Summary of Safety and Effectiveness Data

NIR ON™ Ranger™ w/SOX™ and NIR ON™ Ranger™ Premounted Stent Systems

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NIR ON™ Ranger™ w/SOX™ and NIR ON™ Ranger™ PREMOUNTED STENT SYSTEMS

1. GENERAL INFORMATION

Device Generic Name:	Intravascular Stent
Device Trade Name:	NIR ON™ Ranger ™ Premounted Stent System NIR ON™ Ranger ™ w/SOX™ Premounted Stent System
Applicant Name and Address:	Boston Scientific Corporation One Boston Scientific Place Natick, MA 01760-1537
PMA Application Number:	P980001
Date of Notice of Approval to the Applicant:	August 11, 1998

2. INDICATIONS FOR USE

The NIR™ Stent is indicated for improving coronary luminal diameter in the following:

- patients with symptomatic ischemic disease due to discrete *de novo* lesions in native coronary arteries (length ≤ 25 mm) with a reference vessel diameter of 3.0 to 4.0 mm;
- treatment of abrupt or threatened closure in patients with failed interventional therapy in lesions with reference diameters in the range of 2.5 to 4.0 mm;
- patients with symptomatic ischemic heart disease due to lesions in saphenous vein bypass grafts with lesion length ≤ 30 mm and reference vessel diameter in the range of 3.0 to 4.0 mm.

Long-term outcome (beyond 6 months) for this permanent implant is unknown at present.

(see also Section **11.3 Labeling**)

3. DEVICE DESCRIPTION

The NIR ON™ Ranger ™ Premounted Stent System with and without SOX™ is a balloon expandable stent premounted on an over-the-wire (OTW) dual lumen coaxial catheter. The stent is made from sheets of 316L surgical grade stainless steel, etched into a pre-specified geometric pattern, which is then folded and welded into cylindrical stents. The geometry is a continuous, uniform multicellular design, with adaptive cells capable of differential lengthening. Two distal radiopaque markers aid in the accurate placement of the stent. The distal expandable balloon enables high-pressure inflation that can be used for dilation after stent placement. The NIR ON™ Ranger ™ Premounted Stent System is available in stent lengths of 9, 16, 25, and 32 mm and balloon diameters of 2.5, 3.0, 3.5, and 4.0 mm.

The NIR ON™ Ranger™ with SOX™ Premounted Stent System (NIR ON™ Ranger™ w/SOX™) is comprised of the NIR ON™ Stent pre-mounted on an OTW dual lumen coaxial catheter that has elastomeric retaining sleeves (SOX™) that cover approximately 1 mm of the distal and proximal ends of the crimped stent. The retaining sleeves provide an additional mechanism to securely attach the stent to the delivery balloon in order to minimize the risk of stent embolization during delivery to the target lesion site. The NIR ON™ Ranger™ without SOX™ Premounted Stent System (NIR ON™ Ranger™) has a distal balloon/stent portion that is identical to the NIR ON™ Ranger™ w/SOX™ Premounted Stent System without the retaining sleeves.

Unless specifically indicated, the two devices will hereafter be referred to as the NIR™ Stent. Tables 1 and 2 list the balloon and stent specifications for both devices.

Table 1. NIR ON™ Ranger™ w/SOX™ Balloon and Stent Specifications

Stent Length (mm)	System/ Balloon Diameter (mm)	NIR™ Stent Cells	Balloon Length (mm)	Nominal Pressure During Stent Deployment (ATM)	Rated Burst Pressure (ATM)	Minimum I.D of Guide Catheter (inches)
16	2.5	7	17	7	18	.064
16	3.0	7	17	7	18	.064
16	3.5	7	17	7	16	.064
16	4.0	9	17	7	16	.072
25	2.5	7	26	7	18	.064
25	3.0	7	26	7	18	.064
25	3.5	7	26	7	16	.064
25	4.0	9	26	7	16	.072
32	2.5	7	33	7	18	.064
32	3.0	7	33	7	18	.064
32	3.5	7	33	7	16	.064
32	4.0	9	33	7	16	.072

Table 2. NIR ON™ Ranger™ Balloon and Stent Specifications

Stent Length (mm)	System/ Balloon Diameter (mm)	NIR™ Stent Cells	Balloon Length (mm)	Nominal Pressure During Stent Deployment (ATM)	Rated Burst Pressure (ATM)	Minimum I.D. of Guide Catheter (inches)
9	2.5	7	13	7	14	.064
9	3.0	7	13	7	14	.064
9	3.5	7	13	7	12	.064
9	4.0	9	13	7	12	.072
16	2.5	7	20	7	14	.064
16	3.0	7	20	7	14	.064
16	3.5	7	20	7	12	.064
16	4.0	9	20	7	12	.072
25	2.5	7	29	7	14	.064
25	3.0	7	29	7	14	.064
25	3.5	7	29	7	12	.064
25	4.0	9	29	7	12	.072
32	2.5	7	36	7	14	.064
32	3.0	7	36	7	14	.064
32	3.5	7	36	7	12	.064
32	4.0	9	36	7	12	.072

4. CONTRAINDICATIONS

The NIR™ Stent is contraindicated for use in:

- Patients in whom antiplatelet and/or anticoagulant therapy is contraindicated
- Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon.

5. WARNINGS AND PRECAUTIONS

(see also Section 11.3 **Labeling**)

Warnings

- The device carries an associated risk of subacute thrombosis, vascular complications, and/or bleeding events. Therefore, patients should be carefully selected.
- Persons allergic to 316LS stainless steel may suffer an allergic reaction to this implant.
- Implantation of the stent should be performed only by physicians who have received appropriate training.
- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Subsequent restenosis may require repeat dilation of the arterial segment containing the stent. The long-term outcome following repeat dilation of coronary stents is unknown at present.
- When multiple stents are required, stent materials should be of similar composition.

5.2 Precautions

5.2.1 Stent Handling

- **For single use only.** Do not resterilize or reuse. Note product "Use Before" date.
- The NIR ON™ Ranger™ w/SOX™ is designed for use as a unit. The stent is **not** to be removed from its delivery balloon. The stent is not to be crimped onto another balloon. Removing the stent from its delivery balloon may damage the stent and/or lead to stent embolization.
- Special care must be taken not to handle or in any way disrupt the stent position on the delivery device. In addition, care must be taken when handling the NIR ON™ Ranger™ w/SOX™ Premounted Stent System so as not to disrupt the SOX™ which cover the ends of the stent. This is most important during catheter removal from packaging, placement over guidewire, and advancement through hemostasis valve adapter and guiding catheter hub.
- Excessive manipulation, e.g., rolling the mounted stent, may cause dislodgment of the stent from the delivery balloon, or disruption of the SOX™.
- Use only the appropriate balloon inflation media (see Labeling section **9. OPERATOR'S INSTRUCTIONS**). Do not use air or any gas medium to inflate the balloon.

- **For single use only.** Do not resterilize or reuse. Note product "Use Before" date.
- The NIR ON™ Ranger™ is designed for use as a unit. The stent is **not** to be removed from its delivery balloon. The stent is not designed to be crimped onto another balloon. Removing the stent from its delivery balloon may damage the stent and/or lead to stent embolization.
- Special care must be taken not to handle or in any way disrupt the stent position on the delivery device. This is most important during catheter removal from packaging, placement over guidewire, and advancement through hemostasis valve adapter and guiding catheter hub.

5.2.2 Stent Placement

- The safety and effectiveness of the use of the NIR™ Stent in the treatment of restenotic lesions have not been established.
- The target lesion should be pre-dilated with a conventional balloon angioplasty catheter prior to stent deployment.
- **Do not prepare or pre-inflate balloon prior to stent deployment** other than as directed. Use balloon purging technique described in the Operator's Instructions.

- Implanting a stent may lead to dissection of the vessel distal and/or proximal to the stented portion, and may cause acute closure of the vessel requiring additional intervention (e.g., CABG, further dilation, placement of additional stents, or other).
- When treating multiple lesions, the distal lesion should be initially stented, followed by stenting of the more proximal lesion(s). Stenting in this order obviates the need to cross the proximal stent in placement of the distal stent and reduces the chances for dislodging the proximal stent.
- Do not expand the stent if it is not properly positioned in the vessel. (See Stent System Removal - Precautions)
- Placement of the stent has the potential to compromise side branch patency.
- Balloon pressures should be monitored during inflation. **Do not exceed rated burst pressure as indicated on product label** (see Labeling Table 6). Use of pressures higher than specified on product label may result in a ruptured balloon and potential intimal damage and dissection.
- Stent retrieval methods (use of additional wires, snares and/or forceps) may result in additional trauma to the vascular site. Complications can include bleeding, hematoma or pseudoaneurysm.

5.2.3 Stent System Removal - Precautions

If Stent System removal is required prior to deployment, ensure the guiding catheter is co-axially positioned relative to the Stent System and cautiously withdraw the Stent System into the guiding catheter.

Should unusual resistance be encountered when withdrawing the stent towards the guiding catheter, the Stent System, and the guiding catheter should be removed as a single unit. This must be done under direct visualization with fluoroscopy.

When removing the entire Stent System as a single unit:

- **Do not pull the Stent System into the guiding catheter.** Maintain guidewire placement across the lesion and carefully pull back the Stent System until the proximal balloon marker of the Stent System is aligned with the distal tip of the guiding catheter.
- The guiding catheter and the Stent System should be carefully removed from the coronary artery as a single unit.
- The Stent System should be pulled back into the descending aorta toward the arterial sheath. As the distal end of the guiding catheter enters into the arterial sheath, the catheter will straighten allowing safe withdrawal of the Stent System into the guiding catheter and the subsequent removal of the Stent System and the guiding catheter from the arterial sheath.
- Failure to follow these steps, and/or applying excessive force to the Stent System can potentially result in loss or damage to the stent, or Stent System components such as the balloon.

5.2.4 Post Implant

- Care must be exercised when crossing a newly deployed stent with an intravascular ultrasound (IVUS) or a coronary guidewire, or a balloon catheter to avoid disrupting the stent geometry.
- Do not perform Magnetic Resonance Imaging (MRI) scan on patients post-stent implantation until the stent has been completely endothelialized (eight weeks) to minimize the potential for migration. The stent may cause artifacts in MRI scans due to distortion of the magnetic field.

6. ADVERSE EVENTS

6.1 Observed Adverse Events

A total of 1564 patients were enrolled in six multi-center clinical studies as summarized in Table 3.

Table 3. Patient Enrollment in Clinical Studies

All patients in all studies (n =1564)

	NIR™ Stent	Palmaz-Schatz®	Patient Totals
Study Group			
Feasibility Study	111		111
NIRVANA (NIR™ Vascular Advanced North American) Trial			
NIRVANA Randomized Trial	418	430	848
NIRVANA Abrupt or Threatened Closure (AC/TC) Registry	207		207
NIRVANA Saphenous Vein Graft (SVG) Registry	155		155
NIR ON™ Ranger™ w/SOX™ Studies			
NIR ON™ Native Arteries Registry	162		162
NIR ON™ AC/TC Registry	31		31
NIR ON™ Ranger™ Study	50		50
Patient Totals	**1134**	**430**	**1564**

Patients from the NIRVANA Randomized Trial, the Abrupt or Threatened Closure (AC/TC) Registry, and the Saphenous Vein Graft (SVG) Registry form the basis of the observed adverse events reported in Table 4 (n=848+207+155=1210).

