Summary of Safety & Effectiveness Data

The Novoste™ Beta-Cath™ System

Novoste™ Corporation

1. **General Information**

   1.1 Device Generic Name
   Intravascular Brachytherapy System

   1.2 Device Trade Name
   Beta-Cath™ System

   1.3 Applicant's Name and Address
   Novoste Corporation
   3890 Steve Reynolds Boulevard
   Norcross, GA 30093
   USA

   1.4 PMA Number
   P000018

   1.5 Date of Panel Recommendation
   September 11, 2000

   1.6 Date of Notice of Approval to the Applicant

2. **Indications for Use**

   The **Beta-Cath™** System is intended to deliver beta radiation to the site of successful Percutaneous Coronary Intervention (PCI) for the treatment of in-stent restenosis in native coronary arteries with discrete lesions (treatable with a 20 mm balloon) in a reference vessel diameter ranging from 2.7 mm to 4.0 mm.

3. **Contraindications**
   (See Labeling)

4. **Warnings and Precautions**
   (See Labeling)

5. **Device Description**

   The **Beta-Cath™** System is an integrated system comprised of four components: the **ß- Cath™** Delivery Catheter, the Transfer Device, the Source Train, and the System Accessories. The System is designed so that the Transfer Device and the Delivery Catheter are exclusively compatible.

   The β-**Cath™** Delivery Catheter provides the path through which the Source Train is delivered to and retrieved from the site of interventional injury. The Delivery Catheter has a total length of 155cm, with a working length of 135cm. It is compatible with guide catheters having an internal diameter of ≥0.078" and 0.014"guidewires. The main body of the catheter consists of three lumens that allow for the passage of the guidewire, source train, and hydraulic fluid. The source train and hyrdraulic fluid lumens are closed at the distal end, while the guidewire lumen remains open to the vasculature. The treatment zone of the delivery catheter is marked by 2 radiopaque markers. These markers are used to position the catheter at the interventional injury site prior to radiation treatment. The intraluminal connector provides a fluid connection between the source train and hydraulic lumens, and serves as the "stop" for the source train. A black ink depth marker is provided approximately 90cm from the distal tip.

The ergonomically designed Transfer Device stores and shields the Source Train when not in use, and controls the hydraulic delivery and return of the Source Train during the treatment procedure. The Transfer Device features a series of electronic and mechanical mechanisms that are intended to maintain the proper position of the Source Train.

The Beta-Cath System also includes a non-active Transfer Device, containing a non-active Source Train. The non-active Transfer Device is used to ensure the integrity of the Delivery Catheter prior to use.

The Source Train consists of a series of individual, cylindrical, sealed sources containing Sr90/Y90 and an inactive marker at each end. The Source Train consists of 12 active seeds and features a length of 30 mm. The Source Train provides the radiation dose during the treatment procedure.

The System Accessories are the ancillary components of the Beta-Cath™ System. The System Accessories include: a Procedure Accessory Pack, an optional Protective Sheath, an optional Extension Tubing Set, an Emergency Storage Container, a Response Kit, and a Medical Physicist Kit. The System Accessories are intended to: (1) ensure sterility and facilitate operation of the system during a clinical procedure, (2) permit temporary storage of System components in the event of a disrupted clinical procedure, (3) facilitate handling of Source Train components if located outside of the System, (4) facilitate Medical Physicist's operations, and/or (5) enable transport of the System components and Medical Physicist's Kit.

6. Alternative Practices and Procedures

Treatment of patients with coronary artery disease including in-stent restenosis may include exercise, diet, drug therapy, percutaneous coronary interventions and coronary artery bypass surgery.

7. Marketing History

The **Beta-Cath™** System is commercially marketed in the following countries:

Australia	Austria	Belgium	China	Denmark
Finland	Germany	Greece	Iceland	Ireland
Israel	Italy	Liechtenstein	Luxembourg	New Zealand
Netherlands	Norway	Portugal	Spain	Sweden
Switzerland	Turkey	India		

The **Beta-Cath™** System has not been the subject of regulatory action in any country for any reasons relating to the safety and/or effectiveness of the device.

8. Potential Adverse Effects on Health

8.1 Adverse Effects of the Device on Health

A total of 476 patients were enrolled in this multi-center clinical study to evaluate the safety and effectiveness of the **Beta-Cath™** System for the treatment of in-stent restenosis of native coronary arteries. Of these, 244 received active Sr-90 brachytherapy and 232 received in-active placebo via the **Beta-Cath™** System. These patients form the basis for the observed events reported.

8.2 Observed Adverse Events

The observed adverse events are summarized in the following table.

Table 1. Major Adverse Events – In-Hospital and Out-of-Hospital (to 8 months)
All Patients Treated (N=476)

	Sr-90 (N=244 Patients)		Placebo (N=232 Patients)		All Randomized (N=476 Patients)	
Combined (In- and Out-of-Hospital) Complications to 240 Days	Number	%	Number	%	Number	%
Any MACE (Death, MI, Emergent CABG, TVR)	44	18.0%	60	25.9%	104	21.8%
Death	3	1.2%	1	0.4%	4	0.8%
Myocardial Infarction (Q or Non-Q)	4	1.6%	7	3.0%	11	2.3%
Q Wave MI	0	0.0%	0	0.0%	0	0.0%
Non-Q Wave MI	4	1.6%	7	3.0%	11	2.3%
Emergent CABG	1	0.4%	0	0.0%	1	0.2%
Target Lesion Revascularization	32	13.1%	52	22.4%	84	17.6%
TL-CABG	20	8.2%	24	10.3%	44	9.2%
TL-PTCA	12	4.9%	30	12.9%	42	8.8%
Target Vessel Revascularization not involving the TL*	11	4.5%	15	6.5%	26	5.5%
TV-CABG	2	0.8%	2	0.9%	4	0.8%
TV-PTCA	9	3.7%	13	5.6%	22	4.6%
Target Vessel Revascularization	39	16.0%	56	24.1%	95	20.0%
TV-CABG	21	8.6%	24	10.3%	45	9.5%
TV-PTCA	19	7.8%	34	14.7%	53	11.1%
Stent Thrombosis (to 30 days)	0	0.0%	1	0.4%	1	0.2%
Site Thrombosis (Days 31-240)	0	0.0%	0	0.0%	0	0.0%
Abrupt Closure	0	0.0%	1	0.4%	1	0.2%
Subacute Closure	0	0.0%	1	0.4%	1	0.2%
Bleeding Complications	4	1.6%	4	1.7%	8	1.7%
Vascular Complications	4	1.6%	3	1.3%	7	1.5%
CVA	1	0.4%	1	0.4%	2	0.4%

