% (67/ 278)	21.4% (31/ 145)	0.547	25.3% (40 / 158)
Baseline Lesion & Vessel Characteristics				
No Calcification	50.4% (139/ 276)	42.3% (60/ 142)	0.122	64.9% (98/ 151)
Unilateral Calcification	27.2% (75/ 276)	23.2% (33/ 142)	0.411	27.2% (41/ 151)
Bilateral Calcification	22.5% (62/ 276)	34.5% (49/ 142)	0.010	7.9% (12/ 151)
Lesion Length(mm)				
Mean ± SD (N)	14.55± 7.14 (276)	14.84± 7.82 (142)	0.707	16.17± 7.45 (157)
Range (min, max)	(0.00, 56.51)	(3.57, 43.81)		(4.72, 50.37)
Minimum Lumen Diameter (MLD, mm)				
Mean ± SD (N)	1.35± 0.56 (276)	1.21± 0.53 (142)	0.013	1.37± 0.64 (156)
Range (min, max)	(0.10, 3.57)	(0.00, 3.03)		(0.10, 3.15)
Percent Diameter Stenosis (%DS)				
Mean ± SD (N)	69.93±10.86 (276)	73.04±10.13 (142)	0.005	72.62±10.99 (156)
Range (min, max)	(31.03, 95.95)	(47.40, 100.0)		(42.96, 98.14)
High-Risk Inclusion Criteria	**% (n/N)**	**% (n/N)**		**% (n/N)**
Medical/Surgical Co-morbidities				
Two or More Diseased Coronary Arteries	27.7% (77/ 278)	25.5% (37/ 145)	0.647	28.5% (45/ 158)
Unstable Angina	7.9% (22/ 278)	6.9% (10/ 145)	0.847	7.6% (12/ 158)
MI Prior 30d & Need Carotid Artery Revasc.	3.6% (10/ 278)	2.1% (3/ 145)	0.556	4.4% (7/ 158)
Need CABG or Valve Surgery	14.0% (39/ 278)	15.2% (22/ 145)	0.772	19.0% (30/ 158)
Contralateral Occlusion of ICA	16.2% (45/ 278)	12.4% (18/ 145)	0.318	20.9% (33/ 158)
On List For Major Organ Transplant	0.0% (0/ 278)	0.7% (1/ 145)	0.343	0.0% (0/ 158)
Ejection fraction < 30% or NYHA ≥ III	38.8% (108/ 278)	27.6% (40/ 145)	0.024	29.7% (47/ 158)
FEV_1 < 30% (Predicted)	3.2% (9/ 278)	4.8% (7/ 145)	0.429	5.1% (8/ 158)
Dialysis-dependent Renal Failure	2.2% (6/ 278)	2.1% (3/ 145)	1.000	5.1% (8/ 158)
Uncontrolled Diabetes	0.0% (0/ 278)	0.7% (1/ 145)	0.343	0.0% (0/ 158)
Restenosis after previous CEA	34.2% (95/ 278)	35.9% (52/ 145)	0.748	36.1% (57/ 158)
Unfavorable Anatomic Conditions				
Radiation Treatment to Neck	6.5% (18/ 278)	6.9% (10/ 145)	0.840	7.0% (11/ 158)
Radical Neck Surgery	2.2% (6/ 278)	4.8% (7/ 145)	0.146	3.2% (5/ 158)
Surgically Inaccessible Lesions	6.5% (18/ 278)	9.0% (13/ 145)	0.432	8.9% (14/ 158)
Spinal Immobility	2.9% (8/ 278)	6.2% (9/ 145)	0.119	0.0% (0/ 158)
Presence of Tracheostomy Stoma	1.4% (4/ 278)	2.1% (3/ 145)	0.695	1.9% (3/ 158)
Contralateral Laryngeal Nerve Paralysis	0.4% (1/ 278)	0.7% (1/ 145)	1.000	0.6% (1/ 158)

[1]Statistical test of difference between ARCHeR 2 and ARCHeR 3, using Fisher's exact test for categorical values and t-Test for continuous variables.

10.3 Results

The primary and secondary endpoints presented in Table 9 for the three studies were evaluated and categorized as either safety or efficacy endpoints.