Table 4. Adverse Events during the First 6 Months

% [±95% Confidence Interval] (Number), All patients in Randomized Trial, AC/TC Registry, and SVG Registry (n=1210)

	Randomized NIR™ n=418	Palmaz-Schatz® n=430	AC/TC n=207	SVG n=155
ANY Adverse Event	16.3% [12.9%,20.2%] (68)	17.0% [13.6%,20.9%] (73)	30.0% [23.8%,36.7%] (62)	19.4% [13.5%,26.5%] (30)
Early (in-hospital)	7.9% [5.5%,10.9%] (33)	7.9% [5.5%,10.9%] (34)	13.5% [9.2%,19.0%] (28)	5.2% [2.3%,9.9%] (8)
Out-of-hospital	9.1% [6.5%,12.3%] (38)	10.2% [7.5%,13.5%] (44)	18.4% [13.3%,24.3%] (38)	14.2% [9.1%,20.7%] (22)
Non-Q-Wave MI Total	3.6% [2.0%,5.9%] (15)	3.5% [2.0%,5.7%] (15)	5.3% [2.7%,9.3%] (11)	4.5% [1.8%,9.1%] (7)
Early (in-hospital)	3.6% [2.0%,5.9%] (15)	2.8% [1.5%,4.8%] (12)	4.8% [2.3%,8.7%] (10)	2.6% [0.7%,6.5%] (4)
Out-of hospital	0% [0%,0.9%] (0)	0.7% [0.1%,2.0%] (3)	0.5% [0%,2.7%] (1)	1.9% [0.4%,5.6%] (3)
Q-Wave MI Total	0.7% [0.1%,2.1%] (3)	0.7% [0.1%,2.0%] (3)	1.4% [0.3%,4.2%] (3)	0.6% [0%,3.5%] (1)
Early (in-hospital)	0.5% [0.1%,1.7%] (2)	0.7% [0.1%,2.0%] (3)	1.0% [0.1%,3.4%] (2)	0.6% [0%,3.5%] (1)
Out-of hospital	0.2% [0%,1.3%] (1)	0% [0%,0.9%] (0)	0.5% [0%,2.7%] (1)	0% [0%,2.4%] (0)
CABG Total	1.7% [0.7%,3.4%] (7)	2.3% [1.1%,4.2%] (10)	3.9% [1.7%,7.5%] (8)	1.3% [0.2%,4.6%] (2)
Early (in-hospital)	0.2% [0%,1.3%] (1)	0.2% [0%,1.3%] (1)	1.4% [0.3%,4.2%] (3)	0% [0%,2.4%] (0)
Out-of-hospital	1.4% [0.5%,3.1%] (6)	2.1% [1.0%,3.9%] (9)	2.4% [0.8%,5.5%] (5)	1.3% [0.2%,4.6%] (2)
Stent Thrombosis Total	0.5% [0.1%,1.7%] (2)	0.5% [0.1%,1.7%] (2)	1.0% [0.1%,3.4%] (2)	1.3% [0.2%,4.6%] (2)
Early (in-hospital)	0.5% [0.1%,1.7%] (2)	0.2% [0%,1.3%] (1)	0.5% [0%,2.7%] (1)	0.6% [0%,3.5%] (1)
Out-of-hospital	0% [0%,0.9%] (0)	0.2% [0%,1.3%] (1)	0.5% [0%,2.7%] (1)	0.6% [0%,3.5%] (1)
Death Total	0.7% [0.1%,2.1%] (3)	0.7% [0.1%,2.0%] (3)	3.4% [1.4%,6.8%] (7)	5.2% [2.3%,9.9%] (8)
Early (in-hospital)	0% [0%,0.9%] (0)	0.2% [0%,1.3%] (1)	0.5% [0%,2.7%] (1)	0.6% [0%,3.5%] (1)
Out-of hospital	0.7% [0.1%,2.1%] (3)	0.5% [0.1%,1.7%] (2)	2.9% [1.1%,6.2%] (6)	4.5% [1.8%,9.1%] (7)
Bleeding Complications	1.0% [0.3%,2.4%] (4)	1.4% [0.5%,3.0%] (6)	4.3% [2.0%,8.1%] (9)	2.6% [0.7%,6.5%] (4)
Vascular Complications	5.0% [3.1%,7.6%] (21)	4.0% [2.3%,6.3%] (17)	7.2% [4.1%,11.7%] (15)	3.2% [1.1%,7.4%] (5)
Cerebrovascular Accidents	0.2% [0%,1.3%] (1)	0.5% [0.1%,1.7%] (2)	0.5% [0.1%,1.7%] (2)	1.3% [0.2%,4.6%] (2)
Stent Delivery Failures	2.2% [1.0%,4.0%] (9)	3.0% [1.6%,5.1%] (13)	12.6% [8.4%,17.9%] (26)	1.3% [0.2%,4.6%] (2)

Early (in-hospital) refers to events during the hospitalization for the initial stent placement.
In cases where a patient experienced both an in-hospital event and an out-of hospital event, they are counted once in each group. They are counted only once in the event total. Hence, the sum of the in-hospital event rate and the out-of-hospital event rate may not equal the total event rate.
ANY Adverse Event includes death, Q wave MI, non-Q wave MI, emergent CABG, target lesion revascularization, stent thrombosis, bleeding complications, vascular complications, and CVA.

Three (3) patients who received the NIR™ Stent died during the NIRVANA Randomized Trial. The deaths occurred between 42 and 118 days post stenting due to sudden cardiac death (n=2), and respiratory failure/cardiomyopathy (n=1).

Seven (7) NIRVANA AC/TC Registry patients died during the clinical study. Of these, two deaths were early (within 30 days of stenting) due to sub-acute thrombosis. Five (5) deaths were late and occurred between 50 and 201 days post stenting due to sudden cardiac death (n=1), coronary arteriosclerosis, not related to the stent (n=1), renal failure/sepsis (n=1), head trauma (n=1), and sepsis (n=1).

Eight (8) NIRVANA SVG Registry patients died during the clinical study. Of these, one death was early (within 30 days of stenting) due to sub-acute thrombosis. Seven (7) deaths were late and occurred between 95 and 205 days post stenting due to cardiac arrest (n=2), sudden cardiac death (n=2), congestive heart failure (n=1), and cancer (n=2).

Five (5) feasibility patients died during the clinical study. All deaths were late (>30 days post stenting), and occurred due to cardiac arrest (n=3), cancer (n=1), and cerebrovascular accident (n=1).

The NIR ON™ Ranger™ w/SOX™ Studies were conducted to demonstrate the safety of the over-the-wire version of the delivery system during a follow-up period of 14 days. The results were compared to the rapid exchange delivery system used in the NIRVANA Randomized Trial. Twelve of the 193 patients (6.2%) treated with the NIR™ Stent in the NIR ON™ Ranger™ w/SOX™ Studies experienced one or more adverse events (death, Q wave MI, emergent CABG, TLR, stent thrombosis, bleeding complications, vascular complications and CVA) during 14 days of follow-up compared to 27 of 418 (6.4%) of the patients in the NIRVANA Randomized Trial, difference -0.2% [-4.4%, 3.9%]. No deaths occurred during the NIR ON™ Ranger™ w/SOX™ Studies.

The NIR ON™ Ranger™ Study was conducted to demonstrate the safety of the over-the-wire version of the delivery system (the NIR ON™ Ranger™ without SOX™) during hospitalization. The results were compared to the rapid exchange delivery system used in the NIRVANA Randomized Trial. Of the 50 patients treated with the NIR™ Stent in the NIR ON™ Ranger™ without SOX™ Study, one patient (2.0%) experienced one or more adverse events (death, Q wave MI, emergent CABG, TLR, stent thrombosis, bleeding complications, vascular complications and CVA) throughout their hospitalization compared to 22 of 418 (5.3%) of the patients in the NIRVANA Randomized Trial, difference -3.3% [-7.7%, 1.2%]. No deaths occurred during the NIR ON™ Ranger™ without SOX™ Study.

6.2 *Potential Adverse Events*

Adverse events (in alphabetical order) which may be associated with the use of a coronary stent in native coronary arteries (including those listed in Tables 4-6):

- Acute myocardial infarction
- Arrhythmias, including VF and VT
- Death
- Dissection
- Drug reactions to antiplatelet agents/contrast medium
- Emboli, distal (air, tissue or thrombotic emboli)
- Emergent Coronary Artery Bypass Surgery
- Hemorrhage, requiring transfusion
- Hypotension/Hypertension
- Infection and/or pain at the access site
- Ischemia, myocardial
- Perforation
- Pseudoaneurysm, femoral
- Restenosis of stented segment
- Spasm
- Stent embolization
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident
- Total occlusion of coronary artery

7. ALTERNATE PRACTICES AND PROCEDURES

Alternative treatments of coronary atherosclerotic disease include, diet, medication (e.g. thrombolysis), atherectomy, balloon angioplasty, coronary artery bypass (CABG) surgery or stenting with commercially available stents.

8. MARKETING HISTORY

The NIR™ Stent was registered for sale in the following countries:

Argentina	Egypt	Lebanon	People's Republic of China
Austria	England	Liechtenstein	Saudi Arabia
Australia	Finland	Kuwait	South Africa

Bahrain	France	Malaysia	Scotland
Barbados	Germany	Mexico	Singapore
Belgium	Greece	Malta	Sri Lanka
Bermuda	Hungary	Netherlands	Sweden
Brazil	Iceland	Norway	Switzerland
Chile	India	New Zealand	Taiwan
Columbia	Indonesia	Oman	Thailand
Costa Rica	Ireland	Pakistan	Tunisia
Cyprus	Israel	Peru	Turkey
Czech Republic	Italy	Philippines	Uruguay
Denmark	Jordan	Portugal	Venezuela
Ecuador	Korea	Qatar	United Arab Emirates

At the time of release in 1996, all stents sold were bare stents (not mounted on any delivery catheter) and composed of 316L stainless steel. As of August, 1996, 316L stents were replaced by 316LS stainless steel. Through December, 1997, a total of approximately 107,000 bare NIR™ Stents have been sold outside the United States. Eighty-two (82) complaints have been received on bare NIR™ Stents representing a complaint rate of 0.077 percent. The device has not been withdrawn from marketing for any reason related to the safety and effectiveness of the device.

9. SUMMARY OF PRECLINICAL STUDIES

The following *in-vitro* tests were performed in accordance with the FDA Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices, May 1994.

In-Vivo Animal Testing

An animal study was conducted to evaluate the acute and long-term pathologic response of the NIR™ Stent in a non-diseased swine coronary artery model. Additional studies were performed to evaluate the performance of various delivery systems including the NIR PRIMO™ Premounted Stent System (as used in the NIRVANA Randomized Trial) and the NIR ON™ Ranger™ Premounted Stent System. These studies are listed below.

9.1.1 Washington Hospital Center Study (GLP 102)

In this study NIR™ Stents were hand crimped on VIVA! PRIMO™ PTCA catheters. The VIVA! PRIMO™ PTCA catheter is a single operator exchange catheter commercially used in Europe. Stents were implanted in swine for either 72-hour or 30-day sacrifice. Angiographic, hemodynamic, and histologic response data were collected and analyzed from thirty-seven animals implanted with the NIR™ Stent.

Seventy-two hour post implant data demonstrated an acceptable morphometric and vascular response. The average lumen reduction was less than 7.5%. This study group demonstrated minimal internal elastic lamina (IEL), external elastic lamina (EEI), and medial disruption less than 5%, 0%, 2% respectively. The observed inflammatory response in all stented tissue sections was consistent with the known response following balloon deployment of a coronary stent in a swine model. The data from the computer assisted morphometric measurements, including percent stenosis (11%) and intimal thickness (0.1mm), compared well with the published data from other studies. Scanning Electron Microscopy (SEM) integrity analysis of explanted stents revealed no structural failure or areas of abnormal surface changes when compared to non-implanted stents.

Thirty days post implantation histologic analysis detected no changes within the EEL (0%), minimal changes in the IEL (3 0%) and limited medial disruption (2.1%). Thirteen (13) vessel segments were assessed for the presence of an inflammatory response and thrombus formation. One animal exhibited an inflammatory response consistent with contamination of the stent. The remaining 12 stented vessel segments showed no inflammation at 30 days. No significant differences in morphometric measurements were observed based on stent diameter or length. SEM analysis of the implantation sites in 3 stented vessel segments demonstrated mature endothelial cells with both pavement and spindle shapes covering the stented lumen surface. All side branches observed were patent.

9.1.2 Mayo Study (GLP 112)

This study was performed in 5 animals to evaluate the NIR™ PRIMO™ Premounted Stent System's overall handling characteristics and safety of operation, and to determine it's equivalence to the hand crimped system (used in Europe). Total of 20 3.0-mm and 4.0-mm diameter, 32-mm long NIR™ Stents (which present the greatest challenge for stent delivery and system compatibility) were implanted. Heart rate, arterial pressure, ECG, and activated clotting time (ACT) were also monitored during the procedure to assure that the physiological conditions of the animal were within normal ranges. Animals were sacrificed immediately after implantation. Following sacrifice gross necropsy of the chest cavity was performed and all abnormal observations noted. The acute angiographic results and X-rays of the excised heart showed no structural damage or surface abnormality of any of the stents.

9.1.3 Stent and Delivery System Performance Evaluation - Physician

In this study, the system performance of the NIR™ Stent hand crimped on a VIVA! PRIMO™ PTCA Catheter was compared to that of the NIR PRIMO™ Premounted Stent System. Physician satisfaction and overall impression of the systems were directly ranked by the performing physicians, on a scale of 1 to 5 (1= poor, 5= excellent). The overall ease of preparation, guide wire loading, loading into the guide catheter, pushability, trackability, and flexibility were all rated excellent for both delivery systems. Radiopacity of the NIR™ Stent was rated acceptable.