*Target vessel revascularization not involving the target lesion was defined as target vessel revascularization at a site other than the target site with or without concomitant target lesion revascularization.

Three (3) patients who received radiation died during the START trial. The deaths occurred between 167 and 225 days. One (1) patient died due to coronary artery disease, congestive heart failure, and multi-system dysfunction. It could not be determined if the cause of death was device-related. The cause of death for the other two patients was determined not to be device-related.

8.3 Potential Adverse Events

The following adverse events were NOT observed during the clinical investigation, but are recognized as potential adverse events associated with the non-radioactive portion of vascular brachytherapy (not limited to):

- Arrhythmia
- Slow Flow-Phenomenon
- Arterial Damage, Dissection or Perforation
- AV Fistula
- Vascular Access Site Hematoma
- Pseudoaneurysm
- Contrast-Induced Nephrotoxicity
- Left Ventricular Dysfunction
- Neurologic Complications
- Systemic Atheroembolization

- Allergic Reactions
- Endocarditis
- Infection
- Distal Embolizations
- Stroke
- Vasospasm
- Thrombotic Occlusion
- Arterial Perforation
- Renal Insufficiency
- Retroperitoneal Hematoma
- Coronary Artery Bypass Graft Surgery

Additional potential Adverse Events associated with the radiation portion of vascular brachytherapy include, but are not limited to:

- Radiation Induced Malignancy
- Aneurysm
- Excessive radiation exposure to patient/staff
- Arterial Damage
- Coronary Artery Bypass Graft Surgery
- Thrombosis
- Restenosis
- Myocardial Infarction
- Death

9. Summary of Pre-Clinical Studies

9.1 Biocompatibility Testing

Biocompatibility testing was performed on the **ß-Cath™** Delivery Catheter in accordance with ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing". The **ß-Cath™** Delivery Catheter passed cytotoxicity, sensitization, intracutaneous toxicity, systemic toxicity, hemolysis, and thromboresistance testing.

9.2 Sterility Testing

The **ß-Cath™** Delivery Catheter and Procedure Accessory Pack are sterilized using a 100% ETO process that has been validated per ANSI/AAMI/ISO 11135-1994 to yield a minimum SAL of 10^{-6}. The **ß-Cath™** Delivery Catheter and Procedure Accessory Pack meet the ETO residual limit requirements specified in ISO 10993-7:1995.

10. Animal Testing

Multiple animal studies have been performed to evaluate the performance of the Beta-Cath™ System and the effects of radiation in a simulated clinical setting. All studies have demonstrated that the Beta-Cath™ System meets its performance specifications.

A short-term animal study was conducted using a specialized Strontium 90 source train delivery system developed by Novoste. This system was used to deliver 7, 14, 28, and 56 Gy at 2 mm from the centerline of the sources in less than 1.5, 3, 6, and 12 minutes, respectively. The summary of the results indicate that the beta radiation, when compared by dosing, had a similar histological and histomorphometric result to the gamma radiation, beta radiation was effective in preventing neointimal proliferation in a dose-dependent fashion (maximum treatment effect with 28 Gy), and higher doses of beta radiation (up to 56 Gy) were used without resulting in acute vessel injury.

Additional animal studies were conducted to verify the intended performance of the Beta-Cath System and to study the long-term effects of radiation therapy (6 and 12 months). The animal studies performed used both balloon overstretch injury and oversized stent injury to induce atheromatous human coronary stenosis in the pig coronary vasculature. The results of these studies demonstrated that the performance of the Beta-Cath System as compared to the control group, had no discernable

11

impact on neointimal formation, and the addition of radiation therapy did not demonstrate an adverse effect on the repair mechanisms of the arteries.

11. Bench Testing

11.1. ß-Cath™ Delivery Catheter

11.1.1. *Tensile Strength*
Tensile testing was performed for the main body, tip, and all joints of the Delivery Catheter per the requirements of product requirements established by Novoste and ISO 10555-1:1995. The Delivery Catheter met all tensile strength specifications.

11.1.2. *Marker Band Attachment Strength*
Testing was performed to determine the forces required to dislodge and remove the proximal marker band from the Delivery Catheter. The external marker band was required to have a dislodgment force with a lower statistical tolerance limit >0.5 lbs and a removal force of >1.5 lbs as established by Novoste in the product requirements. The external marker met the dislodgement and removal force specifications.

11.1.3. *Source Train Transport*
Testing was performed to determine the time required to transport the Source Train between the Transfer Device and distal end of the Delivery Catheter at various transport pressures, and to assess the ability of the Source Train to successfully navigate the catheter within simulated tortuous anatomy models. Novoste established the acceptance criteria of upper statistical tolerance limit ≤5.0 seconds @ 60 psi in the product requirements. The system met the Source Train transport specifications.