Table 12 presents the periprocedural (30 day) safety endpoints related to short-term patient outcome. The 30-day primary endpoint rate (death, stroke, or MI within 30 days) was 7.59%, 8.63%, and 8.28% for ARCHeR 1, 2, and 3 respectively. Rates for each of the contributors to the composite rate are presented, as well as rates of other adverse events related to evaluation of procedure safety.

Table 13 presents efficacy endpoint and procedural success data. The one-year primary endpoint event rates (30-day primary endpoint + ipsilateral stroke between 31 and 365 days) were 8.28% and 10.22% for ARCHeR 1 and 2 respectively. These rates are estimated via Kaplan-Meier analysis presented in Figures 1 and 2. Device, procedural and clinical success rates for all devices in all trials exceeded 91%.

To investigate the long-term stroke prevention capabilities of the ACCULINK™ Carotid Stent, the primary endpoint Kaplan-Meier curves shown in Figures 1 and 2 were extended out with all available follow-up data for the ARCHeR 1 and ARCHeR 2 studies. Median time for follow-up of the ARCHeR 1 study is 726 days; the accompanying table presents the Kaplan-Meier analysis at 1, 6, 12, 24, and 30 months. Median time for follow-up in the ARCHeR 2 study is 378 days; the accompanying table presents the Kaplan-Meier analysis at 1, 3, 6, 12, and 24 months.

A meta-analysis of all ARCHeR registry patients was conducted to evaluate the clinical efficacy of carotid stenting in Symptomatic (n=138) and Asymptomatic (n=443) subsets. Because MI has not historically been included in the primary endpoint of the landmark symptomatic (NASCET[b]) and asymptomatic (ACAS[c]) trials, a composite of all death and stroke within 30 days plus Ipsilateral Stroke beyond 30 days is presented in Figures 3A and 3B as Kaplan-Meier freedom-from functions. The rate of this composite at 1 and 2.5 years is 12.6% and 14.5% in the Symptomatic subset and 6.8% and 11.0% in the Asymptomatic subset. Another relevant outcome is the composite of all Death and Major Stroke within 30 days and Major Ipsilateral Stroke beyond 30 days (Figures 3C and 3D). The rate of this composite at 1 and 2.5 years is 5.1% and 6.9% in the Symptomatic subset and 2.6% and 4.3% in the Asymptomatic subset.

The relationship of patient and lesion characteristics to periprocedural outcomes (specifically stroke within 30 days and the composite of stroke, death and MI within 30 days) was examined in a multi-variate analysis. The statistically significant predictors of the composite endpoint events of stroke, death or MI were: requirement for coronary artery bypass graft (CABG) or valve surgery, hypertension, and symptomatic carotid stenosis (all $p < 0.05$). The statistically significant predictors of stroke at 30 days were: symptomatic carotid stenosis, hypercholesterolemia, male gender, advanced age, and anatomic risk factors (all $p<0.05$).

The primary objectives of the ARCHeR 1 and ARCHeR 2 trials were met. The upper confidence limits for primary endpoint rates fell below the 14.5% WHC for both studies, demonstrating that carotid stenting is non-inferior to carotid endarterectomy in the studied high-risk population.

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[b] Barnett, H.J., D.W. Taylor, M. Eliasziw, A.J. Fox, G.G. Ferguson, R.B. Haynes, R.N. Rankin, G.P. Clagett, V.C. Hachinski, D.L. Sackett, K.E. Thorpe, and H.E. Meldrum, Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med, 1998. 339(20): p. 1415-25.

[c] ACAS, Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA, 1995. 273(18): p. 1421-8.

The primary objective of the ARCHeR 3 study, that the 30-day primary endpoint for the ARCHeR 3 study was non-inferior to that of the ARCHeR 2 study, was met. The upper bound of the 95% confidence interval of the difference between ARCHeR 3 and ARCHeR 2 is 4.75%, which is less than the delta of 8% (p=0.005). Thus, results from ARCHeR 3 are determined to be non-inferior to those of ARCHeR 2, and the RX and OTW devices are determined to yield similar clinical results.

