

9869 '00 OCT 27 MD:13

## Novoste Corporation

Novoste™ Intravascular Brachytherapy  
System

Beta-Cath™ System

P000018

September 11, 2000

## Overview

Andrew M. Green  
Director, Regulatory Affairs  
Novoste Corporation

## Agenda

- Overview  
Andrew M. Green, Director, Regulatory Affairs
- Device and Procedure Summary  
Burton Speiser, MD, Investigator
- Clinical Results  
Jeffrey J. Popma, MD, Principal Investigator
- Special Topics  
Richard E. Kuntz, MD, M.Sc., Director of CDAC
- Clinical Results  
Jeffrey J. Popma, MD, Principal Investigator

## Program Overview

- PMA P000018 Submitted
  - April 17, 2000
- Beta-Cath™ System (30 mm)
  - Specifically designed for Intravascular Brachytherapy in the Catheterization Laboratory
- START Trial
  - Large scale, multi-center, masked, randomized trial to investigate the treatment of in-stent restenosis of native coronary arteries 2.7 mm to 4.0 mm in diameter

---

---

---

---

---

---

---

---

## Rationale for Use of the Beta-Cath™ System

- Demonstrated Efficacy
  - Improved clinical and angiographic outcomes
- Demonstrated Safety
  - Reduced MACE and no increased risk of thrombosis
- Demonstrated Ease of Use
  - Short treatment times, minimal exposure, and clinicians stay with patient

---

---

---

---

---

---

---

---

## Device and Procedure Summary

**Burton Speiser, MD, MS, FACR**  
**Director, Radiation Oncology**  
St. Luke's Regional Medical Center  
St. Joseph's Hospital & Medical Center

---

---

---

---

---

---

---

---

## Financial Disclosure

---

---

---

---

---

---

---

## Use of Radiation for Proliferative Diseases

Long history of use (>50 yrs)

- External
  - Keloids
  - Heterotopic bone formation
- Brachytherapy (Sr-90)
  - Pterygia

---

---

---

---

---

---

---

## Selection Rationale

- Radiation therapy with Sr-90 has been used to treat benign proliferative conditions
- The primary mechanism of in-stent restenosis is intimal hyperplasia
- The therapeutic ratio (dose to target versus dose to no target) is high

---

---

---

---

---

---

---

## Decay scheme for Sr-90

Strontium-90 (Sr-90) Half life 28.8 years

↓ 0.54 MeV beta

Yttrium-90 (Y-90) Half life 64 hours

↓ 2.27 MeV beta

Zirconium-90 (Zr-90) stable

---

---

---

---

---

---

---

---

## Sr-90 Features

### Dose Rate

- Provides short treatment times (3-5 minutes)

### Long Half-Life

- Allows multiple uses (28.8 year half-life)
- Eliminates problems associated with frequent source replacement

### Limited Dose Penetration

- Dose profile matched to artery
- Minimal exposure to non-target tissues (> 1cm)
- Physician is able to stay with patient

---

---

---

---

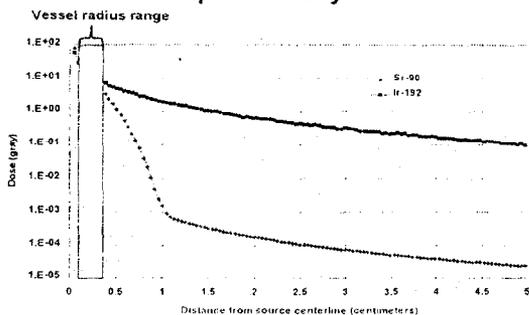
---

---

---

---

## Depth Dose Curves Minimal Exposure Beyond Vessel



---

---

---

---

---

---

---

---

**Radiation Exposure**  
mrem/procedure (whole body)

	<u>Sr-90</u>	<u>Ir-192</u>	<u>Fluoroscopy</u>
Patient	0.3	600	350
RO/IC	0.2 *	<1	4-16

\*Additionally the Radiation Oncologist receives 4 mrem/procedure hand dose due to pre and post treatment device handling

---

---

---

---

---

---

---

---

**Radiation Exposure**

Whole Body Dose Per Procedure From Sr-90

Patient	<0.01% of dose from procedure is from the Sr-90
RO/IC	0.004% of yearly maximum allowable
Cath Lab Personnel	0.0006% of yearly maximum allowable