11.1.4. *Leakage*
Testing was performed to ensure that the Delivery Catheter could withstand internal hydraulic pressures of ≥150 psi without leakage per the Novoste established product requirements. The Delivery Catheter met the leakage specification.

11.1.5. *Burst Pressure*
Testing was performed to demonstrate that the lower statistical limit for burst pressure of the Delivery Catheter main body was ≥200 psi. The Delivery Catheter met the burst pressure specification.

11.1.6. *Introducer Sheath Qualification*
Testing was performed to verify that the addition of the Arrow Super ArrowFlex Sheath to the body of the Delivery Catheter increases the resistance of the catheter to collapse with compressed with a hemostasis valve.

11.1.7. *Radiation Effects*
Testing was performed to demonstrate the radiation resistance of the Delivery Catheter. Catheters were evaluated for functionality and tensile strength following a 15 minute exposure to the radioactive Source Train. All catheters met the respective specifications.

11.1.8. *Shelf Life*
Delivery Catheter functionality and package integrity testing were performed following aging, environmental conditioning, and simulated shipping per ISTA Procedure 2A, and following radiation exposure. The results of this testing support the Delivery Catheter shelf life specification.

11.2. Transfer Device

11.2.1 *Electrical Safety & Electromagnetic Compatibility*
The Transfer Device was tested for electrical safety per the requirements IEC-601-1, General Safety Requirements for Medical Electrical Equipment. The Transfer Device met all electrical safety specifications of IEC-601-1.

12

The following electromagnetic compatibility tests were conducted on the Transfer Device: radiation emissions, electrostatic discharge, radiated electromagnetic fields. The Transfer Device met the respective test requirements.

11.2.2 *Device Functionality*
Testing was performed to ensure functionality of all Transfer Device components including Source Train detection system, gate safety interlocks, pressure indicator, pressure relief valve, and fluid control valve. The Transfer Device met all functionality specifications.

11.2.3 *Working Life*
Cycle testing, radiation resistance testing, fluid ingress testing, battery life analyses, and corrosion analyses have been performed to demonstrate that the working life of the Transfer Device met the Novoste established 6 month or 250 uses working life, which ever occurs first. The results of these activities support the intended working life specification for the Transfer Device.

11.3. Radiation Source Train

11.3.1 *Sealed Source Classification*
Testing was completed to demonstrate that the sources comprising the Radiation Source Train meet the requirements for class C63211 sealed sources per ISO 2919:1999. The sources meet the specification.

11.3.2 *Dose Rate*
Dose rate calibrations traceable to a NIST-calibrated standard are performed for each Radiation Source Train (100%). Testing is also performed to ensure axial dose rate uniformity of each Radiation Source Train.

11.3.3 *Working Life*
Cycle testing, mechanical loading analyses, and corrosion analyses have been performed to demonstrate that the working life of the Radiation Source Train meets the Novoste established product requirements of 1 year of use. The results of these activities support the intended working life specification for the Radiation Source Train.

11.4. Accessories

11.4.1 *Functionality*
Testing was performed to assess the functionality of all **Beta-Cath™** System accessories, including Procedure Accessory Pack, Temporary Storage Container, Response Kit, Medical Physicist's Kit, and Transport System. All accessory components met their functionality specifications.

11.4.2 *Shelf Life*
Functionality and package integrity testing were performed for the Procedure Accessory Pack and its components following aging, environmental conditioning, and simulated shipping per ISTA Procedure 2A. The results of these tests support the Procedure Pack shelf life specification.

12. Summary of Clinical Studies

The objectives of the STents And Radiation Therapy (START) trial were to evaluate the safety and effectiveness of ^{90}Strontium (Sr-90) versus placebo (inactive sources) in patients following successful coronary intervention to treat in-stent restenosis in native coronary arteries.

12.1. Study Design

A total of 476 patients were enrolled at 50 study centers (46 US) in the placebo-controlled, triple-masked, multicenter START trial. All 476 of the enrolled patients were randomized to receive either the active **Beta-Cath™** System (n=244) or placebo **Beta-Cath™** System (n=232). The primary endpoint of 8-month clinical target vessel failure was defined as the composite of death, myocardial infarction (Q-wave and non-Q-wave), coronary artery bypass surgery (CABG), and revascularizations attributed to the target vessel (TVR). A clinical events committee masked to the treatment assignment adjudicated all major endpoints.

Eligible patients, with angina or positive functional study, were identified for elective treatment of in-stent restenosis in a native coronary artery lesion visually estimated to be between 2.7 and 4.0 mm in diameter and treatable with up to a 20 mm (length) angioplasty balloon. These patients underwent successful percutaneous coronary interventions (defined as revascularization by balloon angioplasty, directional and rotational atherectomy, and excimer laser) after which treatment with the randomized **Beta-Cath™** System (active or placebo) was administered. After the vascular brachytherapy treatment, additional percutaneous coronary interventional techniques or devices were utilized as deemed necessary by the clinician. Placement of a new stent, while discouraged, occurred at the discretion of the clinician in 21% (n=101) of the cases.

Clinical follow-up occurred at in-hospital, 1 month, and 8 (±1) months. Angiographic follow-up occurred at 8 months. The study randomization was successful as both treatment groups were found to be demographically equivalent. All randomized patients were included in the intent-to-treat analysis.

12.2. Gender Bias and Demographics

To determine whether gender bias had occurred during this clinical study, the ratio of women to men treated in the Sr-90 group was compared to that of the placebo group. There were no significant baseline differences in patient characteristics between the groups. The baseline characteristics include: age, sex, incidence of diabetes, smoking history, history of peripheral vascular disease, hypertension, hyperlipidemia, prior myocardial infarction, prior by-pass surgery, angina status, and angina class. Differences between the treatment and placebo groups with respect to the study outcome were consistent between the genders.