Table 12. ARCHeR Pivotal Trials - Safety Assessment Event Rates (≤ 30 days)

Event Categories[1]	ARCHeR 2 (N=278)		ARCHeR 3 (N=145)		P value[2]	ARCHeR 1 (N=158)	
	n	%	n	%		n	%
30-Day Primary Endpoint (Death, Stroke, MI)	24	8.63	12	8.28	1.000	12	7.59
All Stroke, Death Endpoint	19	6.83	11	7.59	0.842	10	6.33
Death	6	2.16	2	1.38	0.625	4	2.53
Stroke-Related	2	0.72	0	0.00	0.406	1	0.63
Not Stroke-Related	4	1.44	2	1.38	0.965	3	1.90
Ipsilateral Stroke	14	5.04	7	4.83	0.933	6	3.80
Major	3	1.08	2	1.38	0.802	2	1.27
Minor[2]	11	3.96	5	3.45	0.816	4	2.53
Non-ipsilateral Stroke	1	0.36	1	0.69	0.653	1	0.63
Non-stroke Neurological[3]	6	2.16	1	0.69	0.341	3	1.90
MI	8	2.88	2	1.38	0.406	4	2.53
Procedural Complication	27	9.71	8	5.52	0.194	11	6.96
Hypotension	15	5.40	2	1.38	0.092	6	3.80
Arrhythmia	11	3.96	0	0.00	0.048	5	3.16
Vasospasm	4	1.44	0	0.00	0.238	0	0.00
Dissection	2	0.72	3	2.07	0.223	0	0.00
In-stent Thrombosis	1	0.36	1	0.69	0.653	0	0.00
Emergent CEA	2	0.72	0	0.00	0.406	0	0.00
Emergent Intervention	1	0.36	1	0.69	0.653	0	0.00
Access Site Complication[4]	13	4.68	4	2.76	0.405	9	5.70
Requiring Repair / Transfusion	8	2.88	2	1.38	0.406	6	3.80
Bleeding[5]	7	2.52	6	4.14	0.387	11	6.96
Requiring transfusion	5	1.80	5	3.45	0.310	9	5.70
GI bleeding	0	0.00	2	1.38	0.015	2	1.27
Adverse events related to device failure or malfunction[6]	2	0.72	1	0.69	1.000	0	0.00

[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]Two patients suffered strokes that were determined to be non-serious adverse events. Patient 249-3715 (ARCHeR 2) suffered blurred vision that was subsequently diagnosed by an ophthalmologist as "central retinal artery occlusion with multiple refractile emboli and macular edema". Patient 074-4804 had mild facial weakness that was subsequently diagnosed by MRI as an acute lacunar infarct. Both events resolved without treatment. The Clinical Events Adjudication Committee adjudicated both of these events as strokes. However, because the events did not meet the criteria for a serious adverse event (no intervention to prevent permanent impairment, no persistent or significant disability), they are not included in the accounting of serious adverse events. The events are included as strokes in the composite endpoints.

[3]Includes events such as visual / speech disturbances, confusion, seizure, and TIA.

[4]Includes events such as bruising, hematoma, and bleeding.

[5]Includes events such as non-access site bleeding, anemia up to 30 days, and GI bleed up to 30 days.

[6]Three adverse events counted above were categorized as related to device failure / malfunction:

One dissection in the ARCHeR 2 study was attributed by the physician to the OTW ACCUNET™ System. The physician was not able to cross the lesion with the device.

One CEA in the ARCHeR 2 study resulted when the OTW ACCUNET™ System became entangled with the deployed stent and could not be retrieved by the physician.