---

---

---

---

---

---

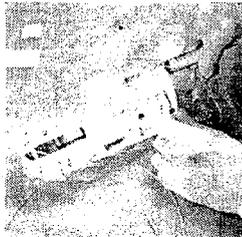
---

---

**Beta-Cath™ System**

Integrated system comprised of four components:

- Source Train
- Transfer Device
- β-Cath™ Delivery Catheter
- System Accessories




---

---

---

---

---

---

---

---

## System Features

- Closed System for Controlled Delivery and Return of Source Train
- Safety Interlocks
- Short Treatment Times (3-5 minutes)
- Physicians Remain with Patient During Entire Procedure

---

---

---

---

---

---

---

---

## System Safety Evaluation

- State of Georgia performed a safety evaluation for the Beta-Cath™ System and issued a Sealed Source and Device Registration Certificate on August 4, 2000 for the Beta-Cath™ System
- The certificate has been included in the Nuclear Regulatory Commission (NRC) Sealed Source and Device Registry

---

---

---

---

---

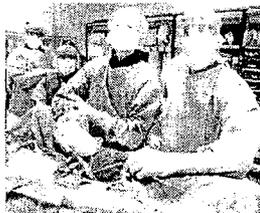
---

---

---

## The Beta-Cath™ System Team

- Radiation Oncologist
- Interventional Cardiologist
- Medical Physicist
- Cath Lab Staff



---

---

---

---

---

---

---

---

### The Beta-Cath™ System Procedure

- Complete angioplasty and prepare the Beta-Cath™ System
- Prescribe dose and treatment time based on visual estimate of reference vessel diameter (RVD)
- Place delivery catheter across injury site
- Deliver radiation
- Remove the system

---

---

---

---

---

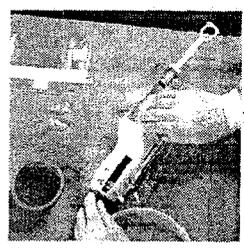
---

---

---

### Beta-Cath™ System Preparation

- Place Transfer Device in Sterile Bag
- Attach Syringe
- Attach Catheter
- Prime System



---

---

---

---

---

---

---

---

### The Beta-Cath™ System Procedure

- Complete angioplasty and prepare the Beta-Cath™ System
- Prescribe dose and treatment time based on visual estimate of reference vessel diameter (RVD)
- Place delivery catheter across injury site
- Deliver radiation
- Remove the system

---

---

---

---

---

---

---

---

## Dose Prescription

- Dose prescribed at a point 2 mm from center of source axis based on visual estimate of reference vessel diameter (RVD) :

18.4\* Gy in RVD  $\geq 2.7$  -  $\leq 3.3$  mm

23\* Gy in RVD  $> 3.3$  -  $\leq 4.0$  mm

\*NIST dose March 2000

---

---

---

---

---

---

---

---

## The Beta-Cath™ System Procedure

- Complete angioplasty and prepare the Beta-Cath™ System
- Prescribe dose and treatment time based on visual estimate of reference vessel diameter (RVD)
- Place delivery catheter across injury site
- Deliver radiation
- Remove the system

---

---

---

---

---

---

---

---

## Delivery Catheter Placement

- Delivery Catheter is placed over existing guide wire and through the guide catheter



- Radiopaque markers facilitate the placement of the Delivery Catheter at the treatment site using fluoroscopy

---

---

---

---

---

---

---

---

## The Beta-Cath™ System Procedure

- Complete angioplasty and prepare the Beta-Cath™ System
- Prescribe dose and treatment time based on visual estimate of reference vessel diameter (RVD)
- Place delivery catheter across injury site
- Deliver radiation
- Remove the system

---

---

---

---

---

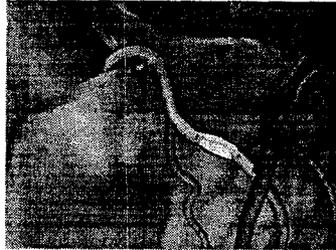
---

---

---

## Source Train Delivery

The Source Train is hydraulically delivered to the treatment site in < 15 seconds



---

---

---

---

---

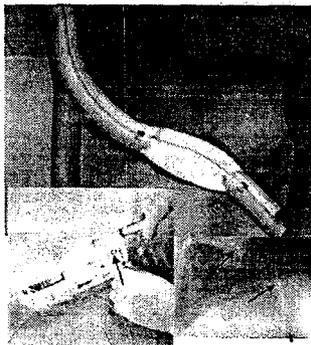
---

---

---

## Treatment Delivery

- The Source Train remains at the treatment site for < 5 minutes
- The Source Train position at the treatment site is monitored with fluoroscopy and the Transfer Device pressure monitor



