

Summary of Safety and Effectiveness Data

The Cordis Checkmate™ System

Cordis Corporation

1. General Information

Device Generic Name	Intravascular Brachytherapy System
Device Trade Name	Cordis Checkmate™ System
Applicant's Name and Address	Cordis Corporation 14201 N.W. 60 th Avenue P.O. Box 025700 Miami, FL 33102-5700
PMA Application Number	P990036
Date of Panel Recommendation	06/19/00
Date of Notice of Approval to the Applicant	TBD

2. Indications and Usage

The Cordis Checkmate System is intended for the delivery of therapeutic doses of gamma radiation for the purpose of reducing in-stent restenosis. The system is for use in the treatment of native coronary arteries with in-stent restenosis following percutaneous revascularization using current interventional techniques.

- This system is for use in vessels 2.75 – 4.0 mm in diameter and for lesions up to and including 45 mm in length.

3. Contra indications

Intracoronary radiation therapy is generally contraindicated in the following patient types:

- Patients in whom antiplatelet and/or anticoagulant therapy is contraindicated.

4. Warnings and Precautions

- 4.1 Warning Checkmate Catheter
- 4.2 Precautions Checkmate Catheter
- 4.3 Warnings Checkmate Delivery System
- 4.4 Precautions Checkmate Delivery System

For additional precautions, see also Section 11, "Operator Manual" in the Instructions for Use.

**4.1 Warnings
Checkmate
Catheter**

- Avoid placement of a new stent during the radiation procedure as it has been associated with a higher rate of late thrombosis in comparison to the placebo arm. Every attempt should be made to avoid new stent placement in the irradiated area. However, if placement of a new stent was necessary, it is recommended that the patient be placed on antiplatelet therapy for 12 months. If no new stent was placed it is recommended to prescribe antiplatelet therapy for 6 months (See also Sections 10.4, 10.5 and 10.6).
- The Cordis Checkmate System should not be used for indexing procedures as it may result in overexposure of overlapping treatment areas.

**4.2 Precautions
Checkmate
Catheter**

- The Cordis Checkmate Catheter should only be used in combination with the Cordis Checkmate Delivery System.
- Only physicians who have received adequate training should perform intravascular brachytherapy.
- Intravascular brachytherapy should only be performed at hospitals with the appropriate licensing from the governing nuclear regulatory agency for use of radiation for intravascular therapeutic purposes.
- Intravascular brachytherapy should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Do not expose the product to solvents (e.g. alcohol, hydrogen peroxide).
- Follow the site specific radiation safety procedures.

**4.3 Warnings
Checkmate
Delivery System**

- Avoid placement of a new stent during the radiation procedure as it has been associated with a higher rate of late thrombosis in comparison to the placebo arm. Every attempt should be made to avoid new stent placement in the irradiated area. However, if placement of a new stent was necessary, it is recommended that the patient be placed on antiplatelet therapy (See also Sections 10.4, 10.5 and 10.6).
- This product contains a gamma radiation emitting source and should be handled only by authorized personnel.
- The Cordis Checkmate System should not be used for indexing procedures as it may result in overexposure of overlapping treatment areas.
- Verify the source location if the deliver device, cart, or catheter are moved or if the patient shifts position during the treatment time to ensure that proper source placement is maintained.

**4.4 Precautions
Checkmate
Delivery System**

General Precautions:

- The Cordis Checkmate Delivery System should only be used in combination with the Cordis Checkmate Catheter.
- Only physicians who have received adequate training should perform intravascular brachytherapy.
- Intravascular brachytherapy should only be performed at hospitals with the appropriate licensing from the governing nuclear regulatory agency for use of radiation for intravascular therapeutic purposes.
- Intravascular brachytherapy should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Do not expose the source ribbon to solvents (e.g. alcohol, hydrogen peroxide).
- If required, the outside of the delivery device may be wiped with a cloth and alcohol solution. Do not pour liquids directly on the device.
- The Checkmate Delivery Device weighs approx. 45 lbs. Use caution when removing the delivery device from the transport container, lifting it or positioning it, to prevent injury. (Two person lift.)
- The delivery device should only be placed on tables or carts (with locking wheels) capable of supporting the device's weight. If accidentally dropped from the table or cart, survey the delivery device to ensure the source is still in the correct position.

Radiation Precautions:

- Follow the As Low As Reasonably Achievable (ALARA) policy guidelines.
- Follow the site specific radiation safety procedures.
- When not in use, the Ir-192 source ribbon and delivery device should be stored in a secure, locked area with restricted access separate from other medical devices. Radiation safety regulations for storage of radioactive material should be strictly adhered to.
- Use radiation detection instruments (Geiger counter or appropriate survey meter) while inspecting, unpacking and using Ir-192 source ribbons.
- Use appropriate radiation detection methods (e.g. film badges, ring dosimeters) when handling radioactive source ribbons per the institutional radiation safety protocol and as defined by the governing nuclear regulatory agency.
- Keep the Ir-192 source ribbon in the delivery device at all times except during use.
- Avoid contact with the seeds in the radioactive source ribbon or any unnecessary radiation exposure. Always use long forceps or tongs when handling Ir-192 source ribbons.
- If a seed is cut accidentally during an emergency procedure, be careful in disposing of the damaged seed (use an appropriately shielded container). Check the tools and area for possible contamination and survey the area thoroughly. Do not use tools again until they are completely clean (free of contamination)

**4.4 Precautions
Checkmate
Delivery System
(Cont.)**

- Use appropriate lead shielding when handling Ir-192 source ribbons.
- Survey the area where the Ir-192 source ribbons are used thoroughly after each use and make sure that no seeds or ribbons are lost. Each Ir-192 seed is a radioactive source and, as such, should be accounted for.
- In case of loss of seed(s) or an accident involving the seed(s), it should be reported immediately to the proper Nuclear Regulatory Agency.
- For safe handling of radioactive sources, three factors (time, distance and shielding) should be observed:
 - Time: Less time, less radioactive exposure.
 - Distance: More distance from the radioactive source, less radiation exposure.
 - Shielding: Better shielding (thicker lead or lead glass shielding), less radiation exposure.

**5. Special
Considerations**

Safety and effectiveness has not been demonstrated in the following populations:

- Patients with previous intravascular brachytherapy of the same vessel segment or previous radiation treatment in the immediate vicinity.
- Patients who are pregnant.
- Patients with known genetic radiation sensitivity disorders (e.g. ataxia-telangiectasia, etc.)
- Patients with saphenous vein graft disease.