12.3. Patient Description

Four hundred seventy six (476) patients were enrolled between September 21, 1998 and April 30, 1999. Baseline characteristics are detailed in Table 2 below:

Table 2. Baseline Demographics and Clinical Characteristics
All Patients Treated (N=476)

Patient Characteristic	Sr-90 (N=244 Patients)	Placebo (N=232 Patients)	All Randomized (N=476 Patients)	Difference [95% C.I.]
Age (yrs)				
Mean±SD (N)	61.5±11.5 (244)	61.1±10.4 (232)	61.3±10.9 (476)	0.4 [-1.6,2.4]
Range (min, max)	(34.0,87.0)	(34.0,89.0)	(34.0,89.0)	
Number of men	68.4% (167/244)	63.4% (147/232)	66.0% (314/476)	5.1% [-3.4%,13.6%]
Current Smoker	12.5% (29/232)	8.1% (18/223)	10.3% (47/455)	4.4% [-1.1%,10.0%]
History of peripheral vascular disease	10.2% (25/244)	13.4% (31/232)	11.8% (56/476)	-3.1% [-8.9%,2.7%]
Diabetes Mellitus	30.7% (75/244)	32.3% (75/232)	31.5% (150/476)	-1.6% [-9.9%,6.8%]
Hypertension requiring treatment	71.9% (174/242)	73.9% (170/230)	72.9% (344/472)	-2.0% [-10.0%,6.0%]
Hyperlipidemia requiring treatment	76.7% (184/240)	77.0% (177/230)	76.8% (361/470)	-0.3% [-7.9%,7.3%]
Prior MI	46.7% (113/242)	47.8% (110/230)	47.2% (223/472)	-1.1% [-10.1%,7.9%]
Prior CABG	21.4% (52/243)	23.7% (55/232)	22.5% (107/475)	-2.3% [-9.8%,5.2%]
Revascularization for angina or MI	87.7% (214/244)	87.5% (203/232)	87.6% (417/476)	0.2% [-5.7%,6.1%]
Stable exertional angina	13.5% (33/244)	8.2% (19/232)	10.9% (52/476)	5.3% [-0.2%,10.9%]
Unstable angina	73.8% (180/244)	78.9% (183/232)	76.3% (363/476)	-5.1% [-12.7%,2.5%]
Crescendo exertional angina	41.4% (101/244)	39.2% (91/232)	40.3% (192/476)	2.2% [-6.6%,11.0%]
Rest angina	30.7% (75/244)	37.5% (87/232)	34.0% (162/476)	-6.8% [-15.3%,1.7%]
Pain during MI only	1.6% (4/244)	2.2% (5/232)	1.9% (9/476)	-0.5% [-3.0%,1.9%]
Unknown angina status	0.4% (1/244)	0.4% (1/232)	0.4% (2/476)	0.0% [-1.2%,1.1%]
CCS III or IV*	53.7% (130/242)	62.8% (145/231)	58.1% (275/473)	-9.1% [-17.9%,-0.2%]
MI within 72 hours	0.4% (1/242)	0.4% (1/230)	0.4% (2/472)	0.0% [-1.2%,1.2%]
Number of diseased, native, major epicardial coronary arteries				
Single	63.1% (154/244)	55.4% (128/231)	59.4% (282/475)	7.7% [-1.1%,16.5%]
Double	21.3% (52/244)	32.9% (76/231)	26.9% (128/475)	-11.6% [-19.5%,-3.6%]
Triple	15.6% (38/244)	11.7% (27/231)	13.7% (65/475)	3.9% [-2.3%,10.0%]
Ejection Fraction (%)				
Mean±SD (N)	54.2%±10.5% (229)	54.6±12.3% (213)	54.4%±11.4% (442)	-0.4% [-2.6,1.7%]
Range (min, max)	(28.0%,83.0%)	(25.0%,86.0%)	(25.0%,86.0%)	

Numbers are % (counts/sample size) or Mean ± SD.
CI = Confidence Interval
Difference = Sr-90 – Placebo
SE = $\text{sqrt}(p_1*q_1/n_1+p_2*q_2/n_2)$
CI = Diff±1.96*SE
*Canadian Cardiovascular Society angina class.

12.4. Results

The principal safety and effectiveness results are summarized in Table 3 below. Additionally, the freedom from target vessel failure event free survival curve is provided in Figure 1.

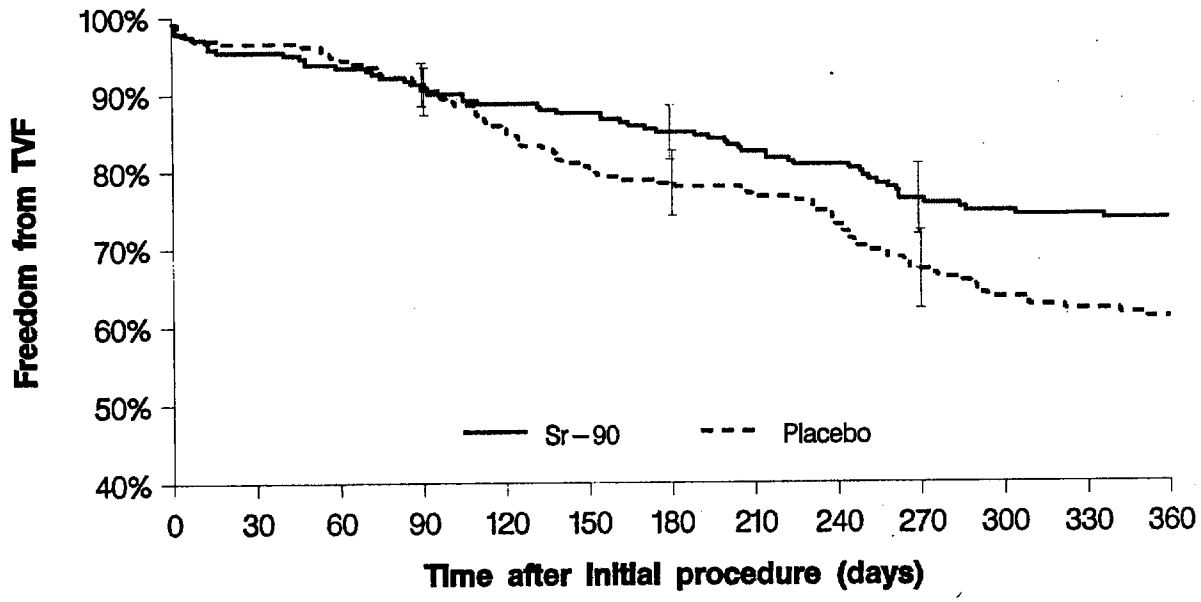
Table 3. Principal Effectiveness and Safety Results
All Patients Treated (N=476)