---

---

---

---

---

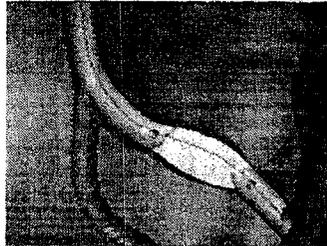
---

---

---

### Source Train Return

- The Source Train is hydraulically returned from the treatment site to the Transfer Device in < 15 seconds



---

---

---

---

---

---

---

---

### The Beta-Cath™ System Procedure

- Complete angioplasty and prepare the Beta-Cath™ System
- Prescribe dose and treatment time based on visual estimate of reference vessel diameter (RVD)
- Place delivery catheter across injury site
- Deliver radiation
- Remove the system

---

---

---

---

---

---

---

---

### Device Performance (START Trial)

#### Device Success

	<u>Patients</u>	<u>Percent</u>
Total Patients Enrolled	476	100.0 %
• Successful Treatment	467	98.1 %
• Catheter not cross lesion	6	1.3 %
• Sources not sent	3	0.6 %

---

---

---

---

---

---

---

---

## Device Performance

### Minor Device Malfunctions (MDMs)

- Total Successful Cases 467/476 (98.1%)
- Successful Cases with MDMs 89/476 (18.7%)
- Reported MDMs
  - Source Transit > 5 secs 54
  - Source/Marker Drift 48
  - Difficult Movement of Catheter 8
  - Others 7

\*Some cases had more than 1 MDM

---

---

---

---

---

---

---

---

## Device Performance

### Observations

- Source Transit > 5 seconds
- Source/Marker Drift

### Causes

- Sub-optimal connection/operation of components
- Inadequate pressure on syringe

---

---

---

---

---

---

---

---

## Response to Experiences from START Trial

- Implemented device modifications to the Beta-Cath™ System submitted to FDA
- Created an in-depth training program that incorporates experiences specifically from the START Trial
- Modified User's Manual to include detailed instructions on component connections, pressure tests and monitoring, and the manual removal procedure

---

---

---

---

---

---

---

---

## Training Program

### Regional Training

- Train individuals and team on device, procedures (treatment and safety), and roles and responsibilities
- Hands on sessions with devices
- Provide detailed instructions for individuals and team, including experiences from trials
- Cross-training for team members on terminology and professional fields
- Radiation Safety Training

---

---

---

---

---

---

---

---

## Training Program

### On-Site (Facility) Training

- Reinforce Training on device, procedures (treatment and safety), and roles and responsibilities
- Provide detailed instructions for individuals and team, including experiences from trials
- Demonstrate procedures used in clinical treatment
- Conduct mock procedure sessions
- Reinforce Radiation Safety Training

---

---

---

---

---

---

---

---

## Training Program

### Proctored Clinical Procedures (3-5)

- Assess team proficiency with procedures and System
- Advise team and individuals on device use and handling

---

---

---

---

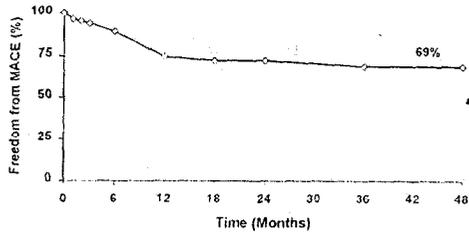
---

---

---

---

### Long Term Safety BERT Trial (4 year freedom from MACE)



Patients at Risk for Each Interval

Time (Months)	0	6	12	18	24	30	36	42	48
Patients at Risk	83	78	74	61	58	--	47	--	17

---

---

---

---

---

---

---

---

---

---

### Clinical Results

Jeffrey J. Popma, MD  
Principal Investigator, START Trial  
Director, Interventional Cardiology  
Brigham & Women's Hospital  
Harvard Medical School

---

---

---

---

---

---

---

---

---

---

### Financial Disclosure

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

---

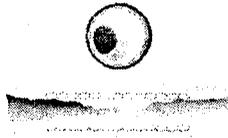
---

---

---

## In-Stent Restenosis

- Over 725,000 percutaneous coronary interventions will be completed in the U.S. each year, of which > 80% will involve a new stent
- Over 100,000 U.S. (20-40%) patients will develop recurrent symptoms due to in-stent restenosis
- Often no effective minimally invasive therapies are available