9.1.4 Stent and Delivery System Performance Evaluation (GLP 103) - Animal

In this animal study, the overall performance and deliverability characteristics of the NIR PRIMO™ Premounted Stent delivery system (as used in the NIRVANA Randomized Trial) were compared to those of the NIR ON™ Ranger™ Premounted Stent System (the subject of this PMA). A total of 12 stents were placed in three animals. Physician judged the overall performance and handling of both systems as acceptable.

9.2 In-Vitro Bench Testing

In-Vitro bench testing of the NIR™ Stent and the two delivery systems was conducted in accordance with the May 1994 FDA "Guidance for the Submission of Research and Marketing Applications: Intravascular Stents". The relevant tests outlined in the guidance were conducted to demonstrate the functional performance characteristics of the device. All testing was conducted on samples that were sterilized.

The following is a brief summary of the bench testing conducted on the device.

9.2.1 Stent Material Specification and Conformance Testing

9.2.1.1 Chemical Analysis

The NIR™ Stent is fabricated from medical grade 316LS stainless steel, which conformed to ASTM-F 139, "Standard Specification for Stainless Steel Sheet and Strip for Surgical Implants," in both the chemical analysis and the inclusion/impurity content.

9.2.1.2 Scanning Electron Microscopy (SEM) Analysis

The NIR™ Stent was examined via SEM at 500X and 1000X to detect evidence of surface contamination or impurities on the stent material not removed by cleaning processes. There was no evidence of contamination above the specified limits.

9.2.1.3 Yield Strength and Elongation

The tensile strength and elongation test was performed to determine the yield strength and percent elongation of the NIR™ Stent material. The nominal tensile strength was 102 ksi and the nominal elongation in 2.0 in was 42%. The yield strength and elongation of the NIR™ Stent met the product specifications.

9.2.2 Stent Integrity Testing

9.2.2.1 Corrosion

The corrosion test was conducted to determine the susceptibility of the NIR™ Stent to corrosion and pitting under potentiodynamic conditions. Testing was conducted in accordance with ASTM-G 61, "Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements for Localized Corrosion Susceptibility of Iron-, Nickel-, or Cobalt-Based Alloys" and ASTM-A 262, Method E (acidic copper sulfate "Strauss Test"). The results indicated that the corrosion resistance of the device met product specifications.

9.2.2.2 Dimensions

The dimensional measurements of the NIR™ Stent were made under light microscope. The dimensional analysis indicated that the NIR™ Stent met the product specifications.

9.2.2.3 Stent-Free Area Percentage

The metal surface coverage as a function of stent diameter was calculated by dividing the total vessel contact metal surface area of the stent structure by the surface area of the vessel at any given stent/vessel diameter. Metal to artery percentage ratios ranged from 14.3% to 24 % for 2.5 mm to 5.0-mm stents, respectively. Length Change

The length change test determined the percent shortening of the NIR™ Stent when expanded to the nominal diameter. Ten (10) stents of each length of both the 7- and 9-cell design were hand crimped onto 3.5-mm and 4.0-mm catheters, respectively. Measurements of stent constrained length were made and recorded for each stent at baseline and after inflation to 5 ATM. Stent foreshortening ranged from 7% to 14% and met the design specifications.

9.2.2.4 Uniformity of Expansion

To determine the uniformity of stent expansion along the stent length, ten (10) stents of each length of both the 7-cell and 9-cell designs were hand crimped onto 4.0-mm and 3.5-mm catheters, respectively and deployed in air at 5 ATM. Measurements taken at 3 points along the stent length (proximal, mid, distal) after inflation were averaged and compared to baseline measurements. All NIR™ Stents met the uniformity expansion specification of $\pm$ 5% from their constrained diameter to 5 ATM with a range of 0.60 % - 2.33. These results indicated that the NIR™ Stent expands uniformly at all diameters and maintains this uniformity upon withdrawal of the balloon.

9.2.2.5 Recoil

Ten (10) NIR™ Stents of each length (both the 7-cell and 9-cell designs) were hand crimped onto 3.5-mm and 4.0-mm catheters, respectively. Measurements were taken at baseline, with the delivery balloon inflated to 5 ATM, and after deflation. Percent recoil ranged from 1.91% – 3.05 %. The recoil of the NIR™ Stent met the product specifications.

9.2.2.6 *Compression - Stiffness (V-Block Test)*

The V-block compression test determined the resistance of the NIR™ Stent (after expansion) to external compression. Three (3) stents of each length of both the 7-cell and 9-cell design were tested at 3.0-mm (7-cell stent) and 4.0-mm (9-cell stent) diameter. Average resistance to compression ranged from 0.23 – 0.32 lbs./mm for the NIR™ Stents. The radial (hoop) strength and irreversible deformation of the NIR™ Stent met the product specifications.

9.2.2.7 *Accelerated Fatigue*

Two separate accelerated fatigue tests were performed on the NIR™ Stent.

9.2.2.7.1 TEN YEAR ACCELERATED FATIGUE TESTING (PULSATILE)

Accelerated *in vitro* fatigue testing of approximately 10 years (400 million cycles) equivalent real time was conducted assuring that the 316L stainless steel NIR™ Stent, when expanded to its largest intended diameter, will not show fatigue failure. The stents were mounted on the outside of a silicone rubber tube and cyclically pressurized with a tubing diameter increase by 0.5% (compliance). There was no evidence of any breaks or cracks noted in any of the struts and weld zones in any of the stents tested at 100X and 500X magnification for either the 80 million or 400 million cycle test results for the 7-cell and 9-cell NIR™ Stent. Additionally, no stents exhibited any structural damage at the end of the testing.

9.2.2.7.2 ACCELERATED FATIGUE TESTING (ROTATIONAL BENDING)

In this test, ten (10) stents of each length of both the 3.0 mm (7 cell) and the 4.0 mm (9 cell) stents were placed in a Rotational Bending Fatigue Tester which was run at 300 rpm. The machine was stopped at 500 rotations and the stents were checked for strut breaks. This process was repeated at every 500 revolutions thereafter until a break in the stent was detected or a maximum of 6,000 cycles was achieved. All 316LS stainless steel NIR™ Stents withstood about 6 times more cycles than 316L NIR™ Stents. The NIR™ Stent met the 10 year accelerated fatigue resistance requirement of the product specifications.

9.2.2.8 *Finite Element Analysis (FEA)*

The FEA evaluated the structural integrity of the NIR™ Stent (316LS) when the stent was subjected to the expected load conditions generated in coronary arteries. The analysis took into account static and fatigue loading at nominal balloon expansion. The results were compared to the measured strain at break point. The strain vs. extension analysis and the Goodman analysis showed that the local deformation did not exceed 23% for the 7-cell stent (3.5 mm diameter), and 31% for the 9-cell stent (5.0 mm diameter), thus meeting the < 55% breakage strain specification. The Goodman analysis showed no fatigue failures will occur at 400 million cycles of loading and is within specification.

9.2.2.9 *Magnetic Resonance Imaging (MRI)*

Ten 9-cell stents were placed into the MRI 2 Tesla magnet in the area of the maximum gradient of the magnetic field to determine whether the weld area of the stent will cause artifacts with magnetic resonance scans due to distortion of the magnetic field. The results of this test indicated that there was no significant distortion of the image and that no movement of the stent was observed. However, as a precaution, the Instructions for Use include a WARNING against performing an MRI until the stent has been completely covered with endothelium.

9.2.3 Stent and Delivery System Testing

9.2.3.1 *NIR ON™ Ranger™ Premounted Stent System*

The following tests were conducted to evaluate performance characteristics and safety of the stent/catheter system. All test results indicated that the devices/samples met or exceeded design specifications

9.2.3.1.1 BALLOON BOND INTEGRITY TESTING

Ten complete catheters (without stents) of the smallest/shortest (2.5 x 13 mm) and largest/longest (4.0 x 36 mm) balloon sizes were inflated to burst to verify that the inflation lumen and balloon bonds are capable of withstanding pressures in excess of the Rated Burst Pressure. All samples passed the test.

9.2.3.1.2 BALLOON INFLATION/DEFLATION TESTING

Ten NIR ON™ Ranger™ Premounted Stent Systems were evaluated to determine the inflation and deflation times for the smallest/shortest (2.5 x 13mm) and largest/longest (4.0 x 36mm) balloon sizes, and to assess balloon preparation and completeness of deflation. For the largest system 4.0 x 36 mm, average inflation time was 3.1 seconds, while average deflation time was 7.6 seconds.

9.2.3.1.3 CATHETER WITHDRAWAL FORCE

The mean force required to withdraw the 4.0 x 36 mm catheter (n=5, worst case size) was 0.348 lbs. demonstrating that the NIR ON™ Ranger™ delivery system catheters can be withdrawn without difficulty through the guide catheter after stent deployment.

9.2.3.1.4 FULL CATHETER TENSILE TEST

Five (n=5) of the largest/longest (4.0 x 36 mm) sizes were tested to determine the tensile strength of the NIR ON™ Ranger™ delivery system catheter. The average tensile strength at failure was 4.08 lbs. and failure occurred at the proximal balloon bond. All NIR ON™ Ranger™ test samples exceeded the minimum catheter tensile strength of 1.12 lbs.

9.2.3.1.5 STENT SECUREMENT FORCE TESTING

To assess the force required to displace a crimped stent from the NIR ON™ Ranger™ and the NIR™ PRIMO™ Premounted Stent Systems, fifteen NIR™ PRIMO™ 2.5 x 13mm and ten 2.5 x 13 mm NIR ON™ Ranger™ Stent systems were tested. Each device was inserted through a hole sized to catch on the stent edges but not drag on the balloon material. The average peak force to displace the stent from the NIR ON™ Ranger™ and the NIR PRIMO™ was 0.793 lbs. and 0.767 lbs., respectively, and met specifications.

9.2.3.1.6 BALLOON BURST TESTING

To verify that the balloon is capable of withstanding pressures in excess of the Rated Burst Pressure, fifteen catheters of the smallest/shortest (2.5 x 13-mm) and largest/longest (4.0 x 36 mm) balloon sizes were tested. Testing demonstrated statistically, with 95% confidence, that at least 99.9% of the balloons will have a burst pressure above the Rated Burst Pressure (RBP) of 14 ATM for 2.5 - 3.0 mm balloons and 12 ATM for 3.5 - 4.0 mm balloons.

9.2.3.1.7 DISTAL OUTER SHAFT BURST TESTING

To verify that the distal outer shaft is capable of meeting the burst specification, fifteen distal outer components were burst tested. Data demonstrated that the mean burst pressure is 366 psi and that the distal outer shaft of the NIR ON™ Ranger™ is able to statistically meet their specification of 310 psi.

9.2.3.1.8 NIR PRIMO™ VS. NIR ON™ RANGER™ CATHETER TRACK TESTING

In this test, three of the smallest/shortest (2.5 x 13mm) and the largest/longest (4.0 x 36mm) catheters (both NIR ON™ Ranger™ and the NIR PRIMO™) were passed through a simulated artery and the force required to track the catheter was determined. In addition, a 3.0 x 15-mm Palmaz-Schatz ® Stent system was tested for comparison. The results indicated that forces required to track the NIR ON™ Ranger are similar to those required to track the NIR PRIMO™ through the same simulated tortuous anatomy.

9.2.3.2 *NIR ON™ Ranger™ w/SOX™ Premounted Stent System*

The performance characteristics and safety of the NIR ON™ Ranger™ w/SOX™ Premounted Stent System were also evaluated per the guidance document (May 1994). The following tests were performed:

- Balloon Bond Integrity
- Catheter Withdrawal Force
- Stent Securement Force
- SOX™ Tensile
- Distal Outer Shaft Burst
- Stent Deployment and Deflatability
- Stent/Balloon Crossing Profile
- Balloon Deflation
- Full Catheter Tensile
- NIR™ PRIMO™ vs. NIR ON™ Ranger™ w/SOX™ Catheter Track
- Balloon Burst
- Balloon/Stent Distention and Compliance
- Repeat Balloon Inflation

All test samples were sterilized, finished products. All samples passed the above tests per product design specifications. The SOX™ tensile test was conducted to demonstrate that the tensile strength of the SOX™ to shaft bond is greater than the force required to tear the polyurethane SOX™ material. Fifteen samples of the 2.5 and 3.5 mm balloon catheters were evaluated with all bond tensile values (averaged from 0.64 to 0.68 lbs.) exceeding the maximum tear strength of the polyurethane material (0.25 lbs.). The Stent/Balloon Crossing Profile test revealed that the average deflated profile of the machine crimped delivery systems ranged from 0.38 to 0.46 in. These stent profiles are comparable to currently marketed stent delivery systems.