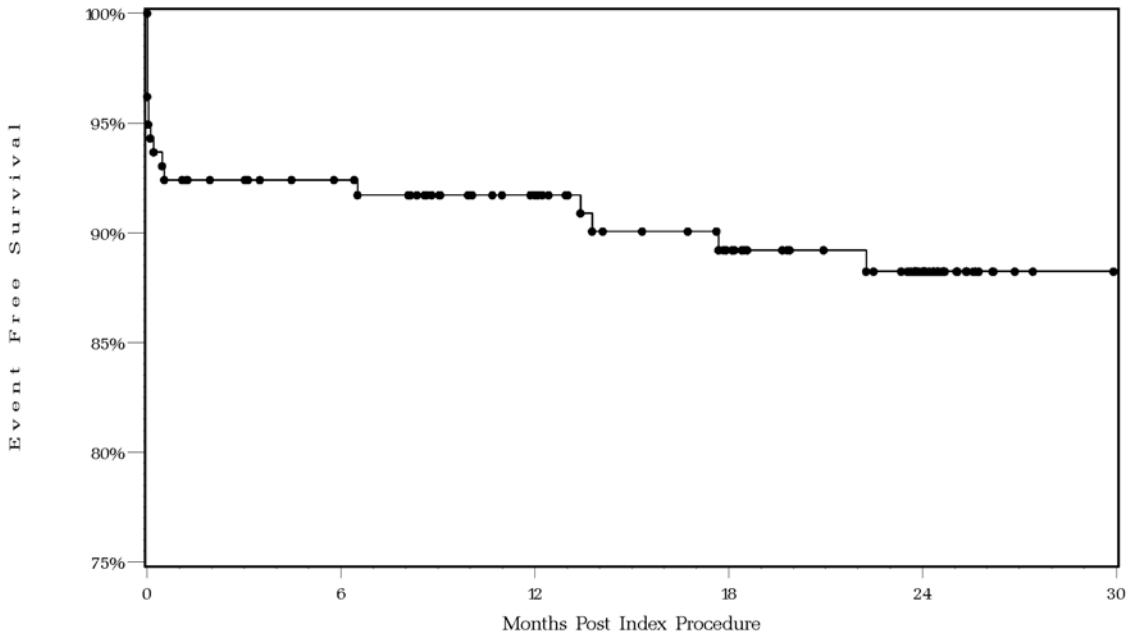
One emergent intervention in the ARCHeR 3 study resulted when the RX ACCUNET™ Filter Basket became entangled with the deployed stent and detached from the guidewire during the retrieval attempt. The physician opted to stent the basket in place in the artery. No additional adverse events related to this device malfunction were reported as of the last patient follow-up (9 months post-procedure).

Table 13. ARCHeR Pivotal Trial Results – Efficacy Assessment Event Rates

Events	ARCHeR 2 n/N	%	ARCHeR 3 n/N	%	P value	ARCHeR 1 n/N	%
One-Year Primary Endpoint (30-Day Primary Endpoint + Ipsilateral Stroke Between 31 and 365 Days)[1] [95% Conf. Interval][2]	10.22% [--, 13.48%]		N/A		N/A	8.28% [--, 12.25%]	
ACCUNET™ Device Success[3]	264/277	95.3	139/145	95.9	1.000	N/A	
ACCULINK™ Device/Procedural Success[4]	268/271	98.9	141/142	99.3	1.000	153/156	98.1
Clinical Success[5]	249/272	91.5	133/142	93.7	0.562	143/156	91.7
Post-procedure In-lesion Minimal Lumen Diameter Mean ± SD (N) Range (min, max)	3.64± 0.78 (272) (1.93, 6.89)		3.79± 0.75 (143) (1.93, 6.29)		0.064	3.95± 0.86 (156) (1.52, 6.67)	
Post-procedure In-lesion Percent Diameter Stenosis Mean ± SD (N) Range (min, max)	18.66±11.88 (272) (0.00, 51.07)		15.85±12.47 (143) (-12.1, 55.66)		0.025	20.40±12.38 (156) (-12.1, 56.06)	
Target Lesion Revascularization (Clinically Indicated)[1, 6]							
at 6 months	1	0.4%	N/A		N/A	1	0.7%
at 12 months	7	2.8%				3	2.2%
at 24 months	8	3.8%				4	3.0%
Ultrasound (Same or decreased stenosis from Baseline exam)							
at 6 months	143/196	73.0	N/A		N/A	84/102	82.4
at 12 months	124/173	71.7				78/97	80.4