In-Stent Restenosis

---

---

---

---

---

---

---

---

## Existing Treatment Options

- PTCA only
- Stent in Stent
- Atherectomy (Rotational, DCA)
- Excimer Laser
- Coronary Artery Bypass Surgery

---

---

---

---

---

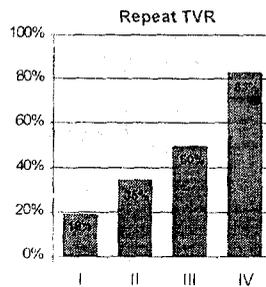
---

---

---

## In-Stent Restenosis Patterns and Recurrence Rates

- Type I**  
≤10mm lesions
- Type II**  
≤10mm Intra-stent lesions
- Type III**  
≤10mm proliferative lesions
- Type IV**  
Total occlusions



Mehran R et al. *Circulation* 1999;100:1872-8.

---

---

---

---

---

---

---

---

## The START Trial

**Purpose:** To assess the safety and effectiveness of intracoronary beta radiation using a Sr-90 source train following successful coronary intervention in patients with "in-stent" restenosis.

---

---

---

---

---

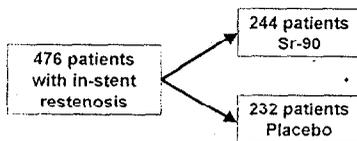
---

---

---

## Trial Design

Prospective, 50 center, triple masked, randomized clinical trial enrolling 476 patients with "in-stent" restenosis



---

---

---

---

---

---

---

---

## Trial Design

**Primary Efficacy Endpoint:** 8-Month Target Vessel Failure (TVF)

**Secondary Efficacy Endpoints:** 8-Month angiographic restenosis, in-stent MLD, and late loss

**Safety Endpoints:** 8-Month MACE and aneurysm formation

---

---

---

---

---

---

---

---

## Endpoint Definitions

### *Target Vessel Failure (TVF)*

- Death, Q wave and non-Q wave MI, and Target Vessel Revascularization (TVR) including CABG that could not be clearly attributed to a vessel other than the target vessel

### *Major Adverse Cardiac Events (MACE)*

- Death, Q wave and non-Q wave MI, emergent CABG, and TVR

---

---

---

---

---

---

---

---

## Endpoint Definitions

### *Target Vessel Revascularization (TVR)*

- Any clinically-driven repeat percutaneous intervention of the target vessel or CABG of the target vessel

### *Target Lesion Revascularization (TLR)*

- Any clinically-driven repeat percutaneous intervention of the target lesion or CABG of the target vessel

---

---

---

---

---

---

---

---

## Trial Support

Data Coordinating Center	CDAC: Richard E. Kuntz, MD
Angiographic Laboratory	CRF: Alexandra J. Lansky, MD
IVUS Core Laboratory	Stanford: Peter J. Fitzgerald, MD
EKG Core Laboratory	CDAC: Peter Zimetbaum, MD
DSMB Committee	Chairman: Thomas Ryan, MD
Clinical Events Committee	Chairman: David Cohen, MD

---

---

---

---

---

---

---

---

### Major Inclusion Criteria

- Single lesion, single vessel intervention
- In-stent restenosis > 50% (by visual estimate)
- Target lesion in vessels between 2.7 and 4.0 mm in diameter
- Target lesion length treatable with 20 mm balloon w/30 mm Source Train or a 30 mm balloon w/40 mm Source Train

---

---

---

---

---

---

---

---

### Major Exclusion Criteria

- Multi-vessel coronary intervention
- Target lesion residual stenosis >30%
- Unprotected left main disease
- Prior chest radiotherapy

---

---

---

---

---

---

---

---

### Dose Prescription

Dose prescribed at a point 2 mm from center of source axis based on visual estimate of reference vessel diameter (RVD) :

- 18.4\* Gy in RVD  $\geq 2.7 - \leq 3.3$  mm
- 23\* Gy in RVD  $> 3.3 - \leq 4.0$  mm

\*NIST dose, March 2000

---

---

---

---

---

---

---

---

## Antiplatelet Therapy (APT)

September 21, 1998

- Protocol Initiation
- APT at Physician Discretion

March 19, 1999

- Modified APT
- Recommended minimum of 90 days with new stents\*

\*Based on the recommendation of the Beta-Cath™ System Trial Data Safety Monitoring Board for the Beta-Cath™ System Trial patients

---

---

---

---

---

---

---

---

## 8-Month Follow-up

	Placebo	Sr-90
Randomized	n=232	n=244
Clinical Follow-up*	96.2%	96.3%
QCA	81.0%	83.2%