9.2.4 Package Integrity Testing

The packaging of the NIR ON™ Ranger™ Premounted Stent System is identical to the NC Ranger™ and other Boston Scientific Corporation (BSC)/SCIMED PTCA catheters (as listed in P860019/S82). The packaging consists of a) plastic carrier tube, b) Tyvek® lidded tray, and c) Tyvek® header pouch. Package accessories include a metal or plastic flushing needle for flushing the guide wire lumen, plastic and metal guide wire insertion tools, and hypotube clips. The packaging of the NIR ON™ Ranger™ w/SOX™ Premounted Stent System is identical to the NIR ON™ Ranger™ system. The package integrity testing described in this PMA submission included:

- Visual examination
- Shipping tests
- Microbial aerosol challenge and sterility testing
- Accelerated aging
- Functional testing of packaging
- Natural aging tests

The results of all of the above tests indicated that a) the packaging integrity was acceptable, b) the sterile barriers remained intact after exposure to shipping tests, and c) the packaging provided adequate microbial barrier over the products shelf-life of one year.

9.2.5 Shelf-Life (Aging) Testing

The NIR ON™ Ranger™ Premounted Stent System is a combination of the NIR PRIMO™ Premounted Stent System and the BSC/SCIMED NC Ranger™ PTCA catheter, utilizing the same components and materials. Because of this combination of design and materials, functional and accelerated (aging) shelf-life testing of some of the delivery system components are referenced to the NC Ranger™ catheter, and serve as a basis for the shelf life testing for the NIR ON™ Ranger™ and the NIR ON™ Ranger™ w/SOX™ Premounted Stent Systems. The tests conducted on the NIR PRIMO™ and the NC Ranger™ catheters met specifications and support a one-year shelf life for these products.

9.3 *Biocompatibility Testing*

Biocompatibility Testing of the device was conducted on the NIR™ Stent and on the NIR ON™ Ranger™ and the NIR ON™ Ranger™ W/SOX™ delivery systems. All tests were conducted in accordance with the International Standard ISO-10993-1, "Biological Evaluation of Medical Devices

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Part-1: Evaluation and Testing," as specified in the FDA Blue Book Memorandum G95-1 for external communicating devices in circulating blood with a limited blood contact of ≤ 24 hours. All of the tests were performed on sterilized devices and yielded a non-toxic response.

9.3.1 NIR™ Stent

Testing performed consisted of the following: Cytotoxicity (MEM Elution), Systemic Injection Study (Sodium chloride and Cottonseed Extracts), Intracutaneous Toxicity (Sodium chloride and Cottonseed Extracts), Direct Hemolysis, Salmonella Mutagenicity Test, Ames Mutagenicity Assay, Kligman Maximization Study Implantation Test (14, 28 and 30 days), and Pyrogen (LAL Test).

9.3.2 NIR ON™ Ranger™ Delivery Catheter

Because the components and materials used for the NIR ON™ Ranger™ Premounted Stent System are the same as those of the BSC/SCIMED NC Ranger PTCA Catheter (P860019/S119) and the NIR PRIMO™ Premounted Stent System, biocompatibility tests conducted on the NC Ranger™ and the NIR PRIMO™ are applicable to the NIR ON™ Ranger™ Premounted Stent System, and included:

- Cytotoxicity (MEM Elution)
- Intracutaneous Toxicity (Sodium chloride and Cottonseed Extracts)
- Salmonella Mutagenicity Test
- Primary Skin Irritation Study
- Implantation Test (7 and 30 days)
- Systemic Injection Study (Sodium chloride and Cottonseed Extracts)
- Direct Hemolysis
- Ames Mutagenicity Assay
- Kligman Maximization Study
- Pyrogen (LAL Test)

9.3.3 NIR ON™ Ranger™ w/SOX™ Delivery Catheter

Biocompatibility testing of the NIR ON™ Ranger™ w/SOX™ delivery catheter included Cytotoxicity (MEM Elution), Systemic Injection Study (Sodium chloride and Cottonseed Extracts), Intracutaneous Toxicity (Sodium chloride and Cottonseed Extracts), Direct Hemolysis, Kligman Maximization Study, and Pyrogen (LAL Test) tests.

10. SUMMARY OF CLINICAL STUDIES

The original NIR™ Stent was a balloon expandable stent premounted on a rapid exchange catheter. Initial clinical testing of the NIR™ Stent was performed in Europe from 1993-1996. Acceptable acute procedure success, subacute thrombosis, 30-day major adverse cardiac event and six month target vessel failure rates were noted in several European registries. In 1996, the stent was accepted and CE marked in Europe for general clinical use. The NIR™ Stent was most frequently delivered on the NIR PRIMO™ Premounted Stent System, a rapid exchange delivery system. Patent problems, however, precluded sale in the U.S. of the rapid exchange delivery system that was tested in the NIRVANA randomized trial and two adjunctive registries. The sponsor , therefore, developed two over-the-wire (OTW) delivery systems for the stent: NIR ON™ Ranger w/SOX™ and the NIR ON™ Ranger™ which were evaluated in separate studies in the U.S. Data from all studies are presented below.

10.1 Objectives

The NIR™ Stent was evaluated as part of the NIR Vascular Advanced North American (NIRVANA) Randomized Trial and three additional studies. The NIRVANA Randomized Trial was designed to compare acute and chronic outcomes of the NIR™ PRIMO™ Premounted Stent System (NIR™ Stent) and the Palmaz-Schatz™ Balloon Expandable Stent with Delivery System (PS® Stent) for treatment of *de novo* and restenotic coronary artery lesions. A total of 1,322 patients were treated at forty-one North American investigational sites in four separate arms of the NIRVANA Randomized Trial, two NIR ON™ Ranger™ w/SOX™ studies, and one NIR ON™ Ranger™ study (Table 3). One hundred-eleven (111) of these patients were treated with the NIR™ Stent in a non-randomized pilot roll-in and 848 patients were treated in the randomized trial (418 analyzable, 1 deregistered in the NIR™ Stent arm [patient withdrew

consent prior to treatment] and 430 patients in the PS® Stent arm). There were 207 patients treated in the Abrupt and Threatened Closure (AC/TC) Registry and 155 patients in the Saphenous Vein Graft (SVG) Registry.

The primary endpoint for the NIRVANA Randomized Trial and the SVG Registry was Target Vessel Failure (TVF) at 9 months. TVF was defined as a composite of death, nonfatal myocardial infarction, and clinically driven target vessel revascularization (TVR). The primary endpoint for the AC/TC Registry was the incidence of abrupt or sub-abrupt closure rate at 30 days.

An independent clinical events committee, masked to treatment assignment, adjudicated all of the major clinical endpoints for the randomized trial. This committee also adjudicated the events for the registries.

10.2 Study Design

Patients with ischemic coronary artery disease with a *de novo* or restenotic lesion of a native coronary artery ≤ 25-mm in length and a visual reference vessel diameter of 3.0 to 4.0 mm were admitted to the randomized trial. Patients with a maximum of two saphenous vein grafts with one or two lesions in each graft were eligible for the SVG Registry if the lesion to be treated had a visual reference vessel diameter of 3.0 to 4.0 mm and a length which could be covered by one or two NIR™ Stents. Patients who experienced abrupt or threatened abrupt closure during treatment with a non-stent device were eligible for the AC/TC Registry if the lesion to be treated was in a native coronary artery with target lesion ≤ 30 mm in length and visual reference diameter of 2.5 to 4.0 mm. Patients were eligible for inclusion if two or more of the following criteria were present: 1) angina or anginal equivalent changes; 2) ischemic electrocardiographic changes; 3) diameter stenosis ≥ 50%; 4) NHLBI Type B or C dissection, with dissection length > 8 mm and ≤ 30 mm; 5) NHLBI Type D, E, or F dissection, with dissection length ≤ 30 mm; or 6) TIMI 0-2 flow due primarily to mechanical obstruction of the treated site.

The patients underwent balloon angioplasty with an appropriate balloon diameter of 0.5 mm smaller than the reference vessel diameter, if balloon dilation was deemed necessary. Post-stent deployment dilations with a high pressure, non-compliant balloon (balloon to artery ratio of 1:1 or 1.1:1.0) were recommended to assure that the stent was in full contact with the arterial wall to leave a residual stent diameter stenosis of less than 10%.

Clinical follow-up was completed at 2 weeks, 30 days, 6 and 9 months. A subset of patients in the randomized trial as well as in the registries underwent angiographic follow-up at 6 months. Baseline characteristics were similar for the two treatment groups in the randomized trial. All treated patients were included in the intent-to-treat efficacy analysis. Anticoagulation included aspirin 325 mg/day for at least 9 months and ticlopidine 250 mg twice a day for 30 days.

10.3 Gender Bias

Study inclusion and exclusion criteria in the NIR™ Stent clinical studies were designed and the study carried out to avoid gender bias in patient enrollment. Of the 1564 patients enrolled, 467 (29.9%) were female.

Statistical analysis of the data from the NIRVANA Randomized Trial did not show an association between gender and the primary and secondary clinical outcomes. An univariate analysis revealed that gender was not a predictor of clinical or angiographic efficacy. In addition, MACE rates were comparable in each study in the male and female groups. These data demonstrated that gender was not an influencing factor on safety or effectiveness.

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10.4 NIRVANA Randomized Trial

The NIRVANA Randomized Trial, conducted at 41 U.S. investigational sites, was a prospective, randomized controlled study. The purpose of the study was to compare acute and chronic outcomes of the NIR™ Stent and the PS® Stent in the treatment of *de novo* and restenotic native coronary lesions.

10.4.1 Description of Patients

There were no major baseline differences in patient characteristics between the two groups (Table 5). The mean age of the pooled population was 62 ± 11 years and 70% of the population was male. Twenty-three per cent of the patient population had diabetes mellitus, 61% had hypertension requiring treatment, and 64% had hyperlipidemia requiring medical intervention. Previous cardiovascular events included myocardial infarction in 40% of patients and 70% of patients had Canadian Cardiovascular Society (CCS) Class III or IV angina. Baseline angiography did not reveal any major differences between the two groups. Sixty-one per cent of patients had single vessel disease, and the mean left ventricular ejection fraction was 55 ± 11%.

Table 5. Patient Demographics - NIRVANA Clinical Trial

	NIR Stent	Palmaz-Schatz Stent	95% CI of Difference
Number Treated	418	430	
Received assigned stent	100%	98.8%	
% Male	69%	68%	-4.1, 6.4%
% Diabetic	23%	22%	-4.5, 6.8%
Hypertension	59%	63%	-10.4, 2.7%
Hyperlipidemia	67%	61%	-1.0, 12.1%
Age (yr.)	62 ± 11	62 ± 11	-1.8, 1.2
Reference vessel diameter (mm)	2.97 ± 0.52 (409)	3.03 ± 0.52 (421)	-0.13, 0.02
% DS pre procedure	65 ± 13% (410)	64 ± 13% (421)	-0.9, 2.7%
MLD (mm) pre procedure	1.03 ± 0.43 (410)	1.08 ± 0.42 (421)	-0.10, 0.02

10.4.2 Acute Procedural Results

Stenting demonstrated early safety and effectiveness in both groups (Table 6). Acute procedural success (% diameter stenosis (DS) ≤ 50% and no death, nonfatal myocardial infarction, CABG or repeat PTCA) was 95.6% (389/407) for the NIR™ Stent versus 94.3 % (394/418) for the PS® Stent (95% CI [-1.7%, 4.3%]). There was no difference in lesion success (% DS ≤50% using any percutaneous method, e.g., the randomized treatment followed by another device), while technical success (%DS ≤ 50% using the assigned treatment device without the use of other types of stents or non-balloon devices) was slightly higher in the NIR™ Stent group (99.8% vs. 97.8%; 95% CI [0.4%, 3.4%]).