6. Device Description

The Cordis Checkmate System consists of 2 components: the Cordis Checkmate Catheter and the Cordis Checkmate Delivery System

6.1

The Cordis Checkmate Catheter includes:

1. **A Radiation Delivery Catheter (Checkmate catheter)**
 - A single lumen catheter with a distal rapid exchange tip which serves as a conduit for the non-radioactive dummy ribbon and the radioactive Ir-192 source ribbon. The catheter contains a single, closed ended source lumen that is isolated from patient and blood contact. The source lumen is accessed through a single port hub.
 - A single radiopaque marker identifies the distal end of the source lumen and is located slightly proximal to the guidewire port.
 - A guidewire (not included) exits the catheter at the port, approximately 4 mm from the distal tip of the catheter.
 - The catheter has two (2) exit markers (optional) along the proximal shaft that indicate, approximately, the exit of the distal tip of the Checkmate Catheter from the guiding catheter (brachial at 90 cm and femoral at 100 cm from the distal tip).
 - An additional (optional) marker indicates the transition from a smaller catheter shaft diameter (distal) to a larger shaft diameter (proximal).
2. **A Non-Radioactive Dummy Ribbon**
 - Provides reinforcement of the Checkmate Catheter during shipment and upon introduction into the vascular system and is used to position the Checkmate Catheter across the target lesion prior to use of a radioactive source ribbon.
 - This yellow ribbon contains a strand of non-radioactive seeds divided and/or bracketed by radiopaque markers that match the length and configuration of the radioactive zone of the source ribbon.
3. **A Source Lumen Plug**
 - Prevents movement of the non-radioactive dummy ribbon during Checkmate Catheter insertion and manipulation and is removable.

6.2

The **Cordis Checkmate Delivery System** includes:

1. **Iridium 192 (Ir-192) Source Ribbon**
 - This ribbon contains a strand of radioactive seeds (6, 10 or 14) with a proximal and distal radiopaque marker.
2. **Delivery Device**
 - Provides the lead shielded housing of the Ir-192 source ribbon during shipment, storage and transportation to and from cath lab. The radioactive section of the source ribbon is completely encased in the shielded delivery device.
 - The proximal end of the source ribbon protrudes from the body of the delivery device and is coiled and held next to the delivery device when not in use.
 - Both ends of the delivery device are protected by latched end caps.
 - A fitting located on the proximal end of the delivery device secures the ribbon in place when not in use.
 - A threaded cap is located on the distal end of the delivery device when not in use. When in use, the threaded cap is replaced with a luer connector.
 - The source ribbon is fed by hand from the proximal end of the delivery device into the Checkmate Catheter, which is attached to the luer connector.
 - Each delivery device is supplied with a Certificate of Activity (Bill of Lading) detailing the radioactive levels and decay profile for the isotope contained within and the "Use By" date of the radioactive source ribbon.

7. 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.

8. Marketing History

The Checkmate catheter and dummy ribbon have been released for sale in Austria, Belgium, Germany, Greece, Italy, the Netherlands and Hong Kong. There have been no countries from which these devices have been withdrawn from marketing for any reason related to safety or effectiveness. The Ir-192 source ribbon packaged in the delivery device described in this PMA has not been released for sale anywhere.

9. Adverse Events

A total of 252 patients were enrolled in a single multi-center randomized clinical trial (GAMMA-I trial) to evaluate the use of the Cordis Checkmate system for treatment of in-stent restenosis. These patients form the basis for the reported observed events (see Table 9.1).

Additionally, data is provided on the SCRIPPS-I trial (single center, randomized trial, 60 patients) and the WRIST trial (single center, randomized trial, 130 patients). Both studies used the Ir-192 Source Ribbon for treatment of in-stent restenosis.

	Radiation (N=131)	Placebo (N=121)	Relative Risk [95% CI]	Difference [95% CI]
Any MACE (Death, MI, Em. CABG, TLR)	28.2% (37/131)	43.8% (53/121)	0.64 [0.46, 0.90]	-15.6% [-27.3%, -3.8%]
Death	3.1% (4/131)	0.8% (1/121)	3.69 [0.49, 28.03]	2.2% [-1.1%, 5.6%]
Myocardial Infarction (Q or Non-Q)	12.2% (16/131)	6.6% (8/121)	1.85 [0.83, 4.10]	5.6% [-1.5%, 12.7%]
Q Wave MI	5.3% (7/131)	3.3% (4/121)	1.62 [0.49, 5.33]	2.0% [-3.0%, 7.0%]
Non-Q Wave MI	6.9% (9/131)	3.3% (4/121)	2.08 [0.68, 6.40]	3.6% [-1.8%, 8.9%]
Emergent CABG	0.0% (0/131)	0.0% (0/121)	- [-,-]	0.0% [0.0%, 0.0%]
Target Lesion Revascularization	24.4% (32/131)	42.1% (51/121)	0.58 [0.41, 0.83]	-17.7% [-29.2%, -6.3%]
TL-CABG	9.9% (13/131)	20.7% (25/121)	0.48 [0.26, 0.88]	-10.7% [-19.6%, -1.9%]
TL-PTCA	19.8% (26/131)	27.3% (33/121)	0.73 [0.46, 1.14]	-7.4% [-17.9%, 3.0%]
Perforation	0.8% (1/131)	0.0% (0/121)	- [-,-]	0.8% [-0.7%, 2.3%]
Bleeding Complications	2.3% (3/131)	0.8% (1/121)	2.77 [0.32, 23.91]	1.5% [-1.6%, 4.5%]
Vascular Complications	3.1% (4/131)	1.7% (2/121)	1.85 [0.35, 9.66]	1.4% [-2.3%, 5.1%]
Hematological Dyscrasia	0.8% (1/131)	1.7% (2/121)	0.46 [0.04, 4.76]	-0.9% [-3.6%, 1.8%]
CVA	0.8% (1/131)	2.5% (3/121)	0.31 [0.04, 2.58]	-1.7% [-4.9%, 1.4%]
Acute Stent Thrombosis (to 30 days)	0.8% (1/131)	1.7% (2/121)	0.46 [0.04, 4.76]	-0.9% [-3.6%, 1.8%]
Late Thrombosis	5.3% (7/131)	0.8% (1/121)	6.47 [0.81, 51.79]	4.5% [0.3%, 8.7%]
Late Total Occlusion	12.6% (14/111)	5.8% (6/103)	2.17 [0.87, 5.42]	6.8% [-0.8%, 14.4%]

Numbers are % (counts/sample size) or Mean ± SD.
 Relative Risk = Radiation/Placebo
 Difference = Radiation - Placebo

SE = $\sqrt{\{(1-p_1)/n_{11} + (1-p_2)/n_{21}\}}$
 SE = $\sqrt{p_1 \cdot q_1/n_1 + p_2 \cdot q_2/n_2}$

CI = Confidence Interval
 CI = $RR \cdot \exp(\pm 1.96 \cdot SE)$
 CI = $Diff \pm 1.96 \cdot SE$

As shown in Table 9.1, 5 patients died during the GAMMA-I trial. The 5 deaths occurred between 0 and 264 days post radiation and were due to: cardiac tamponade (n=1), hemorrhage following by-pass surgery (n=1), sudden cardiac death (n=2) and suicide (n=1). There were no device delivery failures and there were 11 cases of stent thrombosis, 3 acute stent thrombosis and 8 late thrombosis.