Efficacy Measures	Sr-90 (N=244 Patients)	Placebo (N=232 Patients)	Relative Risk [95% C.I.]	Difference [95% C.I.]	P-value
8 Month Stent Segment Binary Restenosis Rate	14.2% (28/197)	41.2% (77/187)	0.3 [0.24,0.51]	-27.0% [-35.5%,-18.4%]	0.0000
8 Month Analysis Segment Binary Restenosis Rate	28.8% (57/198)	45.2% (85/188)	0.6 [0.49,0.83]	-16.4% [-25.9%,-6.9%]	0.0008
TLR-Free at 240 Days*	86.4%	75.6%	1.14 [1.03,1.27]	10.8% [2.5%,19.0%]	0.0090
TVR-Free at 240 Days*	83.5%	73.8%	1.13 [1.01,1.27]	9.7% [1.1%,18.3%]	0.0283
TVF-Free at 240 Days*	81.4%	72.2%	1.13 [1.00,1.27]	9.2% [0.3%,18.1%]	0.0393
MACE-Free at 240 Days*	81.4%	72.2%	1.13 [1.00,1.27]	9.2% [0.3%,18.1%]	0.0393
Target Lesion Success	99.6% (243/244)	99.1% (230/232)	1.0 [0.99,1.02]	0.5% [-1.0%,1.9%]	0.5332
Procedure Success	97.1% (237/244)	97.0% (225/232)	1.0 [0.97,1.03]	0.1% [-2.9%,3.2%]	0.9237
Device Success	98.4% (240/244)	97.8% (227/232)	1.0 [0.98,1.03]	0.5% [-1.9%,3.0%]	0.6796
Post-Procedure Stent Segment Minimal Lumen Diameter (MLD, in mm)					
Mean±SD (N)	2.17±0.42 (242)	2.15±0.42 (229)		0.02 [-0.06,0.09]	0.6503
Range (min, max)	(1.12,3.47)	(1.20,3.40)			
Post-Procedure Analysis Segment Minimal Lumen Diameter (MLD, in mm)					
Mean±SD (N)	1.94±0.39 (243)	1.94±0.41 (230)		-0.00 [-0.08,0.07]	0.9058
Range (min, max)	(1.03,3.02)	(0.98,3.10)			
Post-Procedure Stent Segment Percent Diameter Stenosis (%DS)					
Mean±SD (N)	22.9%±13.5% (242)	22.9±12.9% (229)		0.0% [-2.4,2.4%]	0.9972
Range (min, max)	(-31.1%,53.2%)	(-19.6%,51.9%)			
Post-Procedure Analysis Segment Percent Diameter Stenosis (%DS)					
Mean±SD (N)	31.4%±10.2% (243)	30.7±11.0% (230)		0.7% [-1.2,2.6%]	0.4800
Range (min, max)	(6.7%,57.6%)	(5.8%,62.5%)			
Follow-Up Stent Segment Minimal Lumen Diameter (MLD, in mm)					
Mean±SD (N)	1.96±0.66 (197)	1.47±0.60 (187)		0.49 [0.36,0.62]	0.0000
Range (min, max)	(0.00,3.45)	(0.00,2.65)			
Follow-Up Analysis Segment Minimal Lumen Diameter (MLD, in mm)					
Mean±SD (N)	1.65±0.64 (198)	1.41±0.58 (188)		0.24 [0.12,0.36]	0.0001
Range (min, max)	(0.00,3.18)	(0.00,2.66)			
Follow-Up Stent Segment Percent Diameter Stenosis (%DS)					
Mean±SD (N)	30.4%±22.7% (197)	47.9±20.8% (187)		-17.5% [-21.9,-13.1%]	0.0000
Range (min, max)	(-32.2%,100.0%)	(-4.4%,100.0%)			
Follow-Up Analysis Segment Percent Diameter Stenosis (%DS)					
Mean±SD (N)	41.7%±20.7% (198)	50.1±19.7% (188)		-8.5% [-12.5,-4.4%]	0.0000
Range (min, max)	(-10.4%,100.0%)	(13.4%,100.0%)			
Safety Measures and Other Clinical Events to 240 days					
In-Hospital MACE	2.5% (6/244)	2.2% (5/232)	1.1 [0.35,3.69]	0.3% [-2.4%,3.0%]	0.8255
Out-of Hospital MACE to 240 Days	16.0% (39/244)	24.1% (56/232)	0.7 [0.46,0.96]	-8.2% [-15.3%,-1.0%]	0.0261
In- and Out-of-Hospital MACE to 240 Days	18.0% (44/244)	25.9% (60/232)	0.7 [0.49,0.98]	-7.8% [-15.2%,-0.4%]	0.0388
Aneurysm†	0.5% (1/198)	0.0% (0/188)	- [-,-]	0.5% [-0.5%,1.5%]	0.3292
Stent Thrombosis (to 30 Days)	0.0% (0/244)	0.4% (1/232)	0.0 [-,-]	-0.4% [-1.3%,0.4%]	0.3046
Site Thrombosis (Days 31-240)	0.0% (0/244)	0.0% (0/232)	- [-,-]	0.0% [-,-]	-
Total Occlusions (Angiographic)	4.0% (8/198)	3.7% (7/188)	1.1 [0.40,2.93]	0.3% [-3.5%,4.2%]	0.8720