\* Reflects updated clinical follow-up post 8-month report

---

---

---

---

---

---

---

---

## Baseline Clinical Characteristics

	Placebo (N=232)	Sr-90 (N=244)
Age, yrs	61.1	61.5
Men, %	63.4	68.4
Diabetes, %	32.3	30.7
Prior MI, %	47.8	46.7
Prior CABG, %	23.7	21.4

---

---

---

---

---

---

---

---

### Baseline Angiographic (QCA) Characteristics

	Placebo	Sr-90
Vessel Diameter, mm	2.77	2.76
MLD, mm	0.98	0.98
% Stenosis	64.2	64.2
Lesion Length, mm	16.0	16.3
% LAD	41.3	43.2

### Devices Used

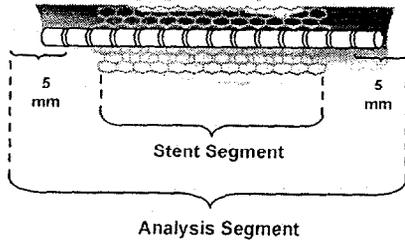
	Placebo	Sr-90
Debulking Devices, %		
DCA	0.9	0.0
RA	39.8	43.9
ELCA	7.4	5.7
New Stents*, %	19.8	20.9

\* Stent placement within the analysis segment was discouraged in the START Trial

### Antiplatelet Therapy

Duration (days)	All Patients (n=476)	Patients with New Stents (n=101)
0 to 30	75%	63%
31 to 60	10%	11%
61 to 90	12%	23%
> 90	3%	3%

### START QCA Analysis




---

---

---

---

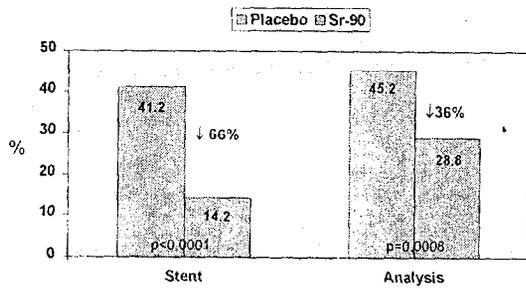
---

---

---

---

### 8-Month Angiographic Restenosis




---

---

---

---

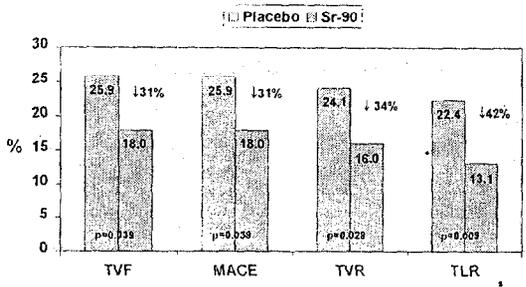
---

---

---

---

### START Trial 8-Month Clinical Outcomes




---

---

---

---

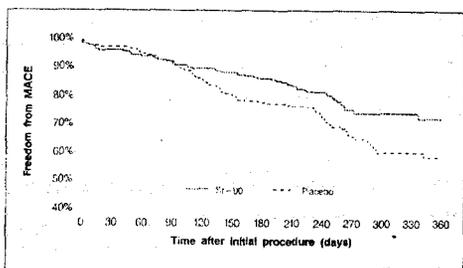
---

---

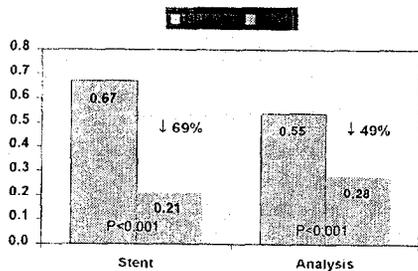
---

---

## MACE-Free Survival



## 8-Month Late Loss (mm)



## Safety Results

	Placebo (n=232)	Sr-90 (n=244)
<b>Thrombosis</b>		
In-hospital-30 days	1 (0.4%)	0 (0.0%)
31-240 days	0 (0.0%)	0 (0.0%)*
<b>Angiographic Total Occlusion at Follow-up</b>		
Total	7 (3.0%)	8 (3.3%)
New stent	4/35	3/42
No new stent	3/153	5/156

\* One patient recently adjudicated by CEC had thrombosis at day 244

## CEC Findings

**Patient 19/2** – On 3/2/99 the patient's mid RCA was successfully treated in the radiation group; post radiation treatment a stent was placed for a Grade A dissection. The residual stenosis was 48% as determined by the angiographic core lab. On 11/1/99 (244 days) patient presented with chest pain and EKG changes (new inferior-posterior lateral Q wave). The angiogram showed a total occlusion of the mid RCA. The proximal and mid RCA were treated with balloon angioplasty and a stent was placed in the mid RCA.