Baseline lesion characteristics were similar between the two groups. The mean reference vessel diameter for all patients was 3.00 ± 0.52 mm while the minimum lumen diameter was 1.06 ± 0.42 mm. The population baseline per cent diameter stenosis was 65 ± 13%. Lesion length was 13.3 ± 7.1 mm and the majority of stents were placed in the LAD (41%), followed by the RCA (38%) and circumflex (21%) arteries. Post-stenting, there was no difference noted for in-stent minimal lumen diameter between the two groups (NIR™ Stent = 2.79 ± 0.42 vs. PS® Stent = 2.79 ± 0.43 mm, 95% CI [-0.06, 0.06]). The post-procedure in-stent per cent diameter stenosis was slightly smaller in the NIR™ Stent group (NIR™ Stent = 7% ± 10% vs. PS® Stent = 9% ± 12% , 95% CI [-3.3%, -0.2%]. Visual inspection of the pre- and post-procedural cumulative frequency distribution curves for per cent diameter stenosis and minimal lumen diameter also indicated that the two groups were well matched, both pre- and post-procedure.

The most common stent length implanted per patient was 16 mm for the NIR™ Stent and 15 mm for the PS® Stent (NIR™ Stent = 59%, PS® = 71% of lesions) followed by 32 mm for the NIR™ Stent and 30

mm for the PS® Stent (NIR™ Stent = 17%, PS® = 23% of patients). The sponsor supplied NIR™ Stent lengths of 9, 16, and 32 mm for this trial. The PS® Stent is only available in a 15 mm length version. The short 9 mm NIR™ Stent was used alone 7% of the time.

The assigned stent could not be implanted (i.e. failure to cross lesion or deliver intended device) in 1% (4/418) of NIR™ Stent patients and 2.1% (9/430) of PS® Stent patients. The assigned stent was never delivered in 5 PS® Stent patients. The 5 PS® Stent patients were subsequently treated as follows; 4 PTCA only and one crossover to the NIR™ Stent. Additional categories of deployment problems (e.g., misplaced deployment, embolization, and balloon burst) are tabulated in the PMA. Review of these data indicated that deployment problems occurred infrequently and that both groups were equally affected. All stent delivery failure cases were individually summarized in the PMA. Review of this information did not raise any safety concerns.

This trial was performed using high pressure balloon inflation to optimize stent deployment when necessary; and with aspirin and ticlopidine, rather than aspirin and coumadin, as the recommended anticoagulation regimen. The rates of stent thrombosis, bleeding, and vascular complications (Table 6) are lower than rates reported in the original PS® Stent study. The incidence of subacute thrombosis (SAT): 0.5% (2/418) in the NIR™ Stent group was similar to the PS® Stent group: 0.5% (2/430), (95% CI [-0.9%, 0.9%]). There were no differences in the rates of bleeding (1.0% NIR™ Stent vs. 1.4% PS® Stent) or vascular complications (5.0% NIR™ Stent vs. 4.0% PS® Stent) between the two groups.

The data on use of post-stent high pressure balloon inflations to optimize stent deployment was examined in detail and is summarized in the PMA. As expected, the majority of stented lesions required a final high pressure balloon inflation to optimize stent deployment. The majority of these high pressure inflations were in the 14 - 18 atmosphere range with a mean for all patients of 16.2 ± 3.2.

Table 6 presents the principal effectiveness and safety results for the NIRVANA Randomized Trial.

Table 6. Principal Effectiveness and Safety Results, NIRVANA Randomized Trial

All Patients in the NIRVANA Randomized Trial (n=848)

	Randomized NIR™ n=418	PALMAZ-SCHATZ® n=430	Difference [95% C.I.]
Efficacy Measures			
Technical Success by QCA	99.8% [98.6%,100%] (406/407)	97.8% [96.0%,99.0%] (409/418)	1.9% [0.4%,3.4%]
Procedure Success by QCA	95.6% [93.1%,97.4%] (389/407)	94.3% [91.6%,96.3%] (394/418)	1.3% [-1.7%,4.3%]
Post Procedure In-Stent % DS	7%±10% (409)	9%±12% (419)	-1.7% [-3.3%,-0.2%]
Range (min,max)	(-39%,39%)	(-30%,100%)	
Post-Procedure In-Stent MLD (mm)	2.79 ± 0.42 (409)	2.79 ± 0.43 (419)	-0.06, 0.06
Net gain (mm) after procedure	1.76 ± 0.48	1.71 ± 0.51	-0.02, 0.25
6 Months Follow-up In-Stent % DS	34%±22% (110)	37%±22% (92)	-2.5% [-8.6%,3.6%]
Range (min,max)	(-31%,100%)	(-35%,100%)	
In-Stent MLD (mm) at 6 months	1.99 ± 0.76 (110)	1.90 ± 0.76 (92)	-0.12, 0.30
6 Months Follow-up In-Stent Binary Restenosis Rate (*de novo* Patient Group)	17.2% [10.2%,26.4%] (16/93)	20.5% [12.2%,31.1%] (16/78)	-3.3% [-15.1%,8.5%]
6 Months Follow-up In-Stent Binary Restenosis Rate	20.0% [13.0%,28.7%] (22/110)	21.7% [13.8%,31.6%] (20/92)	-1.7% [-13.0%,9.5%]
TLR-free at 6 Months* (K-M)	94.1% [91.9%,96.4%]	91.2% [88.4%,93.9%]	3.0% [-0.6%,6.6%]
TVR-free at 6 mo. (KM)	92.2%	90.0%	ns
TVF-free at 6 Months* (K-M)	88.4% [85.3%,91.5%]	86.7% [83.4%,90.0%]	1.7% [-2.8%,6.2%]
Safety Measures			
In-Hospital MACE	4.3% [2.6%,6.7%] (18/418)	4.0% [2.3%,6.3%] (17/430)	0.4% [-2.3%,3.0%]
Out-of-Hospital MACE	7.9% [5.5%,10.9%] (33/418)	10.0% [7.3%,13.2%] (43/430)	-2.1% [-5.9%,1.7%]
Death	0.7% (3/418)	0.7% (3/430)	-1.1, 1.1%
Q-Wave MI	0.7% (3/418)	0.7% (3/430)	-1.1, 1.1%
Non-Q-Wave MI	3.6% (15/418)	3.5% (15/430)	-2.4, 2.6%
TLR-CABG	1.7% (7/418)	2.3% (10/430)	-2.5, 1.2%
TLR Re-PTCA	6.2% (26/418)	8.4% (36/430)	-5.6, 1.3%
Bleeding Complications	1.0% [0.3%,2.4%] (4/418)	1.4% [0.5%,3.0%] (6/430)	-0.4% [-1.9%,1.0%]
Vascular Complications	5.0% [3.1%,7.6%] (21/418)	4.0% [2.3%,6.3%] (17/430)	1.1% [-1.7%,3.9%]
Stent Thrombosis	0.5% [0.1%,1.7%] (2/418)	0.5% [0.1%,1.7%] (2/430)	0% [-0.9%,0.9%]
Survival at 30 Days (K-M)	100% [99.1%,100%]	99.8% [99.3%,100%]	0.2% [-0.1%,0.6%]
Survival at 180 Days (K-M)	99.3% [98.4%,100%]	99.3% [98.4%,100%]	0% [-1.1%,1.1%]
MACE rate at 6 Months	11.5% [8.6%,14.9%] (48/418)	13.0% [10.0%,16.6%] (56/430)	-1.5% [-6.0%,2.9%]
Hospitalization Post-Intervention (days)			
Mean±SD (N)	1.4±0.9 (418)	1.5±1.7 (430)	-0.2 (-0.4,0.0)
Range (min,max)	(1,8)	(0,26)	

Definitions for Table 6:

Technical success: Attainment of <50% residual stenosis (by QCA) and successful delivery and deployment of the assigned stent to the target lesion, without use of a device outside the assigned treatment strategy.

Procedure success: <50% diameter stenosis using the assigned device and no in-hospital major adverse cardiac events (death, MI, emergent CABG, or repeat target lesion revascularization).

QCA: Quantitative Coronary Angiography

% DS: Diameter Stenosis

TLR-free: No target lesion revascularization.

TVF-free: No death, any MI or target vessel revascularization.

In-hospital clinical event: death, MI, emergent CABG, repeat target lesion revascularization, stent thrombosis, or stroke prior to discharge, as determined by the independent Clinical Events Committee.

Out-of-hospital clinical event: death, MI, emergent CABG, repeat target lesion revascularization, stent thrombosis, or stroke after discharge, as determined by the independent Clinical Events Committee.

Bleeding complications: Transfusions due to blood loss resulting from the percutaneous revascularization procedure.

Stent Thrombosis: Angiographic thrombus or subacute closure within the stented vessel, or any death not attributed to a non-cardiac cause in the absence of documented angiographic stent patency within the first 30 days.

MACE: Major Adverse Cardiac Event (Includes death, MI, emergent CABG and target lesion revascularization).

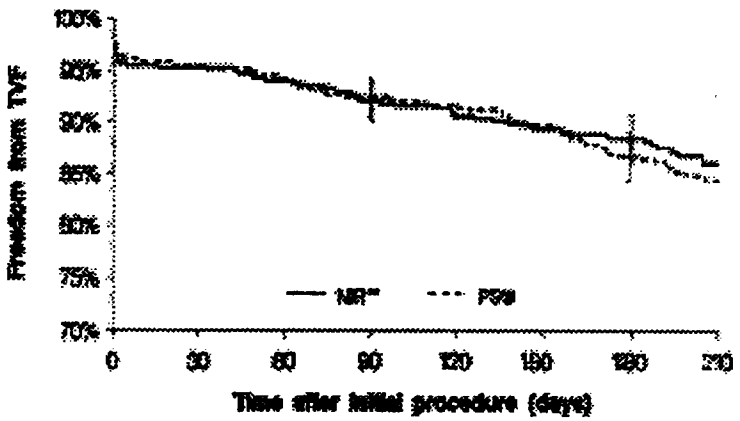
Survival estimates by Kaplan-Meier method; Standard Error estimates by Greenwood formula.

10.4.3 Long Term Results

Six month follow-up was available on 372 of 418 NIR™ Stent patients (89%) and 367 of 430 (85%) of PS® Stent patients. Comparison of six-month endpoints showed no difference between the two groups. The Clinical TVF rate (composite of death, nonfatal myocardial infarction, need for repeat revascularization of the target vessel by CABG or PTCA at six months) as calculated by Kaplan-Meier method was 11.6% for the NIR™ Stent and 13.3% for the PS® Stent (p= 0.29). Individual analysis of event rates for death, nonfatal myocardial infarction, CABG, re-PTCA, Target Lesion Revascularization, (TLR) and in- or out-of-hospital results indicated no difference between the two groups (Table 6). Six-month survival curves for TVF were also constructed. The two curves were similar by Log-Rank and Wilcoxon nonparametric rank sum testing (Figure 1).

Figure 1. Actuarial Freedom from Target Vessel Failure

All Randomized Patients NIRVANA Randomized Trial (n=848)



Interval ending (days)	0	7	14	30	60	90	120	180	210
NIR™ Stent									
# Entered	418	403	399	399	395	386	378	372	333
# Incomplete	0	0	0	3	4	0	0	30	127
# Lost to Follow-up	0	0	0	0	0	0	0	0	0
# At Risk Entering Interval	418	403	399	396	391	386	378	342	206
# Events	15	4	0	1	5	8	6	9	7

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# Events/Month		17	0	2	5	8	6	5	7
% Survived	96.4%	95.5%	95.5%	95.2%	94.0%	92.1%	90.6%	88.4%	86.0%
PS® Stent									
# Entered	430	419	410	407	400	386	378	374	323
# Incomplete	0	3	2	5	9	1	0	32	118
# Lost to Follow-up	0	0	0	0	0	0	0	0	0
# At Risk Entering Interval	430	416	408	402	391	385	378	342	205
# Events	11	6	1	2	5	7	4	19	7
# Events/Month		26	4	4	5	7	4	10	7
% Survived	97.4%	96.0%	95.8%	95.3%	94.1%	92.4%	91.4%	86.7%	84.4%

The equivalence of the major endpoint, TVF was, as expected, largely driven by the rates of revascularization. Substantial bias in the determination of which patients were appropriate for revascularization (due to the non-masked nature of this trial) could significantly impact on interpretation of overall results. The clinical signs and symptoms for the 73 patients who underwent TLR were reviewed by the blinded clinical events committee (CEC). The CEC concluded that 94% (30/32)of the re-PTCA for the NIR™ Stent and 100% of the re-PTCA for the PS® Stent were indicated. The CEC also felt that the 17 CABG procedures were all indicated. Thus, results from an independent review of revascularization procedures supported the long term equivalence of the two stents.