Numbers are % (counts/sample size) or Mean ± SD.
CI = Confidence Interval
N/A = Not applicable.
Relative Risk = Sr-90/Placebo $SE = sqrt\{(1-p_1)/n_{11}+(1-p_2)/n_{21}\}$ $CI = RR*exp(\pm 1.96*SE)$
Difference = Sr-90 – Placebo $SE = sqrt(p_1*q_1/n_1+p_2*q_2/n_2)$ $CI = Diff\pm 1.96*SE$
Target Lesion Success = Attainment of a final residual stenosis of <50% (by QCA) using any percutaneous method. If QCA was not available, the visual estimate of diameter stenosis was used.
Procedure Success = Attainment of a final residual stenosis of <50% (by QCA) using any percutaneous method and no in-hospital major adverse cardiac events (MACE). If QCA was not available, the visual estimate of diameter stenosis was used.
Device Success = Successful delivery of the Beta-Cath™ System.
Footnotes are continued on the following page.

Stent segment was defined as the area confined to the proximal and distal borders of the stent.
Analysis segment was defined as the segment that extends 5 mm proximal and distal to the radiated or injured landmark, whichever was longest in length.
*Survival estimates from Kaplan-Meier method. Standard error estimate from Peto formula.
TLR-free = Freedom from target lesion revascularization.
TVR-free = Freedom from target vessel revascularization.
TVF-free = Freedom from death, MI, and target vessel revascularization.
MACE-free = Freedom from death, MI, emergent CABG, and target vessel revascularization.
In-Hospital MACE = Death, Q wave or non-Q wave MI, emergent CABG, or target vessel revascularization prior to discharge as determined by the independent Clinical Events Committee.
Out-of-Hospital MACE = Death, Q wave or non-Q wave MI, emergent CABG, or target vessel revascularization from hospital discharge through the 240-day contact, as determined by the independent Clinical Events Committee.
Stent thrombosis was defined as angiographic thrombus or subacute closure within the target vessel at the time of the clinically driven angiographic restudy for documented ischemia (chest pain and ECG changes). Any death not attributed to a non-cardiac cause within the first 30 days was considered a surrogate for thrombosis in the absence of documented angiographic stent patency.
Site thrombosis was defined as myocardial infarction attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site >30 days after the index procedure in the absence of an intervening revascularization of the target vessel.
Aneurysm was defined as an expansion of the lumen by at least 20% compared with the normal lumen dimensions in the treatment region (analyzed segment) that extends with a wide or narrow mouth beyond the apparent normal contour.
†Baseline QCA for patient 15/3 revealed the presence of an aneurysm. The Angiographic Core Laboratory reported the absolute size of the aneurysm changed very little from baseline to follow-up and that the larger appearance at follow-up was due to the smaller reference vessel dimension rather than an increase in aneurysm size.
Total Occlusion = An MLD of zero at follow-up as assessed by QCA.

Figure 1. Freedom from Target Vessel Failure (at 12 months)
Event – free Survival ± 1.5SE; All Lesions Treated (n=476)



	Time after initial procedure (days)								
	0	30	60	90	180	210	240	270	360
Sr-90									
# Entered	244	241	231	222	217	201	195	179	151
# Lost to Follow-up	1	1	4	0	1	0	12	19	145
# Incomplete	0	0	0	0	0	0	0	0	0
# At risk	243.5	240.5	229.0	222.0	216.5	201.0	189.0	169.5	78.5
# Events	2	9	5	5	15	6	4	9	5
# Events/Month		9	5	5	5	6	4	3	2
% Survived	99.2%	95.5%	93.4%	91.2%	84.9%	82.4%	80.7%	76.2%	73.6%
% SE	0.6%	1.4%	1.6%	1.9%	2.3%	2.5%	2.7%	3.0%	37.8%
Placebo									
# Entered	232	230	219	213	203	176	172	160	134
# Lost to Follow-up	0	5	1	1	0	0	4	14	122
# Incomplete	0	0	0	0	0	0	0	0	0
# At risk	232.0	227.5	218.5	212.5	203.0	176.0	170.0	153.0	73.0
# Events	2	6	5	9	27	4	8	12	12
# Events/Month		6	5	9	9	4	8	4	4
% Survived	99.1%	96.5%	94.3%	90.3%	78.3%	76.5%	72.9%	67.1%	60.9%
% SE	0.6%	1.3%	1.6%	2.0%	2.8%	2.9%	3.0%	3.3%	38.1%

Tests Between Groups			
Test	Chi-Square	Deg Frdm	P-Value
Wilcoxon	6.05	1	0.0139
Log-Rank	6.90	1	0.0086