	Radiation (N=29)	Placebo (N=31)	Relative Risk [95% CI]	Difference [95% CI]
Any MACE (Death, MI, Em. CABG, TLR)	20.7% (6/29)	22.6% (7/31)	0.92 [0.35, 2.42]	-1.9% [-22.7%, 18.9%]
Death	0.0% (0/29)	0.0% (0/31)	-[-,-]	0.0% [-,-]
Myocardial Infarction (Q or Non-Q)	6.9% (2/29)	3.2% (1/31)	2.14 [0.21, 21.40]	3.7% [-7.5%, 14.8%]
Q Wave MI	0.0% (0/29)	0.0% (0/31)	-[-,-]	0.0% [-,-]
Non-Q Wave MI	6.9% (2/29)	3.2% (1/31)	2.14 [0.21, 21.40]	3.7% [-7.5%, 14.8%]
Emergent CABG	0.0% (0/29)	0.0% (0/31)	-[-,-]	0.0% [-,-]
Target Lesion Revascularization	17.2% (5/29)	22.6% (7/31)	0.76 [0.27, 2.14]	-5.3% [-25.5%, 14.8%]
TL-CABG	3.4% (1/29)	3.2% (1/31)	1.07 [0.07, 16.68]	0.2% [-8.9%, 9.3%]
TL-PTCA	13.8% (4/29)	19.4% (6/31)	0.71 [0.22, 2.27]	-5.6% [-24.3%, 13.2%]
Perforation	0.0% (0/29)	0.0% (0/31)	-[-,-]	0.0% [-,-]
Bleeding Complications	0.0% (0/29)	6.5% (2/31)	0.00 [-,-]	-6.5% [-15.1%, 2.2%]
Vascular Complications	0.0% (0/29)	0.0% (0/31)	-[-,-]	0.0% [-,-]
CVA	0.0% (0/29)	3.2% (1/31)	0.00 [-,-]	-3.2% [-9.4%, 3.0%]
Acute Stent Thrombosis (to 30 days)	3.4% (1/29)	0.0% (0/31)	-[-,-]	3.4% [-3.2%, 10.1%]
Late Thrombosis	0.0% (0/29)	0.0% (0/31)	-[-,-]	0.0% [-,-]
Late Total Occlusion	3.6% (1/28)	0.0% (0/28)	-[-,-]	3.6% [-3.3%, 10.5%]

Numbers are % (counts/sample size) or Mean ± SD. CI = Confidence Interval
 Relative Risk = Radiation/Placebo SE = sqrt $\{((1-p_1)/n_{11} + (1-p_2)/n_{21})\}$ CI = RR*exp(±1.96*SE)
 Difference = Radiation - Placebo SE = sqrt $(p_1*q_1/n_1 + p_2*q_2/n_2)$ CI = Diff±1.96*SE
 Late total occlusions were those occlusions in a patient who had angiographic documentation of 100% stenosis at the target site 31 days or more after the index procedure.

As shown in Table 9.2, there were no deaths in the SCRIPPS-I trial. There were no device delivery failures and there was 1 acute stent thrombosis.

	Radiation (N=65)	Placebo (N=65)	Relative Risk [95% CI]	Difference [95% CI]
Any MACE (Death, MI, Em. CABG, TLR)	29.2% (19/65)	67.7% (44/65)	0.43 [0.29, 0.65]	-38.5% [-54.6%, -22.3%]
Death	4.6% (3/65)	6.2% (4/65)	0.75 [0.18, 3.22]	-1.5% [-9.4%, 6.4%]
Myocardial Infarction (Q or Non-Q)				
Q Wave MI	0.0% (0/65)	0.0% (0/65)	-[-,-]	0.0% [-,-]
Non-Q Wave MI	16.9% (11/65)	12.3% (8/65)	1.38 [0.59, 3.20]	4.6% [-7.7%, 16.9%]
Target Lesion Revascularization	15.4% (10/65)	63.1% (41/65)	0.24 [0.13, 0.44]	-47.7% [-62.6%, -132.8%]
CABG	7.7% (5/65)	6.2% (4/65)	1.25 [0.35, 4.45]	-1.5% [-7.3%, 10.4%]
PTCA	9.2% (6/65)	61.5% (40/65)	0.15 [0.07, 0.33]	-52.3% [-66.3%, -38.3%]
Vascular Complications	12.3% (8/65)	12.3% (8/65)	1.00 [0.40, 2.50]	0.0% [-11.5%, 11.5%]
TVR (not involving target lesion)	12.3% (8/65)	4.6% (3/65)	2.67 [0.74, 9.61]	7.7% [-1.9%, 17.3%]
CVA	0.0% (0/65)	0.0% (0/65)	-[-,-]	0.0% [-,-]
Subacute Closure (to 30 days)	0.0% (0/65)	0.0% (0/65)	-[-,-]	0.0% [-,-]
Late Thrombosis**	3.1% (2/65)	0.0% (0/65)	-[-,-]	3.1% [-1.1%, 7.3%]
Late Total Occlusion**	13.8% (9/65)	1.5% (1/65)	9.00 [1.17, 69.02]	12.3% [3.4%, 21.2%]

Numbers are % (counts/sample size) or Mean ± SD. CI = Confidence Interval
 Relative Risk = Radiation/Placebo SE = sqrt $\{((1-p_1)/n_{11} + (1-p_2)/n_{21})\}$ CI = RR*exp(±1.96*SE)
 Difference = Radiation - Placebo SE = sqrt $(p_1*q_1/n_1 + p_2*q_2/n_2)$ CI = Diff±1.96*SE
 * One patient died on day 212 and one on day 214.
 ** Additionally, the rates of late thrombosis and late total occlusion for the crossover group are 5.1% (2/39) and 12.8% (5/39), respectively.

As shown in Table 9.3, 7 patients died during the WRIST trial. The 7 deaths occurred between 0 and 214 days post radiation, all were cardiac deaths. There were no device delivery failures and there were 2 cases of late thrombosis.

10. Summary of Preclinical Studies

10.1 Laboratory Studies (Summary)

- In-vitro testing conducted on the Cordis Checkmate System components which are included in this submission revealed that the design, specifications, integrity and other physical functions and characteristics of the devices are suitable for their intended use.
- Biocompatibility testing performed in accordance with ISO10993-1 on patient contacting materials revealed that all tested materials are biocompatible and safe for their intended use.

A more detailed description follows in section 10.1.1 – 10.1.5.