A subset, the first 304 patients successfully treated, qualified for angiographic restudy at six months. At the time of PMA submission the sponsor has reported on 109/147 (74%) NIR™ Stent patients and 94/154 (61%) PS® Stent patients. Based on the expected standard deviation, 200 patients (100/group) would be expected to detect a difference of 0.2 mm with 80% power. A 0.2-mm difference has been demonstrated in prior coronary trials to correlate with clinically significant differences between groups. The 6 month data showed no significant differences between the two groups. The six-month angiographic in-stent restenosis rate for the NIR™ Stent was 20.0% (22/110) compared to 21.7% (20/92) for the PS® Stent (95% CI [-13.0%, 9.5%]). The mean per cent diameter stenosis was 34% versus 37% with a 95% CI of [-8.6%, 3.6%] and the minimal lumen diameter was 1.86 versus 1.84 mm [-0.12, 0.30] for the NIR™ Stent and PS® Stents, respectively.

10.4.3.1 Deaths

There were six patient deaths. Three (0.7%) occurred in the NIR™ Stent group and three (0.7%) occurred in the PS® Stent group (95% C.I. [-1.1%, 1.1%]). Each death was individually reviewed. Review of this information did not raise any safety concerns for either device.

10.4.3.2 Myocardial Infarctions

A total of six patients had a Q-wave MI: 3 (0.7%) for the PS® Stent group and three (0.7%) for the NIR™ Stent group. A total of 30 patients had non-Q-wave MI: 15 (3.5%) in the PS® Stent group and 15 (3.6%) in the NIR™ Stent group. Each myocardial infarction was individually reviewed. Review of this information did not reveal any unexpected findings.

10.4.3.3 Revascularization Procedures

Total revascularization rates and cumulative revascularization rates over time were similar between the two groups. Seventeen (17) patients underwent CABG: 7 (1.7%) in the NIR™ Stent group and 10 (2.3%) in the PS® Stent group. Sixty-two patients underwent repeat PTCA: 26 (6.2%) in the NIR™ Stent group and 36 (8.4%%) in the PS® Stent group. Each CABG and re-PTCA was individually reviewed. Review of this information did not reveal any unexpected findings.

10.4.3.4 Restenotic Lesions

Restenotic lesions were included in this trial because literature data has suggested that the chronic TVF rate for stented restenotic lesions is very similar to the chronic rate for stented *de novo* lesions when important covariates such as diabetes mellitus and lesion size are properly taken into account. The sponsor expected a 70%/30% enrollment of *de novo* and restenotic lesions into the NIRVANA Randomized Trial. Fifty restenotic lesions (12%) were treated in the NIR™ Stent group and 45 (10.5%) lesions were treated in the PS® Stent group. Baseline and acute post-procedural information for the *de novo* and restenotic lesions enrolled in the randomized trial was presented. Review of this subgroup information did not suggest any striking differences between the groups. Acute and chronic success rates were analyzed separately. An acute procedure success rate of 95.7% and a 6 month MACE rate of 14.0% was noted for the NIR™ Stent restenotic population. These values are similar with corresponding *de novo* NIR™ Stent and PS® Stent results. In addition, multivariate statistical modeling did not indicate that prior restenosis was a risk factor for chronic target vessel failure. A more formal comparison is limited by the small patient numbers.

10.5 NIRVANA AC/TC Registry

The NIRVANA Abrupt and Threatened Closure AC/TC Registry was a consecutive registry of stent bailout for abrupt or threatened abrupt closure from non-stent procedures. There were 207 patients (with 213 lesions) treated in this registry. Patients with lesions >30mm in length in a native coronary artery whose visual reference vessel diameter was <2.5mm and >4.0mm were eligible.

10.5.1 Description of Patients

Baseline demographics were similar between the NIR™ Stent AC/TC and PS® Stent groups with regard to percentage of men, incidence of cigarette use, hypertension, or diabetes (Table 7). The NIR ™ Stent AC/TC registry did have more patients who were hyperlipidemic requiring medication (71% vs. 61%, 95% CI = [1.8, 17.5%]) and more patients with prior CABG (15% vs. 8%, 95% CI= [1.8, 12.9%]).

Procedural Quantitative Coronary Angiography (QCA) analysis was completed on 95% (203/213) of the NIR ™ Stent AC/TC lesions at the time of PMA submission. Due to the extended eligibility criteria for reference vessel diameter (2.5 - 4.0 mm NIR ™ Stent AC/TC vs. 3-4 mm NIRVANA Randomized Trial), the NIR ™ Stent AC/TC reference vessel diameter was smaller (2.78 $\pm$ 0.59 mm vs. 3.03 $\pm$ 0.52 mm, 95% CI [-0.34, -0.16]). The initial NIR ™ Stent AC/TC minimal lumen diameter was correspondingly smaller, while the pre-procedure per cent diameter stenosis was slightly larger (Table 7). Lesion length was longer in the NIR ™ Stent AC/TC registry (16.7 $\pm$ 8.8 mm vs. 13.3 $\pm$ 7.2 mm, 95% CI [2.01, 4.73]).

Table7. Patient Demographics - Abrupt and Threatened Closure (AC/TC) Registry

	Abrupt and Threatened Closure Registry	PS® Stent Results from NIRVANA Trial	95% CI of Difference
Number Treated	207	430	
Per cent receiving assigned stent	94%	98.8%	
% Male	67%	68%	-8.3, 7.3%
% Diabetic	23%	22%	-6.3, 7.5%
Hypertension	69%	63%	-2.0, 13.6%
Hyperlipidemia	71%	61%	1.8, 17.5%
Prior CABG	15%	8%	1.8, 12.9%
Age (yr.)	63 ± 12	62 ± 11	-1.4, 2.4
Reference vessel diameter (mm)	2.78 ± 0.59 (200)	3.03 ± 0.52 (421)	-0.34, -0.16
% DS pre procedure	68 ± 17% (203)	64 ± 13% (421)	1.7, 6.6%
MLD (mm) pre procedure	0.86 ± 0.48 (203)	1.08 ± 0.42 (421)	-0.29, -0.14

10.5.2 Acute Procedural Results

The acute procedure success rate in the NIR ™ Stent AC/TC registry was 90.5%, a value slightly lower than the procedure success rate obtained in the PS® Stent arm of the randomized trial for elective stenting (PS® Stent = 94.3%, 95% CI [-8.5, -1.3]). Any delivery failure of the NIR™ Stent (failure to deliver first or second stent, or assigned stent never delivered) was noted for 23 (11%) lesions. For 14 of the 23 lesions the assigned stent could not be delivered. Treatment in 13 of these cases consisted of PTCA or CABG and in one case another commercially available stent was placed. Stent delivery failure cases were individually reviewed.

Post-procedure acute gain and % diameter stenosis were similar to the respective PS® Stent values (Table 9). Rates for stent thrombosis (1.0%), bleeding complications (4.3%), and vascular complications (7.2%) tended to be higher than the PS® Stent but were within an acceptable range for the population studied.

10.5.3 Long-Term Results

At the time of PMA submission the following extended follow-up was available: 5 month clinical follow-up on 88% of patients (183/207), 6 month clinical follow-up on 73% (151/207) of patients, and 6 month angiographic follow-up on 68% (36/53) of patients. The 6 month TVF-free, TVR-free, TLR-free rates for NIR ™ Stent AC/TC patients were lower, and the MACE rate was higher, than PS® Stent patients from the NIRVANA Randomized Trial (Table 9). All components of these composite endpoints (death, CABG, re-PTCA, and non-fatal myocardial infarction) tended to be higher in the NIR ™ Stent AC/TC registry. The poorer long term clinical outcome for AC/TC patients was not unexpected. No differences were seen when six month angiographic results (MLD, % diameter stenosis) from the NIR™ Stent AC/TC arm were compared to the elective PS® Stent patients from the NIRVANA Randomized Trial.

At 6 months there were seven (3.4%) deaths, three (1.4%) Q-wave myocardial infarctions. 11 (5.3%) non-Q-wave myocardial infarctions, seven (3.4%) CABG procedures, and 24 (11.6%) re-PTCA procedures in the NIR™ Stent arm. Each of these complications has been reviewed. No unexpected problems were noted.

There were 54 patients in the NIR™ Stent AC/TC arm assigned to undergo repeat angiography based upon day of enrollment. Follow-up QCA was available on 34 of 53 NIR™ Stent patients (64%). Baseline QCA was performed pre-procedure, after the abrupt/threatened closure event, following device deployment, and after final treatment. This registry was powered to examine the incidence of subabrupt closure at 30 days. Other endpoints to be evaluated included procedural success, MACE and TVF up to 9

months post-procedure, and angiographic restenosis (defined as >50% diameter stenosis) at 6 months for patients in the prespecified angiographic subset. An independent clinical events committee, blinded to treatment assignment, adjudicated all of the major clinical endpoints.

This prospective registry demonstrated that the NIR™ Stent was successfully deployed in 91.1% of lesions experiencing abrupt or threatened closure following treatment with a non-stent device. Following stent deployment, the in-stent percent diameter stenosis was 9%. The 30-day primary endpoint MACE rate was 2.4% (5/207), significantly ($p<0.001$) lower than the pre-specified 30 day clinical event rate of 14% (10% expected MACE rate plus 4% delta equivalency) expected from historical controls. At 6 months, freedom from TVR was 82.4%. Stenting of AC/TC lesions produced acceptable acute and chronic safety and effectiveness results. The observed MACE rate at 30 days was 2.4%, a value that was significantly less than the null hypothesis value of 14% ($p < 0.001$). Comparison of these data to electively stented PS® Stent patients from the randomized trial demonstrated, as expected, that nonelective stenting is associated with a higher rate of adverse events. Nonetheless, the NIR™ Stent data were in a clinically acceptable range for a higher risk nonelective subgroup.

10.6 NIRVANA SVG Registry

The NIR™ Stent Saphenous Vein Graft (SVG) Registry was a consecutive registry of saphenous vein graft lesions treated with the NIR™ Stent. There were 155 patients (with 163 lesions) treated in this registry. Patients with up to four SVG lesion(s), each <30mm in length in, in up to 2 saphenous vein grafts, an SVG whose visual reference vessel diameter is ≥3.0 and ≤5.0mm were eligible.

10.6.1 Description of Patients

A comparison of baseline demographics between the NIR™ Stent SVG and PS® Stent groups showed no difference with regard to incidence of diabetes or hypertension, or ejection fraction (Table 2). The SVG registry did have more male patients (83% vs. 68%, 95% CI = [7.5, 22.3%]), more patients who were hyperlipidemic requiring medication (77% vs. 61%, 95% CI = [8.0, 24.2%]) and fewer cigarette smokers (18% vs. 29%, 95% CI= [-18.5, 3.7%]).

Table 8. Patient Demographics - Saphenous Vein Graft (SVG) Registry

N = 155 patients, 163 lesions

	NIR SVG Registry	Palmaz-Schatz Results from NIRVANA Trial	95% CI of Difference
Number Treated	155	430	
Received assigned stent	100%	98.8%	
% Male	83%	68%	15%* [7.5%, 22.3%]
% Diabetic	28%	22%	-1.8, 14.4%
Hypertension	72%	63%	-0.1, 16.7%
Hyperlipidemia	77%	61%	16%* [8%, 24.2]%
Age (yr.)	67 ± 10	62 ± 11	5* [3, 7]
Reference vessel diameter (mm)	3.38 ± 0.69 (155)	3.03 ± 0.52 (421)	0.35* [0.25, 0.46]
% DS pre procedure	62 ± 17% (155)	64 ± 13% (421)	-4.3, 1.0%
MLD (mm) pre procedure	1.27 ± 0.64 (155)	1.08 ± 0.42 (421)	0.19* [0.11, 0.29]

Procedural QCA analysis was completed on 95% (155/163) of the NIR ™ Stent SVG patients at the time of PMA submission. Due to the extended eligibility criteria for reference vessel diameter (3-5 mm SVG vs. 3-4 mm NIRVANA Randomized Trial), the NIR ™ Stent SVG reference vessel diameter was larger (3.38 ± 0.69 mm vs. 3.03 ± 0.52 mm, 95% CI [0.25, 0.46]). The initial NIR ™ Stent SVG minimal lumen diameter was correspondingly larger, while the pre-procedure per cent diameter stenosis was similar (Table 8). Lesion length was slightly shorter in the NIR ™ Stent SVG registry (11.9 ± 8.6 mm vs. 13.3 ± 7.2 mm, 95% CI [-2.85, -0.94]).