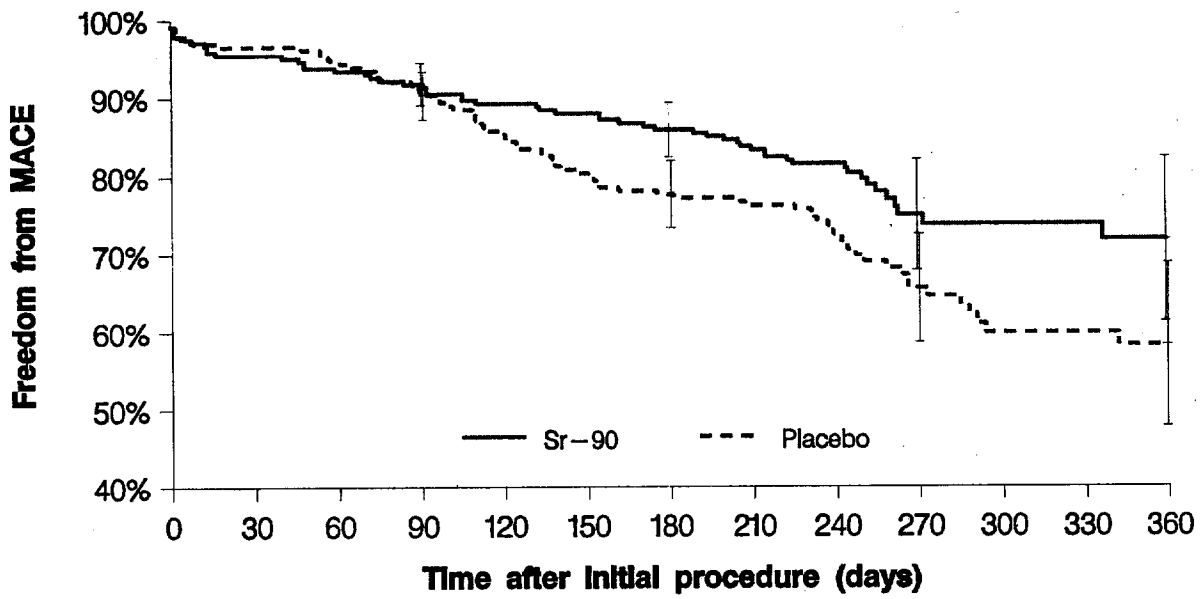
12.5. Acute Procedural Results

Target lesion success was defined as the attainment of a final residual stenosis of <50% (by QCA) using any percutaneous coronary interventional method. Target lesion success was achieved in 99.6% of those patients receiving Sr-90 treatment and 99.1% of the patients receiving placebo. Procedure success was defined as attainment of a final residual stenosis of <50% (by QCA) using any percutaneous method and no in-hospital major adverse cardiac events (MACE). Procedure success was achieved in 97.1% of patients receiving Sr-90 treatment and in 97.0% of patients receiving placebo. Device success was defined as the successful delivery of the Beta-Cath™ System. Device success was achieved in 98.4% of the patients receiving Sr-90 treatment and in 97.8% of patients receiving placebo.

12.6. Survival Analysis

As presented in Figure 2 below, the Kaplan Meier estimate of freedom from MACE (defined as death, Q-wave and non Q-wave myocardial infarction, emergent CABG and target vessel revascularization) at 8 months was 81.4% in the Sr-90 group and 72.2% in the placebo group (p=0.0393).

Figure 2. Freedom from MACE (at 12 months)
Event-free Survival ± 1.5SE; All Patients Treated (N=476)



	Time after initial procedure (days)								
	0	30	60	90	180	210	240	270	360
Sr-90									
# Entered	244	241	230	221	208	202	190	150	37
# Lost to Follow-up	1	2	4	0	1	6	36	81	36
# Incomplete	0	0	0	0	0	0	0	0	0
# At risk	243.5	240.0	228.0	221.0	207.5	199.0	172.0	109.5	19.0
# Events	2	9	5	4	5	6	4	8	1
# Events/Month		9	5	4	2	6	4	3	0
% Survived	99.2%	95.5%	93.4%	91.7%	85.8%	83.2%	81.4%	74.7%	71.4%
% SE	0.6%	1.4%	1.6%	1.8%	2.3%	2.5%	2.9%	4.8%	38.2%
Placebo									
# Entered	232	230	216	209	175	166	156	118	38
# Lost to Follow-up	0	8	2	2	4	7	31	42	37
# Incomplete	0	0	0	0	0	0	0	0	0
# At risk	232.0	226.0	215.0	208.0	173.0	162.5	140.5	97.0	19.5
# Events	2	6	5	9	5	3	7	9	1
# Events/Month		6	5	9	2	3	7	3	0
% Survived	99.1%	96.5%	94.3%	90.2%	77.4%	76.0%	72.2%	65.2%	57.7%
% SE	0.6%	1.2%	1.6%	2.0%	2.9%	3.0%	3.5%	4.7%	37.5%

Tests Between Groups			
Test	Chi-Square	Deg Frdm	P-Value
Wilcoxon	5.28	1	0.0215
Log-Rank	5.77	1	0.0163

12.7. Deaths

Three (3) patients who received radiation died during the START trial. The deaths occurred between 167 and 225 days. One (1) patient died due to coronary artery disease, congestive heart failure, and multi-system dysfunction. It could not be determined if the cause of death was device-related. The cause of death for the other two patients was determined not to be device-related.

12.8. Delivery Failures and Device Malfunctions

There were 476 patients treated with the **Beta-Cath™** System (BCS) in the Stents and Radiation Therapy (START) trial. Device success, defined as successful delivery and treatment with the BCS, was achieved in 467 of the 476 patients (~98%). The table and narratives provided below outline the details of the malfunctions reported as part of the treatment of the 476 patients. The 108 patient treatments with device malfunctions include 89 cases with minor device malfunctions, 10 cases with initial device malfunctions with subsequent treatment success, and 9 device failures preventing treatment success.