---

---

---

---

---

---

---

---

## 8-Month Safety Results

	Placebo (n= 232)	Sr-90 (n= 244)
Death	1 (0.4%)	3 (1.2%)
MI	7 (3.0%)	4 (1.6%)
Q-wave	0	0
non-Q-wave	7	4
Aneurysm	0 (0%)	1 (0.5%)*

\* No aneurysm formation; present at baseline, without significant change at follow-up.

---

---

---

---

---

---

---

---

## Description of Deaths

- **Patient 17/5** – 77 y/o patient successfully treated with radiation on 12/7/98; Died 193 days after treatment following complications, including pneumonia, following surgical resection of a colonic polyp. **Official causes of death were CAD, CHF, and multi-system organ dysfunction.**
  
- **Patient 20/409** – 83 y/o patient successfully treated with radiation (40 mm Source Train) on 3/4/99. Died 225 days after treatment. **Cause of death was metastatic prostate and rectal cancer.**

---

---

---

---

---

---

---

---

## Description of Deaths

- Patient 63/16 – 83 y/o patient successfully treated with radiation on 3/5/99. Died 167 days after treatment, two days following left upper lobectomy for lung cancer. Death reported as post-operative acute MI.
- Patient 56/5 – 69 y/o patient successfully treated in the placebo group on 1/22/99. Died 102 days after treatment, with the official cause of death reported as “cardiac arrest.”

---

---

---

---

---

---

---

---

## START Trial 8-Month Outcome Summary

- Significant Reductions in all outcome parameters (TVF, MACE, TVR, TLR, Angiographic Restenosis, and Late Loss)
- No increased risk of thrombosis
- No aneurysm formation

---

---

---

---

---

---

---

---

## Specific Clinical Topics

Richard E. Kuntz, MD  
Chief, Clinical Biometrics Division  
Brigham & Women's Hospital  
Harvard Medical School

---

---

---

---

---

---

---

---

**Financial Disclosure**

---

---

---

---

---

---

---

---

**Clinical Impact of  
Minor Device Malfunctions  
(MDMs)**

---

---

---

---

---

---

---

---

**MDM Analysis**

87.2% of Minor Device Malfunctions (MDMs) were reported as :

- Source Drift
- Source Transit > 5 sec

Remainder of MDMs were categorized as non-radiation related

---

---

---

---

---

---

---

---

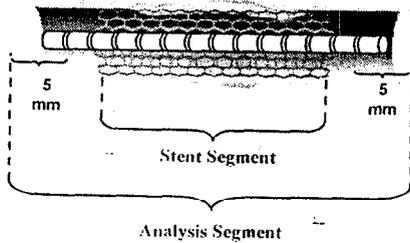


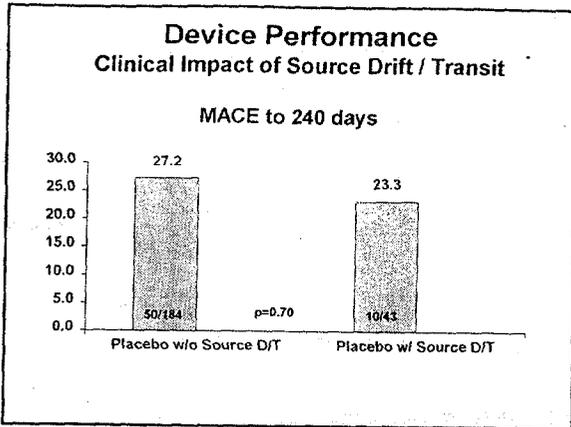
**Device Performance  
Conclusions**

- Source Drift and Source Transit > 5 seconds were prospectively collected and identified as the primary minor device malfunctions
- The sponsor has proposed measures to reduce the occurrence of source drift and source transit
- The clinical impact of MDMs demonstrated no statistical difference in safety and efficacy of the Beta-Cath™ System in the treat of in-stent restenosis