10.6.2 Acute Procedural Results

The acute procedure success rate in the NIR ™ Stent SVG registry was 96.6% and 0 delivery failures were reported. Post-procedure acute gain, % diameter stenosis, and minimal lumen diameter measurements were all better than the respective PS® Stent values (Table 9). There were 2 (1.3%) cases of stent thrombosis. The incidence of stent thrombosis (1.3%), bleeding (2.6%), and vascular complications (3.2%) were similar to results reported for the PS® Stent.

Table 9 shows the principal effectiveness and safety results for the NIR ™ Stent AC/TC and NIR ™ Stent SVG registries. Although statistical comparison is not appropriate, results of the NIR™ Stent arm of the NIRVANA Randomized Trial are included for comparison with these two registries.

Table 9. Principal Effectiveness and Safety Results, NIRVANA Registries

NIRVANA AC/TC Registry and SVG Registry Patients Treated (n=362)

	AC/TC N=207	SVG n=155	Randomized NIR™ n=418
Efficacy Measures			
Technical Success by QCA	96.8% [93.3%,98.8%] (184/190)	98.6% [95.1%,99.8%] (144/146)	99.8% [98.6%,100%](406/407)
Procedure Success by QCA	90.5% [85.4%,94.3%] (172/190)	96.6% [92.25%,98.9%] (141/146)	95.6% [93.1%,97.4%](389/407)
Post Procedure In-Stent % DS Range (min,max)	9%±12% (196) (-41%,47%)	6%±13% (154) (-23%,100%)	7%±10% (409) (-39%,39%)
Post-Procedure In-Stent MLD (mm)	3.17 ± 0.58 (154)	2.79 ± 0.43 (419)	0.38* [0.30, 0.47]
Net gain (mm) after procedure	1.73 ± 0.57	1.71 ± 0.51	-0.07, 0.11
TLR-free at 30 Days* (K-M)	99.1% [97.8%,100%]	98.8% [97.1%,100%]	99.3% [98.5%,100%]
TVF-free at 30 Days* (K-M)	91.8% [88.0%,95.5%]	96.1% [93.1%,99.2%]	95.2% [93.2%,97.3%]
6 months Follow-up In-Stent % DS Range (min,max)	37%±21% (35) (-4%,84%)	38%±32% (36) (-12%,100%)	34%±22% (110) (-31%,100%)
In-Stent MLD (mm) 6 mo.	2.06 ± 1.17 (35)	1.90 ± 0.76 (92)	-0.19, 0.51
6 months Follow-up In-Stent Binary Restenosis Rate	25.7% [12.5%,43.3%] (9/35)	25.0% [12.1%,42.2%] (9/36)	20.0% [13.0%,28.7%] (22/110)
TLR-free at 6 Months* (K-M)	84.6% [79.6%,89.7%]	92.0% [87.6%,96.3%]	94.1% [91.9%,96.4%]
TVR-free at 6 mo. (KM)	90.7%	90.0%	ns
TVF-free at 6 Months* (K-M)	74.8% [68.7%,80.9%]	83.6% [77.6%,89.6%]	88.4% [85.3%,91.5%]
Safety Measures			
In-Hospital MACE	7.2% [4.1%,11.7%] (15/207)	3.2% [1.1%,7.4%] (5/155)	4.3% [2.6%,6.7%] (18/418)
Out-of-Hospital MACE	17.4% [12.5%,23.3%] (36/207)	13.5% [8.6%,20.0%] (21/155)	7.9% [5.5%,10.9%] (33/418)
Death	5.2% (8/155)	0.7% (3/430)	4.5%* [0.9, 8.0%]
Q-Wave MI	0.6% (1/155)	0.7% (3/430)	-1.5, 1.4%
Non-Q-Wave MI	4.5% (7/155)	3.5% (15/430)	-2.7, 4.7%
TLR-CABG	1.3% (2/155)	2.3% (10/430)	-3.3, 1.2%
TLR Re-PTCA	7.7% (12/155)	8.4% (36/430)	-5.6, 4.3%
Bleeding Complications	4.3% [2.0%,8.1%] (9/207)	2.6% [0.7%,6.5%] (4/155)	1.0% [0.3%,2.4%] (4/418)
Vascular Complications	7.2% [4.1%,11.7%] (15/207)	3.2% [1.1%,7.4%] (5/155)	5.0% [3.1%,7.6%] (21/418)
Stent Thrombosis	1.0% [0.1%,3.4%] (2/207)	1.3% [0.2%,4.6%] (2/155)	0.5% [0.1%,1.7%] (2/418)
Survival at 30 Days (K-M)	99.0% [97.7%,100%]	99.3% [98.1%,100%]	100% [99.1%,100%]
Survival at 180 Days (K-M)	97.0% [94.6%,99.4%]	95.9% [92.7%,99.1%]	99.3% [98.4%,100%]
MACE rate at 6 Months	22.7% [17.2%,29.0%] (47/207)	16.1% [10.7%,22.9%] (25/155)	11.5% [8.6%,14.9%] (48/418)
Hospitalization Post-Intervention (days)			
Mean±SD (N)	2.0±2.2 (207)	1.5±1.4 (155)	1.4±0.9 (418)
Range (min,max)	(1,15)	(1,9)	(1,8)

Definitions for Table 9:

Technical success: Attainment of <50% residual stenosis (by QCA) and successful delivery and deployment of the assigned stent to the target lesion, without use of a device outside the assigned treatment strategy.

Procedure success: <50% diameter stenosis using the assigned device and no in-hospital major adverse cardiac events (death, MI, emergent CABG, or repeat target lesion revascularization).

QCA: Quantitative Coronary Angiography

% DS: Diameter Stenosis

TLR-free: No target lesion revascularization.

TVF-free: No death, any MI or target vessel revascularization.

In-hospital clinical event: death, MI, emergent CABG, repeat target lesion revascularization, stent thrombosis, or stroke prior to discharge, as determined by the independent Clinical Events Committee.

Out-of-hospital clinical event: death, MI, emergent CABG, repeat target lesion revascularization, stent thrombosis, or stroke after discharge, as determined by the independent Clinical Events Committee.

Bleeding complications: Transfusions due to blood loss resulting from the percutaneous revascularization procedure.

Stent Thrombosis: Angiographic thrombus or subacute closure within the stented vessel, or any death not attributed to a non-cardiac cause in the absence of documented angiographic stent patency within the first 30 days.

MACE: Major Adverse Cardiac Event (Includes death, MI, emergent CABG and target lesion revascularization).

**Survival estimates by Kaplan-Meier method; Standard Error estimates by Greenwood formula.*

10.6.3 Long-Term Results

At the time of PMA submission 6 month clinical follow-up had been obtained on 73% (113/155) of patients and angiographic follow-up had been obtained on 77% (36/47) of patients scheduled for 6 month angiography. The TVF-free rate at 6 months for the NIR ™ Stent SVG registry was similar to the PS® Stent group (SVG = 83.6% vs. PS® Stent = 86.7%). The major outcome measures (6 month TLR-free and TVR-free rates, the hierarchical MACE rate, and the six month indices) were similar between the two treatment groups.

Individual rates for myocardial infarction, CABG, and re-PTCA were similar, while the death rate was increased in the NIR™ Stent SVG arm (Table 9). There were eight deaths, one Q-wave myocardial infarctions, seven non-Q-wave myocardial infarctions, two CABG procedures, and 12 re-PTCA procedures. Each complication was summarized in the PMA and raised no new safety concerns.

There were 52 patients in the NIR™ Stent arm assigned to undergo repeat angiography. Five patients died prior to the 6-month follow-up, leaving 47 patients eligible for angiographic follow-up. Follow-up QCA was available on 36 of 47 NIR™ Stent patients (77%). Baseline QCA was performed pre-procedure, following device deployment, and after final treatment. The pre-specified primary endpoint for this trial was TVF at 9 months. The secondary endpoints included procedural success, MACE up to 9 months post-procedure, and angiographic restenosis (defined as >50% diameter stenosis) at 6 months for patients in the angiographic subset. An independent clinical events committee, blinded to treatment assignment, adjudicated all of the major clinical endpoints.

This prospective registry demonstrated that the 6-month TVF rate was 16.4% (27/155 patients), significantly (p=0.001) lower than the pre-specified 6-month TVF rate of 26.6% (1.5 times the observed [14.4%] rate seen in the PS® Stent plus 5% delta equivalency). The acute procedure success rate for in the NIR™ Stent SVG trial was 96.6%, and the In-Hospital MACE rate was 3.2%.

10.7 NIR ON™ Ranger™ w/SOX™ Registry

This study was conducted to evaluate in-hospital and out-of-hospital safety of a modified delivery system, the NIR ON™ Ranger w/SOX™ (1) in the elective treatment of native coronary arteries (*de novo*/restenotic) and (2) for treatment of patients with abrupt or threatened abrupt closure in native coronary arteries (AC/TC). The study consisted of 193 patients, 162 patients in the elective *de novo*/restenotic registry, and 31 patients in the NIR ™ Stent AC/TC registry. Since the main focus of this trial was clinical evaluation of the modified delivery system, clinical evaluation focused on acute endpoints - both in-hospital and at 14 days. The study was conducted at 21 centers. The Inclusion/Exclusion criteria were similar to the corresponding Inclusion/Exclusion criteria contained in the NIRVANA Randomized Trial and NIR ™ Stent AC/TC arm. Endpoints were analyzed on an intent-

to-treat basis and an independent angiographic clinical events committee adjudicated all of the major endpoints. Any patient who had a major adverse cardiac event had his/her films reviewed at the angiographic core laboratory.

10.7.1 Patient Demographics

Baseline demographics were not unusual in either the elective or NIR ™ Stent AC/TC arms (Table 10). In the elective arm the mean age was 64 years, 70% of patients were male, 27% had a history of diabetes, and 6% had restenotic lesions. In the NIR ™ Stent AC/TC arm the mean age was 65 years, 52% of patients were male, 45% had a history of diabetes, and 9% had restenotic lesions.

Baseline demographics and clinical characteristics for patients in the elective registry revealed a mean age of 64 years, 70% (113/161) men, 27% (43/162) with a history of diabetes mellitus, and 6.0% (9/162) with restenotic lesions. For patients in the NIR ™ Stent AC/TC registry, the mean age was 65 years, 52% (16/31) men, 45% with a history of diabetes mellitus, and 9.0% with prior restenosis in lesions.

Table 10. Patient Demographics NIR On™ Ranger™ with Sox Clinical Trial

	Elective (De Novo or Restenotic Lesion) Registry	Abrupt or Threatened Closure Registry	All Patients
Number Patients Treated	162	31	193
Per cent receiving assigned stent	99%	100%	99%
% Male	70%	52%	67%
% Diabetic	27%	45%	30%
Hypertension	66%	45%	63%
Hyperlipidemia	50%	32%	47%
Age (yr.)	64 ± 12	65 ± 12	64 ± 12
Reference vessel diameter (mm)	3.26 ± 0.43 (160)	2.89 ± 0.35 (32)	3.20 ± 0.44 (192)
% DS pre procedure	86 ± 8% (162)	89 ± 8% (32)	86 ± 8% (194)

10.7.2 Results

No major acute deployment problems were noted with the NIR ON™ Ranger w/SOX™ System (Table 11). The overall clinical procedure success (final diameter stenosis < 50% without in-hospital occurrence of death, Q-wave myocardial infarction, target lesion revascularization, or stent thrombosis) and technical procedure success (successful delivery and deployment of the NIR™ Stent to the target lesion without balloon rupture, embolization, guidewire fracture, or use of a device outside the planned stent strategy) rates were both 99% (191/193).

Table 11. Principal Safety and Effectiveness Results for the NIR ON™ Ranger w/SOX™ System

	Elective (De Novo or Restenotic Lesion) Registry	Abrupt or Threatened Closure Registry	All Patients
Clinical Procedure success	100% (162/162)	93.5% (29/31)	99% (191/193)
Technical success	98.8% (160/162)	100% (31/31)	99% (191/193)
MACE (Death, MI, TLR, Angiographic Stent Thrombosis)-Free at 14 Days	100%	93.5%	99%
Death	0%	0%	0%
Q-Wave Myocardial Infarction	0%	3.2% (1/31)	0.5 (1/193)%
Non-Q-Wave Myocardial Infarction	5.6% (9/162)	12.9% (4/31)	6.7% (13/193)
TLR-CABG	0%	0%	0%
TLR Re-PTCA	0%	0%	0%
Stent Thrombosis	0%	3.2% (1/31)	1% (1/193)
Bleeding Complications	1.9% (3/162)	6.5% (2/31)	3% (5/193)
Vascular Complications	4.3% (7/162)	6.5% (2/31)	5% (9/193)

Any delivery failure of the NIR™ Stent (failure to deliver first or second stent, or assigned stent never delivered) was noted for 2 (1%) lesions. Both cases were elective lesions. Treatment for these cases consisted of additional PTCA. Delivery of a different model stent was not attempted. There was one (1.0%) case of stent thrombosis, five (3%) bleeding complications, and nine (5%) vascular complications.