10.1.1 Laboratory Testing

Product testing of the Cordis Checkmate Catheter, dummy ribbon, the source lumen plug, Ir-192 source ribbon and delivery device was conducted to ensure that these components perform in accordance with their design specifications. The following tests were successfully performed.

Test and Test Results	
1.	<i>Visual Inspection of Packaging:</i> Ninety (90) packages were visually inspected; all units met the test acceptance criteria.
2.	<i>Functional Testing of Pouch:</i> Functional testing was performed on 15 pouches, 45 pouches were visually inspected; all units met the test acceptance criteria.
3.	<i>Visual Inspection of the Catheter, Dummy Ribbon and Source Ribbon:</i> Forty-five (45) catheters, 60 dummy ribbons and 24 source ribbons were visually inspected; all units met the test acceptance criteria.
4.	<i>Dimensional Inspection of the Catheter, Dummy Ribbon and Source Ribbon:</i> Sixty (60) catheters, 60 dummy ribbons and 24 source ribbons were dimensionally inspected to ensure compliance with the product labeling; all units met the acceptance criteria.
5.	<i>Simulated Use Testing:</i> Forty-five (45) catheters, packaged with dummy ribbons and source lumen plugs, were tested under conditions that simulate the clinical use of the product; all tested units met the acceptance criteria.
6.	<i>Pull Testing:</i> Pull testing was performed on the distal catheter joint (n=45), the catheter hub bond (n=45) and the dummy ribbon (n=60); all tested units met the acceptance criteria.
7.	<i>Exit Marker Integrity Test:</i> Ten (10) catheters were tested to demonstrate the integrity of the exit markers on the catheter shaft; all tested units met the USP acceptance criteria for small volume injections.
8.	<i>Prolapse Pull Test:</i> Forty-five (45) catheters were tested to demonstrate the pull strength of the catheter tip and the failure mode of the catheter in the event of a guidewire prolapse; all tested catheters met the acceptance criteria.
9.	<i>Source Lumen Integrity Test:</i> Forty-five (45) catheters were tested to verify that the source lumen of the catheter does not allow blood contact; all tested catheters met the acceptance criteria.
10.	<i>Uni-Dummy Ribbon Testing:</i> Testing to compare the uni-dummy ribbon to the dummy ribbon was performed on 3-5 uni-dummy ribbons, 6-seed dummy ribbons and 14-seed dummy ribbons; all tested units met the acceptance criteria.
11.	<i>Radiation Exposure Testing:</i> Six (6) catheters and 10-27 source ribbons were tested to demonstrate that exposure to radiation does not affect the integrity of the device; all tested units met the acceptance criteria.
12.	<i>Source Reproducibility Testing/Verification of Dosimetric Parameters:</i> The activity of a 6-seed source ribbon was measured and compared to TG-43 calculated and MCNP modeled data; a good correlation between the measured and MCNP modeled data was shown.

Product testing of the Checkmate Delivery Device was conducted to ensure that this component performs in accordance with its design specifications. The following tests were successfully performed:

Test and Test Results	
1.	<i>Visual Inspection of Packaging:</i> Three (3) packages were visually inspected; all units met the test acceptance criteria.
2.	<i>Packaging Functional Testing:</i> One (1) unit was tested, the tested unit met the test acceptance criteria.
3.	<i>Visual Inspection:</i> Three (3) delivery devices were visually inspected; all units met the test acceptance criteria.
4.	<i>Functional Testing:</i> Three (3) delivery devices underwent functional testing; all units met the test acceptance criteria.
5.	<i>Simulated Use Testing:</i> Three (3) delivery devices were tested under conditions that simulate the clinical use of the product; all units met the test acceptance criteria.

**10.1.2
Biological
Testing**

Biocompatibility testing was performed on tissue contacting materials in accordance with ISO10993-1; these tests indicated that the materials were biocompatible and non-toxic. The tests that were performed include: cytotoxicity, hemolysis, systemic toxicity, intracutaneous injection, sensitization, pyrogenicity, USP aqueous extraction and thromboresistance or hemocompatibility testing.

**10.1.3
Useful Life –
Reuse Testing**

Reuse testing was performed on the delivery device and the source ribbon to ensure that these components perform in accordance with their design specifications. The following tests were successfully performed:

Test and Test Results	
1.	<i>Cycling Testing of the Delivery Device:</i> Three (3) delivery devices and simulated source ribbons underwent cycle testing, all tested units met the acceptance criteria.
2.	<i>Cycling Testing of the Source Ribbon:</i> Ten (10) aged source ribbons underwent cycle testing out of the delivery device into a Checkmate Catheter (placed in a test fixture to simulate a tortuous clinical anatomy) and back; all units met the test acceptance criteria.
3.	<i>Post-Cycling Visual Inspection:</i> Ten (10) aged source ribbons were visually inspected after the cycling testing; all units met the test acceptance criteria.
4.	<i>Post-Cycling Dimensional Inspection:</i> Ten (10) aged source ribbons were dimensionally inspected to ensure compliance with the product labeling after cycling testing; all units met the acceptance criteria.

**10.1.4 Useful
Life – Shelf Life
Testing**

Shelf life testing was performed on Checkmate Catheters and dummy ribbons after these devices were subjected to an accelerated aging protocol, simulating a shelf life of 2 years. The following tests were successfully performed:

Test and Test Results	
1.	<i>Visual Inspection of Packaging:</i> Fifty-five (55) packages were visually inspected after aging; all units met the test acceptance criteria.
2.	<i>Functional Testing of Pouches:</i> The pouches underwent the following functional testing after aging: Seal strength (n=5), Burst Strength (n=5), Package Challenge (n=30), Dye Penetration (n=30). All units met the test acceptance criteria.
3.	<i>Visual Inspection of the Catheter and Dummy Ribbon:</i> Fifteen (15) catheters and 15 dummy ribbons were visually inspected after aging; all units met the test acceptance criteria.
4.	<i>Dimensional Inspection of the Catheter and Dummy Ribbon:</i> Fifteen (15) catheters and 15 dummy ribbons were dimensionally inspected to ensure compliance with the product labeling after aging; all units met the acceptance criteria.
5.	<i>Simulated Use Testing:</i> Fifteen (15) catheters, packaged with dummy ribbons and source lumen plugs, were tested, after aging, under conditions that simulate the clinical use of the product; all tested units met the acceptance criteria.
6.	<i>Pull Testing:</i> Pull testing, after aging, was performed on the distal catheter joint (n=15), the catheter hub bond (n=15) and the dummy ribbon (n=15); all tested units met the acceptance criteria.
7.	<i>Exit Marker Integrity Test:</i> Ten (10) catheters were tested to demonstrate the integrity of the exit markers on the catheter shaft after aging; all tested units met the USP acceptance criteria for small volume injections.
8.	<i>Prolapse Pull Test:</i> Fifteen (15) aged catheters were tested to demonstrate the pull strength of the catheter tip and the failure mode of the catheter in the event of a guidewire prolapse; all tested catheters met the acceptance criteria.
9.	<i>Source Lumen Integrity Test:</i> Fifteen (15) catheters were tested to verify that the source lumen of the catheter does not allow blood contact; all tested catheters met the acceptance criteria.