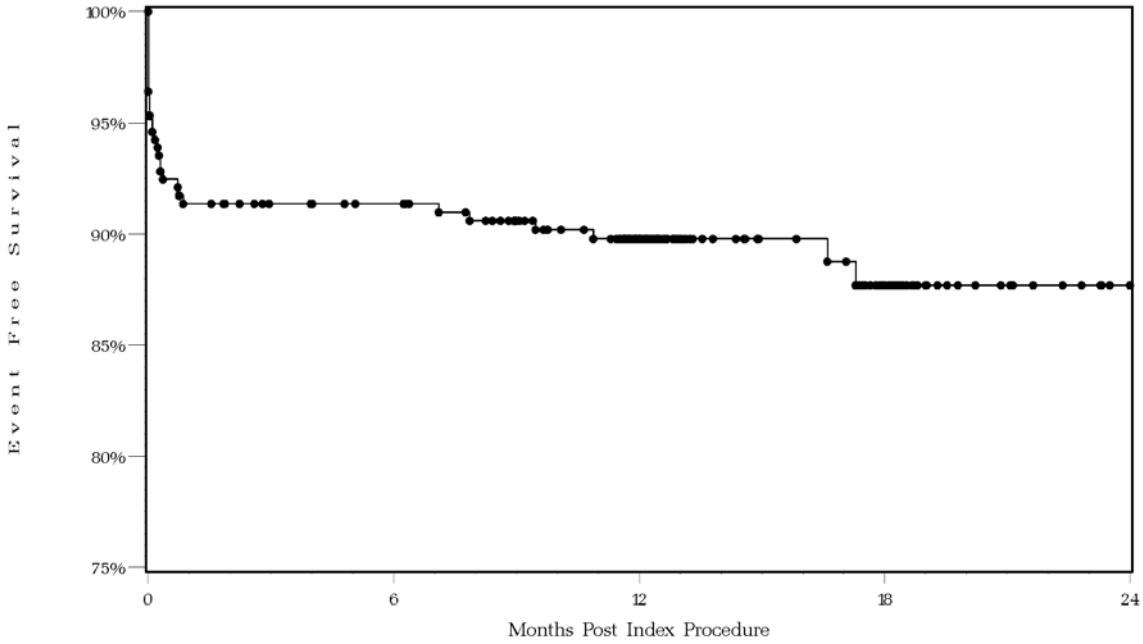
[1] Estimated via Kaplan-Meier analysis.
[2] 95% 1-sided confidence interval by normal approximation, using Peto's formula for the Kaplan Meier standard error.
[3] Device delivered, placed, and retrieved as described in protocol.
[4] Stent successfully deployed and residual stenosis < 50% following stent placement, per core lab reading.
[5] ACCULINK™ device / procedural success in the absence of death, emergency endarterectomy, repeat PTA / thrombolysis of the target vessel, stroke, or MI, within seven days of procedure
[6] TLR is defined as any repeat invasive procedure, including angioplasty, stenting, endarterectomy or thrombolysis, performed to open or increase the luminal diameter inside or within 10mm of the previously treated lesion. To be considered clinically indicated, the patient must be symptomatic with ≥50% stenosis or asymptomatic with ≥80% stenosis.

Figure 1. ARCHeR 1 Study, Freedom from composite endpoint of Stroke, Death, and MI within 30 days and Ipsilateral Stroke between days 31 and 910



Months After Index Procedure	0	1	6	12	24	30
# At Risk	158	152	146	135	102	70
# Events	6	12	12	13	17	17
% Event Free	96.2%	92.4%	92.4%	91.7%	88.2%	88.2%

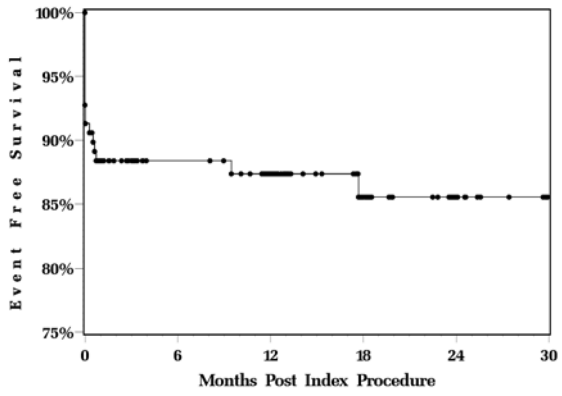
Figure 2. ARCHeR 2 Study, Freedom from composite endpoint of Stroke, Death, and MI within 30 days and Ipsilateral Stroke between days 31 and 730