At the time of PMA submission 14 day clinical follow-up had been obtained on 88% (142/162) of elective patients and 94% (29/31) AC/TC patients. The overall MACE-free rate at 14 days was 99.0% (191/193). The individual elective and AC/TC rates were 100% and 94% respectively. Employing the overall 99% MACE-free value at 14 days the null hypothesis was rejected ($p < 0.0001$), and the alternative hypothesis that the 14 day MACE-free rate < 8.4% was accepted.

The 14-day clinical results demonstrated that the NIR ON™ Ranger™ w/SOX™ Stent System was safe and acutely effective in the treatment of elective *de novo* and restenosed coronary lesions, and in lesions experiencing abrupt or threatened closure from non-stent interventions. The clinical procedural success rate was 99%, the technical success rate was 99% and freedom from 14 day MACE rate was 99%, using Kaplan-Meier methods.

There were no deaths, one Q-wave myocardial infarctions in the AC/TC arm, 13 non-Q-wave myocardial infarctions (9 elective, 4 AC/TC), and no target lesion revascularizations. Major complications were summarized in the PMA. Review of this information did not reveal any unexpected problems.

The NIR ON™ Ranger™ w/SOX™ Stent System was not associated with acute safety or effectiveness problems. Analysis of the combined 14 day MACE rate and individual endpoints suggests that this delivery system is an acceptable over-the-wire system for delivering the NIR™ Stent.

10.8 NIR ON™ Ranger™

This study was conducted to evaluate in-hospital safety of a modified delivery system, the NIR ON™ Ranger™ Premounted Stent System in the treatment of native coronary artery lesions. This study was a prospective, multi-center (5 centers), non-randomized study with a minimum of 50 patients. The primary endpoint of this study was hierarchical combined in-hospital MACE defined as death, Q-wave MI without death, TLR without death or Q-MI, or angiographic stent thrombosis without death, Q-MI or TLR. The Inclusion/Exclusion criteria were similar to the corresponding Inclusion/Exclusion criteria in the

NIRVANA Randomized Trial. An independent clinical events committee adjudicated all major clinical endpoints. A separate angiographic committee was responsible for reviewing films of patients who had any of the following events: death, nonfatal myocardial infarction, target lesion revascularization, stent thrombosis, or abrupt or sub-abrupt closure.

10.8.1 Patient Demographics

Data from all 50 patients in the study were analyzed on an intent-to-treat basis. Baseline demographics were similar to those in the NIRVANA Randomized Trial. The mean age was 66 years, 72% of patients were male, 22% had a history of diabetes, 62% were hypertensive, and 48% were hyperlipidemic.

10.8.2 Results

No major acute deployment problems were noted. The overall clinical procedure success (final diameter stenosis < 50% using the NIR ON™ Ranger™ Premounted Stent System without in-hospital occurrence of death, Q-wave myocardial infarction, target lesion revascularization, or stent thrombosis) and technical procedure success (successful delivery and deployment of the NIR™ Stent to the target lesion without balloon rupture, embolization, guidewire fracture, or use of a device outside the planned stent strategy) rates were both 98% (49/50).

The clinical procedural success rate was 98% (49/50), and the technical success rate, defined as successful delivery and deployment of the NIR ON™ Ranger™ to the target lesion without balloon rupture, embolization, guidewire fracture, or use of a device outside the treatment strategy, was 98% (49/50). The incidence of MACE was 0%. There were no cases of death, nonfatal myocardial infarction, or target lesion revascularization. Compared to the pooled sample of patients in the NIR™ Stent and the PS® Stent arms of the NIRVANA Randomized Trial, the incidence of the primary endpoint of hierarchical MACE was lower in the NIR ON™ Ranger™ study at the p=0.1 level of significance (difference [95% confidence interval of difference]=-1.2%[-1.9%, -0.5%]). There were one (2%) vascular complication, no stent thrombosis, and no bleeding complications,.

The NIR ON™ Ranger™ Premounted Stent System without Sox was not associated with acute safety or effectiveness problems. Analysis of the in-hospital MACE rate and individual endpoints suggested that this delivery system is an acceptable over-the-wire system for delivering the NIR™ Stent.

10.9 Non-US Clinical Studies

The NIR™ Stent was also evaluated in several single and multi-center trials worldwide. The results of these studies were reviewed and are presented here for information only, but were not included in the overall assessment for approval of the device.

Summary of Studies

The first clinical application and angiographic outcome of unselected lesions was evaluated in a single center study in Milan, Italy. In this study an unselected lesion was defined as any lesion encountered. Ninety-three stents of various lengths were implanted in 64 lesions in 41 patients. All patients were treated with aspirin and ticlopidine and all lesions were evaluated before and after treatment with QCA. Clinical follow-up was available in all patients and angiographic follow-up was performed at a mean interval of 5.4months.

Failure to deploy the stent occurred in (3%) of the patients. Major adverse cardiac events included 1 in hospital non-Q wave MI, 1 sudden death after 40 days, and 17 lesions required TLR. Angiographic restenosis was documented in 19 lesions. Restenosis was more frequent in vessels with a reference diameter smaller than 2.5 mm and for lesions longer than 15 mm.

In a multi-center study to determine the feasibility, safety and efficacy of elective and urgent deployment of the NIR™ stent in patients with coronary artery disease, the NIR™ Stent implantation was attempted in 255 patients. Seventy-four percent of patients underwent elective stenting for primary or restenotic lesions, 21% for a suboptimal angioplasty result, and 5% for threatened or abrupt vessel closure. Fifty-two percent of patients presented with unstable angina, 48% had a previous MI, and 45% had multivessel disease. Coronary lesions were frequently complex, occurring in relatively small arteries. Patients were followed for 6 months for the occurrence of major adverse cardiovascular events. In this multi-center study stent deployment was accomplished in 98% of lesions. Mean percent diameter stenosis decreased from 61 $\pm$13% before to 17 $\pm$ 7% after intervention. A successful interventional procedure with <50% diameter stenosis of all treatment site lesions and no major adverse cardiac events within 30 days occurred in 95% of patients. Event-free survival at 6 months was 82%. Ninety-four percent of surviving patients were either asymptomatic or had mild stable angina at 6 month follow-up.

In another multi-center study the primary objective was to assess the safety and feasibility of the NIR™ Stent in patients eligible for PTCA of a *de novo* stenotic lesion, with ticlopidine plus aspirin treatment. A total of 156 patients were enrolled in 12 clinical centers in Europe and 2 centers in Israel. Forty percent of the patients had unstable angina, 54% of the patients had stable angina and 7% had silent ischemia. In 155 patients the NIR™ Stent implantation was technically successful. However, in 22 patients more than 1 stent was necessary, either because the original lesion was not completely covered or because of a proximal or distal dissection. Clinical and angiographic data were analyzed using the intent-to-treat principle. Procedure success was 97.4%, event-free survival at 1 month and 6 months were 98% and 86.5%, respectively. The TLR rate was 9.6% and major bleeding complications were noted in 2.6% of the patients. No mortality at 6 months was observed.

In a multi-center Japanese study of the NIR™ Stent, a total of 87 patients were treated at two institutions. Sixty-three patients underwent elective stenting of *de novo* stenotic lesions and 24 patients received stents as a bail-out procedure following PTCA. Sixty-five percent of elective patients and 67% of bail-out patients experienced a MI prior to stenting. All but two patients suffered from angina at the time of treatment. Clinical follow-up was required at one, three and six months. QCA was performed at baseline, after balloon inflation and immediately after stent deployment.

11. CONCLUSIONS DRAWN FROM THE STUDIES

11.1 Safety

The preclinical studies conducted on the NIR™ Stent included biocompatibility, sterilization, and *in vitro* bench testing (stent material specifications and conformance, stent integrity, stent and Delivery System performance, package integrity and shelf-life). The results of biocompatibility testing demonstrated that the stent material is acceptable for long-term (implant, circulating blood) invasive use in the cardiovascular system.

The results of *in-vitro* bench testing demonstrated that the performance characteristics of both stents and their delivery system met product specifications and that they are safe for clinical use.

The results of acute and chronic *in-vivo* animal testing to assess performance characteristics demonstrated that the NIR™ Stent is safe for clinical use.

11.2 Effectiveness

The results of the clinical studies indicate that the objectives of each study were met, the MACE rates between groups are comparable, the TVF rates are low, and that the data support the indications for use of the NIR™ Stent. The acute, 30 day, and six-month clinical and angiographic point estimates obtained for major safety and effectiveness variables support the clinical use of the NIR™ Stent.

The *in-vivo* and *in-vitro* nonclinical laboratory studies together with the clinical investigations provide valid scientific evidence and provide reasonable assurance that the NIR ON™ Ranger™ and NIR ON™ Ranger™ w/SOX™ Stent Delivery Systems are safe and effective for their intended use.

11.3 Labeling

To provide additional insight in selecting and treating patients with a coronary artery stent, labeling for these devices will contain the following statements:

- The risks and benefits described above should be carefully considered for each patient before use of the NIR™ Stent. Patient selection factors to be assessed should include a judgment regarding risk of prolonged anticoagulation. Stenting is generally avoided in those patients at heightened risk of bleeding (e.g., those patients with recently active gastritis or peptic ulcer disease, see Section 4 CONTRAINDICATIONS).

- Premorbid conditions that increase the risk of poor initial results or the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed. The relation of baseline and procedural variables to target vessel failure (TVF) was examined. The only significant predictor of TVF was post-procedural mean minimum lumen diameter (MLD). TVF was less likely with larger MLD.

- Thrombosis following stent implantation is effected by several baseline angiographic and procedural factors. These include vessel diameter less than 3.0 mm, vessel thrombosis, poor distal flow, and/or dissection following stent implantation. In patients that have undergone coronary stenting, the persistence of a thrombus or dissection is considered a marker for subsequent thrombotic occlusion. These patients should be monitored very carefully during the first month after stent implantation because stent thrombosis may occur during this period.

- The safety and effectiveness of the NIR™ Stent has not been established for patients with any of the following characteristics:
  - Patients with **unresolved vessel thrombus at the lesion site**.
  - Patients with coronary artery **reference vessel diameters < 2.5 mm**.
  - Patients with **lesions located** in the unprotected left main coronary artery, ostial lesions, or lesions located at a bifurcation.
  - Patients with diffuse disease or **poor outflow distal** to the identified lesions.
  - Patients with recent **acute myocardial infarction** where there is evidence of thrombus or poor flow.
  - Patients with **more than two overlapping stents** due to risk of thrombus.
  - Patients for longer than 6 months follow-up.

  The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters), or laser angioplasty catheters, to treat in-stent stenosis has not been established.

11.4 Post-Approval Studies

Although enough information has been presented for approval purposes, there is much that can be gained from continued analysis of the sponsor's data. Conditions of approval indicate that complete follow-up of the randomized patient group be obtained at six months, one year, and then

yearly thereafter for a total of five years, and that the sponsor make a concerted effort to obtain autopsies on patients who die.

12. PANEL RECOMMENDATION

Pursuant to section 515(c)(2) of the Federal Food, Drug, and Cosmetic Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory panel, for review and recommendation because the information in the PMA substantially duplicated information previously reviewed by this panel.

13. FDA DECISION

The FDA issued an approval order to Boston Scientific on August 11, 1998. The approval order stipulated that in addition to the standard postapproval requirements, the following information must be submitted: (1) the postapproval reports must include information further characterizing long-term safety and effectiveness by following for 5 years from implant at least 400 of the patients implanted with the NIR ™ Stent in the NIRVANA trial and associated U.S. registries; (2) the protocol for this study and study time lines will be submitted to the agency for review within 30 days of approval, and the final protocol will be developed interactively with the FDA review team; and, (3) summary reports will be submitted to the agency annually and a final report at the end of the study.

FDA performed an inspection and found the applicant in compliance with the Quality System Regulation (21 CFR Part 820).

14. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to health from use of the device: See indications, contraindications, warnings, precautions and adverse events in the labeling.

Postapproval requirements and restrictions: See approval order.

The Approval Order, Summary of Safety and Effectiveness Data, and labeling can be found on the Internet at address http: //www.fda.gov/cdrh/pmapage.html.