Shelf life testing was performed on the source ribbons after these devices were subjected to real time aging, supporting a shelf life of 35 days. Reuse testing was performed on the delivery device to support a 35 day cycle time. The following tests were successfully performed:

Test and Test Results	
1.	<i>Visual Inspection of the Source Ribbon:</i> Twenty-four (24) source ribbons were visually inspected after aging; all units met the test acceptance criteria.
2.	<i>Dimensional Inspection of the Source Ribbon:</i> Twenty-seven (27) source ribbons were dimensionally inspected to ensure compliance with the product labeling after aging; all units met the acceptance criteria.
3.	<i>Cycling Testing of the Delivery Device:</i> Three (3) delivery devices and simulated source ribbons underwent cycle testing, all tested units met the acceptance criteria.
4.	<i>Cycling Testing of the Source Ribbon:</i> Ten (10) aged source ribbons were cycled forty times out of the delivery device into an Checkmate catheter (placed in a test fixture to simulate a tortuous clinical anatomy) and back; all units met the test acceptance criteria.

Test and Test Results	
5.	<i>Post-Cycling Visual Inspection:</i> Ten (10) aged source ribbons were visually inspected after the cycling testing; all units met the test acceptance criteria.
6.	<i>Post-Cycling Dimensional Inspection:</i> Ten (10) aged source ribbons were dimensionally inspected to ensure compliance with the product labeling after cycling testing; all units met the acceptance criteria.
7.	<i>Pull Testing:</i> Pull testing, after aging, was performed on the source ribbon (n=10); all tested units met the acceptance criteria.

10.1.5 Useful Life – Sterilization Testing

EtO residual testing and D-value testing was performed on the Checkmate Catheter, dummy ribbon and source lumen plug. Additionally, pyrogenicity testing was performed on the Checkmate Catheter. The testing demonstrated that these devices can be sterilized (with a SAL level of 10^{-6}) using validated EtO sterilization cycles.

10.2 Animal Testing

The function and handling characteristics of the Cordis Checkmate System were evaluated in a porcine model. The study concluded that the performance of the system was acceptable.

11. Summary of Clinical Studies

11.1 Objective

The objective of the pivotal GAMMA-I trial was to determine the safety and effectiveness of localized radiation therapy following percutaneous revascularization using current interventional techniques in patients with restenotic native coronary artery lesions.

11.2 Study Design

The GAMMA-1 trial was a multi-center, prospective, randomized, two-arm, double blind study of patients with in-stent restenosis who were scheduled to undergo a current interventional procedure for restenotic coronary lesions.

11.3 Description of Patients and Gender Bias

For the 252 patients enrolled in the GAMMA-1 study, the mean age was 60 years, 74.6% were male. Inclusion criteria, exclusion criteria and study enrollment procedures were designed to avoid gender bias. This fraction ($74.6\%/25.4\% = 2.94$) is typical of studies of coronary artery disease. Separate analysis of safety and effectiveness data for males and females indicated no difference between genders; hence, the results presented in the following analysis are representative for both women and men.

11.4 Results

The results of the GAMMA-I trial are summarized in Table 11.1

**Table 11.1 GAMMA-I Principal Effectiveness and Safety Results (to 270 days)
All Patients Treated (N=252)**

Effectiveness Measures	Radiation (N=131)	Placebo (N=121)	Relative Risk [95% CI]	Difference [95% CI]
Lesion Success	100.0% (131/131)	98.3% (119/121)	1.02 [0.99, 1.04]	1.7% [-0.6%, 3.9%]
Procedure Success	100.0% (131/131)	98.3% (119/121)	1.02 [0.99, 1.04]	1.7% [-0.6%, 3.9%]
Device Success	100.0% (131/131)	98.3% (119/121)	1.02 [0.99, 1.04]	1.7% [-0.6%, 3.9%]
Post Procedure In-Stent Percent Diameter Stenosis (% DS) Mean±SD (N) Range (min, max)	8.8%±17.9% (129) (-49.9%, 48.8%)	8.9%±19.0% (117) (-55.8%, 59.1%)	N/A	-0.1% [-4.8%, 4.5%]
Follow-Up In-Stent Percent Diameter Stenosis (% DS) Mean±SD(N) Range (min, max)	33.6%±32.3% (111) (-48.5%, 100.0%)	50.8%±22.0% (103) (-0.8%, 100.0%)	N/A	-17.2% [-24.7%, -9.7%]
In-Stent Late Loss (mm) Mean±SD (N) Range (min, max)	0.73±0.79 (111) (-0.56, 3.37)	1.14±0.65 (101) (-0.47, 3.30)	N/A	-0.40 [-0.60, -0.20]
6 Month In-Lesion (Stent+Probe+Edge) Binary Restenosis Rate	32.4% (36/111)	55.3% (57/103)	0.59 [0.43, 0.80]	-22.9% [-35.9%, -9.9%]
6 Month In-Stent Binary Restenosis Rate	21.6% (24/111)	50.5% (52/103)	0.43 [0.29, 0.62]	-28.9% [-41.2%, -16.5%]
Difference of Index and F/U Mean Difference of Stent and Lumen	-0.75±1.13 (35) (-3.80, 2.14)	-1.55±1.15 (33) (-4.48, 0.20)	N/A	0.80 [0.25, 1.35]
TLR-Free at 270 days*	74.8% [65.7%, 83.9%]	56.7% [46.1%, 67.3%]	1.32 [1.06, 1.65]	18.1% [4.1%, 32.1%]
TVR-Free at 270 days*	66.2% [56.3%, 76.1%]	52.5% [41.9%, 63.1%]	1.26 [0.98, 1.62]	13.8% [-0.7%, 28.2%]
TVF-Free at 270 days*	62.3% [52.1%, 72.5%]	51.6% [41.0%, 62.3%]	1.21 [0.93, 1.57]	10.7% [-4.1%, 25.4%]
MACE-Free at 270 days*	70.8% [61.2%, 80.4%]	55.0% [44.4%, 65.7%]	1.29 [1.02, 1.63]	15.8% [1.4%, 30.1%]
Safety Measures and Other Clinical Events				
In-Hospital MACE	2.3% (3/131)	3.3% (4/121)	0.69 [0.16, 3.01]	-1.0% [-5.1%, 3.1%]
Out-of-Hospital MACE to 270 days	26.7% (35/131)	42.1% (51/121)	0.63 [0.45, 0.90]	-15.4% [-27.0%, -3.8%]
Bleeding Complications to 270 days	2.3% (3/131)	0.8% (1/121)	2.77 [0.32, 23.91]	1.5% [-1.6%, 4.5%]
Vascular Complications to 270 days	3.1% (4/131)	1.7% (2/121)	1.85 [0.35, 9.66]	1.4% [-2.3%, 5.1%]
Hematologic Dyscrasia to 270 days	0.8% (1/131)	1.7% (2/121)	0.46 [0.04, 4.76]	-0.9% [-3.6%, 1.8%]
CVA to 270 days	0.8% (1/131)	2.5% (3/121)	0.31 [0.04, 2.58]	-1.7% [-4.9%, 1.4%]
Acute Stent Thrombosis	0.8% (1/131)	1.7% (2/121)	0.46 [0.04, 4.76]	-0.9% [-3.6%, 1.8%]
Late Thrombosis	5.3% (7/131)	0.8% (1/121)	6.47 [0.81, 51.79]	4.5% [0.3%, 8.7%]
Late Total Occlusion	12.6% (14/111)	5.8% (6/103)	2.17 [0.87, 5.42]	6.8% [-0.8%, 14.4%]