**Edge Analysis**

**START QCA Analysis**






---

---

---

---

---

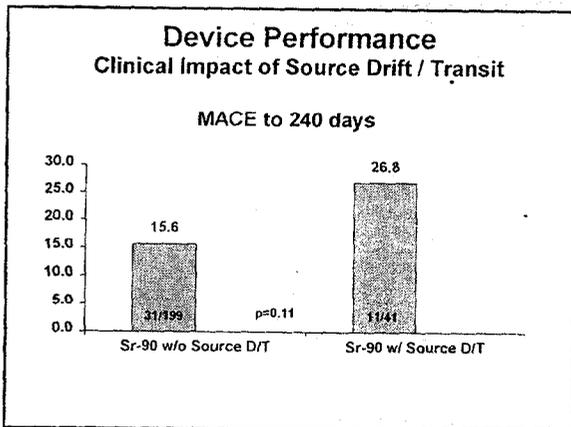
---

---

---

---

---




---

---

---

---

---

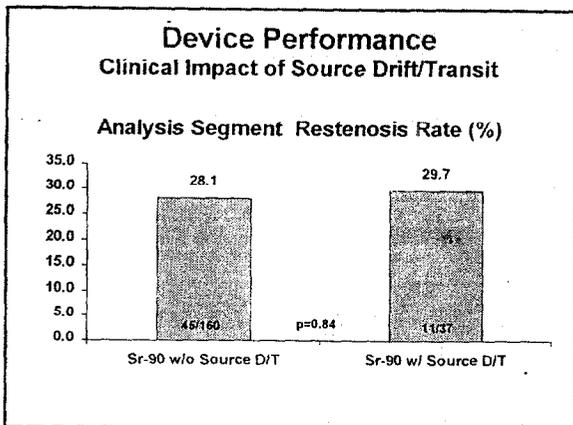
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

**Device Performance  
Conclusions**

- Source Drift and Source Transit > 5 seconds were prospectively collected and identified as the primary minor device malfunctions
- The sponsor has proposed measures to reduce the occurrence of source drift and source transit
- The clinical impact of MDMs demonstrated no statistical difference in safety and efficacy of the Beta-Cath™ System in the treat of in-stent restenosis