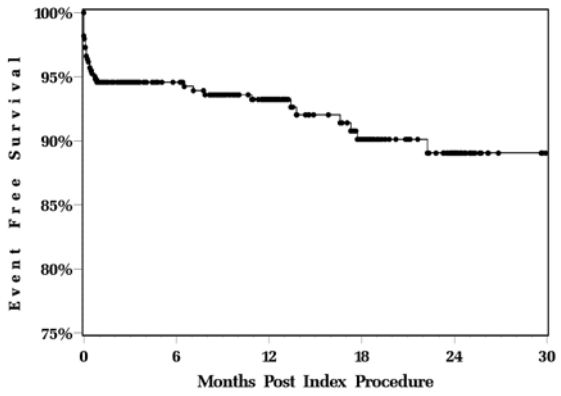
Months After Index Procedure	0	1	3	6	12	24
# At Risk	278	268	254	246	231	164
# Events	10	24	24	24	28	30
% Event Free	96.4%	91.4%	91.4%	91.4%	89.8%	87.7%

Figure 3. Symptomatic and asymptomatic registry patients in ARCHeR 1, 2 and 3

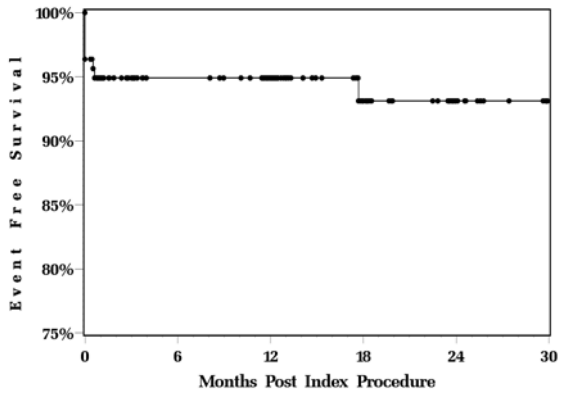
A. Symptomatic patients, freedom from composite of all Death or Stroke <30days, and Ipsilateral Stroke days 31-910



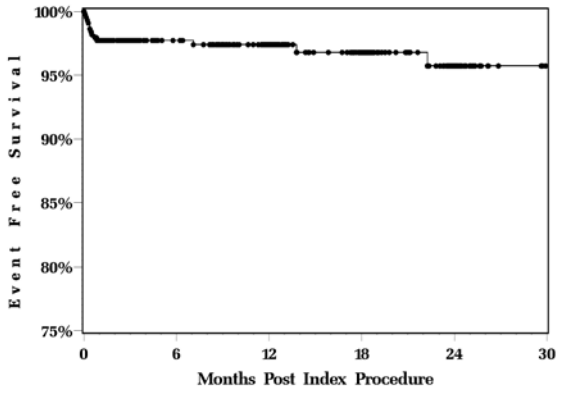
B. Asymptomatic patients, freedom from composite of all Death or Stroke <30days, and Ipsilateral Stroke days 31-910



C. Symptomatic patients, freedom from composite of all Death or Major Stroke <30days, and Major Ipsilateral Stroke days 31-910



D. Asymptomatic patients, freedom from composite of all Death or Major Stroke <30 days, and Major Ipsilateral Stroke days 31-910



11.0 CONCLUSIONS DRAWN FROM STUDIES

The preclinical studies indicate that the RX and OTW ACCULINK Carotid Stent System used with embolic protection meet or exceed safety and performance specifications. Multicenter clinical data have demonstrated that the RX and OTW ACCULINK Carotid Stent Systems used with embolic protection are safe and effective as a treatment for carotid artery disease in the population indicated. 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 August 300, 2004. The applicant's manufacturing facilities were inspected on April 16th and 26th, 2004 and were found to be in compliance with the Quality System Regulation (21 CFR 820).

The RX and OTW ACCULINK Carotid Stent Systems were granted expedited review status on April 28, 2004 because these devices could offer a viable alternative to the current standard of care for patients with carotid artery disease. Because these devices may represent a reduced risk compared to existing technology, the FDA granted expedited review to the ACCULINK™ Carotid Stent System and RX ACCULINK™ Carotid Stent System.

14.0 APPROVAL SPECIFICATIONS

Directions for Use: See the Labeling

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

Post-approval Requirements and Restrictions: See approval order.