Numbers are % (counts/sample size) or Mean±SD

Relative Risk = Radiation/Placebo

Difference = Radiation - Placebo

N/A = Not Applicable

Lesion Success = Attainment of a <50% residual stenosis using any percutaneous method.

Procedure Success = Attainment of a <50% residual diameter stenosis using any percutaneous method and no in-hospital MACE.

Device Success = Attainment of a <50% residual stenosis and successful delivery of the radiation device.

Restenosis was defined as ≥50% in-stent diameter stenosis at the follow-up angiogram.

*Survival Estimates from Kaplan-Meier estimate. Standard Error estimates by Peto formula.

KM Relative Risk = $S_{\text{Radiation}}/S_{\text{Placebo}}$

$SE_{RR} = \sqrt{\left(\frac{SE_{\text{Radiation}}}{S_{\text{Radiation}}}\right)^2 + \left(\frac{SE_{\text{Placebo}}}{S_{\text{Placebo}}}\right)^2}$

CI = Confidence Interval

CI = $RR \cdot \exp(\pm 1.96 \cdot SE)$

CI = $Diff \pm 1.96 \cdot SE$

KM Difference = $S_{\text{Radiation}} - S_{\text{Placebo}}$

$SE_{Diff} = \sqrt{SE_{\text{Radiation}}^2 + SE_{\text{Placebo}}^2}$

TLR-Free = No target lesion revascularization.

TVR-Free = No target vessel revascularization.

TVF-Free = No death, MI, or target lesion revascularization.

MACE-Free = No death, Q wave or non-Q wave MI, emergent CABG, or target lesion revascularization.

MACE = Death, Q wave or non-Q wave MI, emergent CABG, or target lesion revascularization.

In-Hospital MACE = Death, Q wave or non-Q wave MI, emergent CABG, or target lesion revascularization prior to hospital discharge.

Out-of-Hospital MACE = Death, Q wave or non-Q wave MI, emergent CABG, or target lesion revascularization after hospital discharge.

Bleeding Complications = Transfusions of blood products due to blood loss resulting from the percutaneous revascularization procedure.

Vascular Complications = Hematoma > 4 cm, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, and vascular surgical repair.

CVA = Acute neurological deficits recorded by the clinical sites that persisted > 24 hours.

Acute Stent Thrombosis = Angiographic thrombus or subacute closure within the stented vessel at the time of the clinically driven

Angiographic restudy for documented ischemia (chest pain or ECG changes). Any death not attributed to a non-cardiac cause within

the first 30 days was considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.

Late Thrombosis = Myocardial infarction attributable to the target vessel with angiographic documentation (site-reported

or by QCA) of thrombus or total occlusion at the target site and in a newly implanted bypass graft at the target site > 30 days after the index

procedure in the absence of an intervening revascularization of the target vessel.

Late Total Occlusion = Consists of Late Thrombosis and Total Occlusion.

11.5 Other Studies

Clinical Trials Comparison

Trial	GAMMA-I		SCRIPPS-I		WRIST		SCRIPPS-III		WRIST Plus	
	Pivotal Trial Multi center, prospective, randomized 252	Supportive Trial Single center, prospective, randomized 60	Supportive Trial Single center, prospective, randomized 130	Supportive Trial Single center, prospective, randomized 500	Supportive Trial Single center, prospective, randomized 120	Supportive Trial Multi center, registry	Supportive Trial Single center, registry			
Total # of Patients Enrolled	252	60	130	500	120					
Patients Studied	Native coronary arteries 2.75 - 4.0 mm diameter < 45 mm length 6, 10 or 14 seed ribbons 4F Catheter	Native coronary arteries and SVG's 3.0 - 5.5 mm diameter <30 mm length 5 or 9 seed ribbon 4F Catheter	Native coronary arteries and SVG's 3.0 - 5.0 mm diameter < 50 mm length 5, 9 or 13 seed ribbon 5F Catheter	Native coronary arteries and SVG's 2.75 - 4.0 mm diameter < 81 mm length 6 - 22 seed ribbons 4F Catheter	Native coronary arteries and SVG's 2.5 - 5.0 mm diameter < 80 mm length 6-23 seed ribbons 4F or 5F Catheter					
Devices Used	6, 10 or 14 seed ribbons 4F Catheter	5 or 9 seed ribbon 4F Catheter	5, 9 or 13 seed ribbon 5F Catheter	6 - 22 seed ribbons 4F Catheter	6-23 seed ribbons 4F or 5F Catheter					
Methods	Outlined on previous page	Similar to GAMMA-I	Similar to GAMMA-I	Similar to GAMMA-I	Similar to GAMMA-I					
Dosimetry	IVUS based 800-3000 cGy	IVUS based 800-3000 cGy	No IVUS 1500 cGy at 2 mm from the center of the source	No IVUS 1400 cGy at 2 mm	No IVUS 1400 cGy or 1500 cGy at 2 mm from the center of the source					
Antiplatelet Therapy	8-weeks if new stent was placed	2 weeks if new stent was placed	4 weeks (all patients)	6 months if no new stent 12 months if new stent is placed	6 months (all patients)					
Follow-up	6 months angiographic 1 & 9 months clinic 2, 24, 36 months telephone FU	6 & 36 months angiographic 12, 24, 36, 48, 60 months telephone FU	6 months angiographic 1, 6, 12 & 24 months clinic	1 & 9 months clinic 2 & 12 months telephone FU	6 & 24 months angiographic 1 & 12 months clinic					