---

---

---

---

---

---

---

---

**Edge Analysis**

---

---

---

---

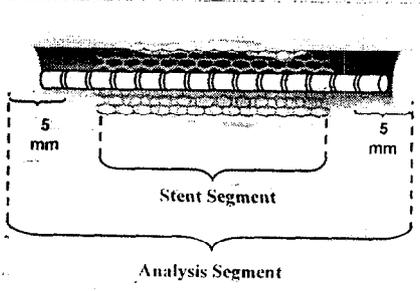
---

---

---

---

**START QCA Analysis**



---

---

---

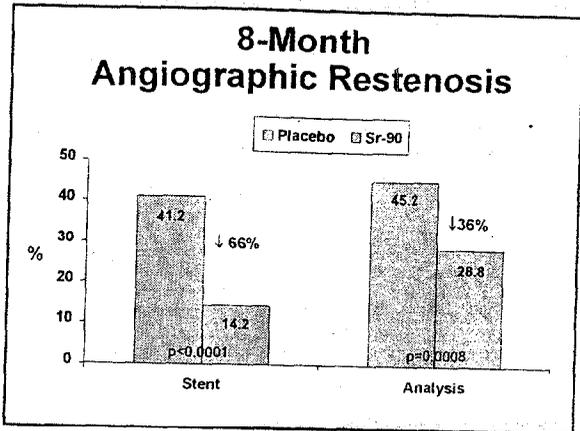
---

---

---

---

---




---

---

---

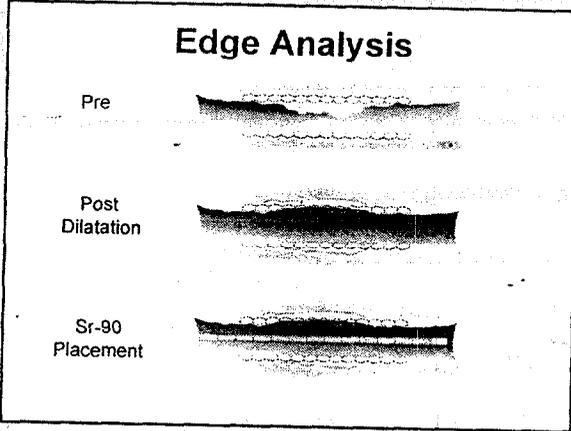
---

---

---

---

---




---

---

---

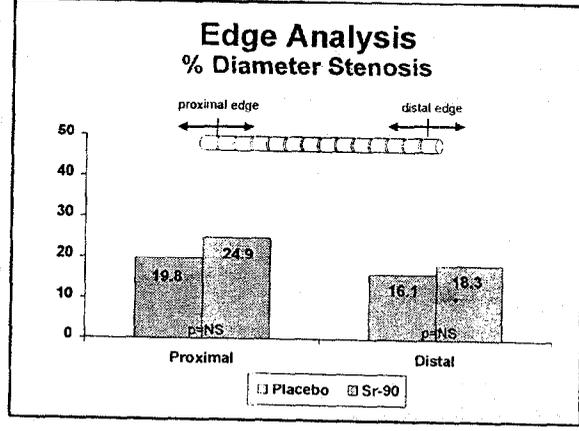
---

---

---

---

---




---

---

---

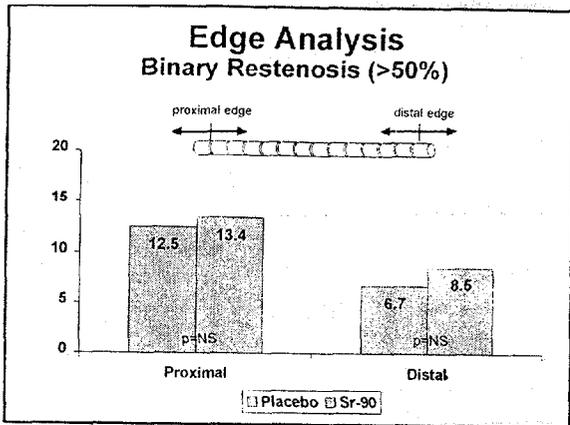
---

---

---

---

---




---

---

---

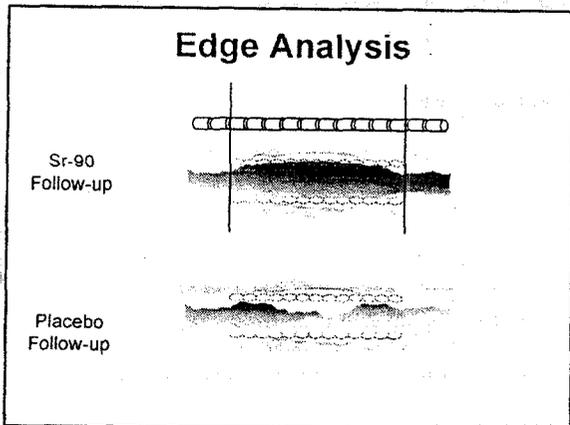
---

---

---

---

---




---

---

---

---

---

---

---

---

### Edge Analysis Conclusions

Difference in restenosis rates between the analysis and stent segments was due in part to :

- the effectiveness of the treatment of Sr-90 and
- the masking of the progression of disease in the analysis segment

---

---

---

---

---

---

---

---

## Conclusions

Jeffrey J. Popma, MD  
Principal Investigator, START Trial  
Director, Interventional Cardiology  
Brigham & Women's Hospital  
Harvard Medical School

---

---

---

---

---

---

---

---

## Conclusions

- Medical Need to treat in-stent restenosis
  - Difficult and growing population
  - No approved minimally invasive alternatives
- START Trial
  - Conclusions based on randomized, triple-masked, placebo-controlled study
  - Largest in-stent restenosis device trial

---

---

---

---

---

---

---

---

## Clinical Conclusions

**Pre-specified hypotheses were achieved with statistical significance**

- TVF reduced by 31% (p=0.039)
- MACE reduced by 31% (p=0.039)
- TVR reduced by 34% (p=0.026)
- TLR reduced by 42% (p=0.008)

---

---

---

---

---

---

---

---

## Angiographic Conclusion

Pre-specified restenosis hypotheses were achieved with statistical significance

- Stent Segment reduced by 66% (p<0.001)
- Analysis Segment reduced by 36% (p=0.001)

---

---

---

---

---

---

---

---

## Safety Conclusions

Sr-90 vs Placebo

- No difference in death (3 vs 1)
- No difference in MI (4 vs 7)
- No difference in Late Thrombosis (1\* vs 0)
- No difference in Total Occlusions (8 vs 7)
- No difference in Aneurysm (1\* vs 0)

---

---

---

---

---

---

---

---

## Conclusions

- Statistically significant differences in all safety and efficacy endpoints demonstrate that the Beta-Cath™ System is a viable treatment for in-stent restenosis.
- The safety and efficacy outcomes justify the risk/benefit ratio for the use of the Beta-Cath™ System for the treatment of in-stent restenosis.

---

---

---

---

---

---

---

---