Summary of Device Malfunctions	# of Patients
Number of patients enrolled in START trial	**476**
Number of Cases with Device Malfunctions	**108**
Number of Cases with unsuccessful delivery and treatment with the BCS	9
Number of cases reporting initial device malfunctions with subsequent treatment success	10
Number of minor malfunctions not affecting Ability to Treat	89
Number of Cases Resulting In Use of the Temporary Storage Container* (included in the Device Malfunctions category listed above)	**6**
Patients Unsuccessfully Treated and Involving Use of the Temporary Storage Container*	1

*(Bail-Out is defined as physician use of the Novoste Temporary Storage Container)

13. Conclusions Drawn from the Studies

13.1. Safety

The preclinical studies conducted on the **Beta-Cath™** System included biocompatibility, sterilization, and bench testing. The results of the biocompatibility testing demonstrated that the system is acceptable for its intended use in the coronary vasculature. The results of the bench testing demonstrated that the system met its performance requirements.

The results of animal testing conducted by Novoste™ Corporation demonstrated that the **Beta-Cath™** System is safe for clinical use.

The incidence of Major Adverse Cardiac Events (MACE) was significantly lower over the 8-month follow-up period for the treatment group compared to the placebo. The clinical study protocol defined freedom from MACE events as the study's primary safety endpoint. The above MACE results support the system's safety in clinical use and outcomes.

13.2 Effectiveness

The primary efficacy endpoint defined in the clinical protocol was target vessel failure (TVF). The TVF rate was significantly lower at 8-month follow-up for the treatment group compared to placebo. The results of the study's primary efficacy endpoint at 8-months supports the effectiveness of the **Beta-Cath™** System treatment.

21

The study's secondary efficacy endpoint was binary restenosis, defined as the presence of ≥ 50% stenosis at the treatment site, measured by follow-up angiogram at 8 months. The rate of restenosis was significantly lower for all analyzed segments. The reductions in restenosis rates in these segments support the effectiveness of the **Beta-Cath™** System.

The **Beta-Cath™** System treatment resulted in a significantly larger MLD and a lower late loss index than placebo for all analyzed segments, which demonstrates its effectiveness.

13.3 Complication Rates

The rates of observed complications such as thrombosis, abrupt closure, sub-acute closure, bleeding, vascular sequellae, and cerebrovascular accidents were not significantly different between the treatment and placebo groups.

14. Panel Recommendations

At an advisory meeting held on September 11, 2000, the Circulatory System Devices Panel recommended that Novoste Corporation's PMA for the Beta-Cath System be approved subject to submission to, and approval by, the Center for Devices and Radiological Health (CDRH) of the following:

1. The panel recommended that an analysis of the data obtained using only the 30 mm Source Train be performed. The data analysis of the START investigation included both the 30 and 40 mm Source Trains; however, only the 30 mm model is subject of the PMA. Only 5% (n=13 for Sr-90 & n=11 for control) of the data were obtained using the 40 mm source.

2. The panel recommended that an analysis of the data for treatment effect with lesion length be performed. This analysis should demonstrate the importance of lesion length and the interaction term lesion length/Sr-90 when "forced" into the multivariate models.

3. The panel recommended several changes to the labeling for the Beta-Cath System.

4. The panel recommended several changes to the training program.

5. The panel recommended that 5-year follow-up data be gathered for the START investigation cohort.

6. The panel recommended that an additional investigation be conducted at new sites to demonstrate that the corrective actions intended to minimize the incidence of device failures and malfunctions, are successful in reducing the device failure and malfunction rate.

15. CDRH Decision

CDRH concurred with the Circulatory System Devices Panel recommendation of September 11, 2000, and issued a letter to Novoste Corporation on October 10, 2000, advising that its PMA was approvable subject to the following conditions, as recommended by the Panel and required by FDA. In an amendment received by FDA on October 30, 2000, Novoste Corporation submitted the required information.

1. The panel recommended that an analysis of the data obtained using only the 30mm Source Train be performed. The data analysis of the START investigation included both the 30 and 40mm Source Trains; however, only the 30mm model is subject of the PMA. Only 5% (n=13 for Sr-90 & n=11 for control) of the data were obtained using the 40mm source. The analysis was provided in the September 26, 2000, amendment.

2. The panel recommended that an analysis of the data for treatment effect with lesion length be performed. This analysis should demonstrate the importance of lesion length and the interaction term lesion length/Sr-90 when "forced" into the multivariate models. The analysis was provided in the October 30, 2000, amendment.

3. The panel recommended several changes to the labeling for the Beta-Cath System. These recommendations have been incorporated into the final draft labeling of the device.

4. The panel recommended several changes to the training program. A revised training program that incorporates the panel recommendations is provided in the October 30, 2000 submission.

5. The panel recommended that 5-year follow-up data be gathered for the START investigation cohort. Novoste Corporation has agreed to this postapproval requirement, and an outline of the investigational plan for this study is provided in the October 30, 2000, amendment.

6. The panel recommended that an additional investigation be conducted at new sites to demonstrate that the corrective actions intended to minimize the incidence of device failures and malfunctions, are successful in reducing the device failure and malfunction rate. Novoste Corporation has agreed to this postapproval requirement, and an outline of the investigational plan for this study is provided in the October 30, 2000, amendment.

FDA issued an approval order on _____. The applicant's manufacturing facility was inspected on October 17, 2000, and was found to be in compliance with the device Good Manufacturing Practice regulations.

The Beta-Cath System was granted expedited review status on August 26, 1999, because FDA believed that intravascular radiation systems may offer therapeutic benefit in the treatment of in-stent restenosis compared to current treatment methods. Because no legally marketed therapeutic device was available for this indication for use, FDA decided to grant expedited review to intravascular radiation systems for the treatment of in-stent restenosis.

16. Approval Specifications

Instructions for Use: See the labeling.

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

Postapproval Requirements and Restrictions: See approval order.