**Table 11.2 SCRIPPS-I Principal Effectiveness and Safety Results (to 180 days)
All Patients Treated (N=60)**

Effectiveness Measures	Radiation (N=29)	Placebo (N=31)	Relative Risk [95% CI]	Difference [95% CI]
Lesion Success	100.0% (29/29)	93.5% (29/31)	1.07 [0.97, 1.18]	6.5% [-2.2%, 15.1%]
Procedure Success	100.0% (29/29)	93.5% (29/31)	1.07 [0.97, 1.18]	6.5% [-2.2%, 15.1%]
Device Success	100.0% (29/29)	90.3% (28/31)	1.11 [0.98, 1.24]	9.7% [-0.7%, 20.1%]
Post Procedure In-Stent Percent Diameter Stenosis (% DS)				
Mean±SD (N)	9.4±22.8% (29)	7.0±23.9% (31)	N/A	2.5% [-9.6, 14.5]
Range (min, max)	(-64.1%, 38.0%)	(-36.0%, 46.4%)		
Post-Procedure In-Stent+Border % DS				
Mean±SD(N)	24.4±9.5% (29)	18.9±18.1% (31)	N/A	5.6% [-2.0%, 13.1%]
Range (min, max)	(-0.8%, 39.8%)	(-24.3%, 53.2%)		
6 Month F/U In-Stent+Border % DS				
Mean±SD (N)	43.2±23.5% (28)	41.8±24.2% (28)	N/A	1.4% [-11.4%, 14.2%]
Range (min, max)	(16.5%, 100%)	(-23.8%, 78.6%)		
6 Month F/U In-Stent+Border Late Loss				
Mean±SD (N)	0.66±0.91 (28)	0.78±0.94 (28)	N/A	-0.13 [-0.62, 0.37]
Range (min, max)	(-0.62, 2.73)	(-0.46, 3.49)		
6 Month In-Stent+Border Restenosis Rate	21.4% (6/28)	46.4% (13/28)	0.46 [0.21, 1.00]	-25.0% [-48.9%, -1.1%]
Difference between Post-Procedure and 6-Month F/U Mean Intimal Hyperplasia CSA (mm ²)				
Mean±SD (N)	-0.68±0.97 (18)	-2.14±1.66 (18)	N/A	1.47 [0.55, 2.39]
Range (min, max)	(-2.90, 0.70)	(-5.60, -0.40)		
TLR-Free at 180 days*	82.6% [68.5%, 96.7%]	77.4% [62.4%, 92.5%]	1.07 [0.82, 1.38]	5.2% [-15.4%, 25.8%]
TVR-Free at 180 days*	82.8% [68.7%, 96.8%]	71.0% [54.6%, 87.3%]	1.17 [0.88, 1.55]	11.8% [-9.8%, 33.3%]
TVF-Free at 180 days*	79.3% [64.2%, 94.4%]	71.0% [54.6%, 87.3%]	1.12 [0.83, 1.51]	8.3% [-13.9%, 30.6%]
MACE-Free at 180 days*	79.2% [64.1%, 94.3%]	77.4% [62.4%, 92.5%]	1.02 [0.78, 1.34]	1.7% [-19.6%, 23.1%]
Safety Measures and Other Clinical Events				
In-Hospital MACE	0.0% (0/29)	0.0% (0/31)	- [-,-]	0.0% [-,-]
Out-of-Hospital MACE to 180 days	20.7% (6/29)	22.6% (7/31)	0.92 [0.35, 2.42]	-1.9% [-22.7%, 18.9%]
Bleeding Complications to 180 days	0.0% (0/29)	6.5% (2/31)	0.00 [-,-]	-6.5 [-15.1%, 2.2%]
Vascular Complications to 180 days	0.0% (0/29)	0.0% (0/31)	- [-,-]	0.0% [-,-]
CVA to 180 days	0.0% (0/29)	3.2% (1/31)	1.00 [-,-]	-3.2% [-9.4%, 3.0%]
Acute Stent Thrombosis (to 30 days)	3.4% (1/29)	0.0% (0/31)	- [-,-]	3.4% [-3.2%, 10.1%]
Late Thrombosis	0.0% (0/29)	0.0% (0/31)	- [-,-]	0.0% [-,-]
Late Total Occlusion	3.6% (1/28)	0.0% (0/28)	- [-,-]	3.6% [-3.3%, 10.5%]

Numbers are % (counts/sample size) or Mean ± SD

Relative Risk = Radiation/Placebo

Difference = Radiation - Placebo

N/A = Not applicable.

Device Success = The attainment of a <50% residual stenosis and successful delivery of the radiation device.

Lesion Success = The attainment of a <50% residual stenosis using any percutaneous method.

Procedure Success = The attainment of a <50% residual stenosis using any percutaneous method and no in-hospital MACE.

In-Hospital MACE = Death, Q wave or non-Q wave MI, target lesion revascularization, and emergent CABG prior to hospital discharge.

Out-of-Hospital MACE = Death, Q wave or non-Q wave MI, target lesion revascularization, and emergent CABG after hospital discharge.

*Survival Estimates from Kaplan-Meier estimates. Standard Error estimates from Peto formula.

KM Relative Risk = $S_{\text{Radiation}}/S_{\text{Placebo}}$

$SE_{RR} = \sqrt{\{(SE_{\text{Radiation}}/S_{\text{Radiation}})^2 + (SE_{\text{Placebo}}/S_{\text{Placebo}})^2\}}$

CI = $RR \cdot \exp(\pm 1.96 \cdot SE_{RR})$

KM Difference = $S_{\text{Radiation}} - S_{\text{Placebo}}$

$SE_{Diff} = \sqrt{\{SE_{\text{Radiation}}^2 + SE_{\text{Placebo}}^2\}}$

CI = $Diff \pm 1.96 \cdot SE_{Diff}$

TLR-Free = No target lesion revascularization.

TVR-Free = No target vessel revascularization.

TVF-Free = No death, Q wave or non-Q wave MI, or target vessel revascularization.

MACE-Free = No death, Q wave or non-Q wave MI, target lesion revascularization, or emergent CABG.

Bleeding Complications = Bleeding complications were defined as transfusions of blood products due to blood loss resulting from the percutaneous revascularization procedure.

Vascular Complications = Hematoma > 4 cm, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, and Vascular surgical repair.

CVA = Cerebrovascular accident was defined as acute neurological deficits recorded by the clinical sites that persisted > 24 hours.

Acute Stent Thrombosis = Angiographic thrombus or subacute closure within the stented vessel at the time of the clinically driven angiographic restudy for documented ischemia (chest pain or ECG changes). Any death not attributed to a non-cardiac cause within the first 30 days was considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.

Late Thrombosis = Myocardial infarction attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and in a newly implanted bypass graft at the target site > 30 days after the index procedure in the absence of an intervening revascularization of the target vessel.

Late Total Occlusion = Consists of Late Thrombosis and Total Occlusion.

**Table 11.3 WRIST Principal Effectiveness and Safety Results (to 180 days +/- 30 days)
All Patients Treated (N=130)**

Effectiveness Measures	Radiation (65=Patients, 65=Lesions)	Placebo (65=Patients, 65=Lesions)	Relative Risk (95% CI)	Difference (95% CI)
Lesion Success	100% (64/64)	98.4% (63/64)	1.02 (0.99, 1.05)	1.6 (-1.5, 4.7)
Device Success	100% (64/64)	96.9% (62/64)	1.03 (0.99, 1.08)	3.1 (-1.2, 7.5)
Procedure Success	100% (64/64)	98.4% (63/64)	1.02 (0.99, 1.05)	1.6 (-1.5, 4.7)
Post-Procedure In-Lesion Percent Diameter Stenosis (% DS) Mean±SD (N) Range (min, max)	28.32±11.93 (64) (-10.07, 63.21)	27.30±11.99 (64) (2.29, 55.88)	N/A	1.02 (-3.16, 5.20)
Post Procedure In-Stent Percent Diameter Stenosis (% DS) Mean±SD (N) Range (min, max)	19.77±15.16 (64) (-18.80, 43.01)	20.45±14.75 (64) (-20.23, 50.46)	N/A	-0.68 (-5.91, 4.56)
Late Loss In-Stent (QCA) Mean±SD (N) Range (min, max)	0.24±0.84 (59) (-1.20, 2.95)	0.96±0.68 (55) (-0.82, 2.62)	N/A	-0.72 (-1.01, -0.44)
Restenosis Rate In-Lesion Binary Restenosis Mean Lumen Area at 6 month follow-up (IVUS) Mean±SD (N)	23.7% (14/59) 7.04±2.38 (47)	60.7% (34/56) 4.85±2.88 (50)	0.39 (0.24, 0.65)	-37.0 (-54.1, -19.9)
TLR-free at 6 months	84.6% (55/65)	36.9% (24/65)	2.29 (1.64, 3.20)	(1.12, 3.26)
TVR-free at 6 months	72.3% (47/65)	32.3% (21/65)	2.24 (1.53, 3.28)	47.7 (32.8, 62.6)
MACE-free at 6 months	70.8% (46/65)	32.3% (21/65)	2.19 (1.49, 3.22)	40.0 (24.0, 56.0)
Safety Measures				
In-Hospital MACE	1.5% (1/65)	0.0% (0/65)	3.00 (0.12, 72.31)	1.5 (-1.5, 4.6)
Out-of-Hospital MACE to 6 months	29.2% (19/65)	67.7% (44/65)	0.43 (0.29, 0.65)	-38.5 (-54.6, -22.3)
MACE to 30 days (cumulative)	3.1% (2/65)	1.5% (1/65)	2.00 (0.19, 21.52)	1.5 (-3.7, 6.8)
MACE to 6 months (cumulative)	29.2% (19/65)	67.7% (44/65)	0.43 (0.29, 0.65)	-38.5 (-54.6, -22.3)
Abrupt Closure to 30 days	0.0% (0/65)	0.0% (0/65)		
Subacute Closure to 30 days	0.0% (0/65)	0.0% (0/65)		
Stent Thrombosis to 30 days	0.0% (0/65)	0.0% (0/65)		
CVA to 30 days	0.0% (0/65)	0.0% (0/65)		
In-hospital Vascular Complications	10.8% (7/65)	10.8% (7/65)	1.00 (0.37, 2.69)	0.0 (-10.8, 10.8)
Vascular Complications to 6 months (cumulative)	12.3% (8/65)	12.3% (8/65)	(0.40, 2.50)	0.0 (-11.5, 11.5)
Late Thrombosis	3.1% (2/65)	0.0% (0/65)		3.1 (-1.1, 7.3)
Late Total Occlusion	13.8% (9/59)	1.5% (1/56)*	9.00 (1.17, 69.02)	12.3 (3.4, 21.2)

Numbers are % (counts/sample size) or Mean ± SD
 Relative Risk = p_1/p_2 , $p_1 = n_{11}/n_{1.}$ SE = $\sqrt{\{(1-p_1/n_{11} + (1-p_2)/n_{21})\}}$ CI = Confidence Interval
 Difference = $p_1 - p_2$ SE = $\sqrt{\{(p_1 * q_1/n_{11} + p_2 * q_2/n_{21})\}}$ CI = $RR * \exp(\pm 1.96 * SE)$
 N/A = Not applicable CI = Diff + 1.96 * SE

Lesion success = Lesion success was defined as the attainment of <50% residual stenosis (by QCA) using percutaneous method.
 Device Success = Device success was defined as the attainment of a <50% residual stenosis using assigned treatment and delivery of the ribbon for the desired dwell time.
 Procedure Success = Procedure success was defined as the attainment of a <50% residual stenosis by QCA and freedom from death, Q wave MI or emergent CABG.
 Post-Procedure In-Lesion Percent Diameter Stenosis (% DS) = The % diameter stenosis post procedure was defined as (1-MLD/RVD) * 100 as is identified within the stenotic segment ("in lesion"). Whenever possible, normal and minimal lesion diameters are calculated from two "orthogonal" projections. Range (min, max) measurement of smallest stenosis and largest stenosis, respectively.
 Post Procedure In-Stent Percent Diameter Stenosis (% DS) = The stent % diameter stenosis post procedure was defined as (1-MLD-RVD) * 100 as is identified within the stent ("in stent"). Whenever possible, normal and minimal lesion diameters are calculated from two "orthogonal" projections. Range (min, max) measurement of smallest stenosis and largest stenosis, respectively.
 Late Loss = Late loss is defined as the late change in dimensional minimal lumen diameter that occurred during the follow-up period measured by quantitative coronary angiography based on the average from two orthogonal views after the final post-dilatation to follow-up. Final MLD - FU MLD. Reported for in-stent.
 Binary Restenosis = Angiographic restenosis ≥ 50% minimum lumen diameter stenosis at the follow-up angiogram. Restenosis is recorded for in lesion.
 Mean Lumen Area = Average lumen area over the length of treated segment as measured by intravascular ultrasound at 6 months follow-up in mm².
 TLR-free at 6 months = Target lesion revascularization was defined as a clinically driven repeat revascularization of a target lesion that was angiographically narrowed. The definition of "clinically driven" included a positive functional ischemia study, resting ischemic ECG changes in a distribution consistent with the target vessel, ischemic symptoms, and angiographic minimal lumen diameter stenosis ≥ 50% by QCA; revascularization of a target lesion with diameter stenosis ≥ 70% by QCA without either angina or a positive functional study was also considered clinically driven.

Table 11.3 Continued

- TVR-free at 6 months = Target vessel revascularization was defined as a target lesion revascularization (defined above) or revascularization due to narrowing of any segment of the target vessel proximal or distal to the target lesion. This definition assumed that the entire vessel was vulnerable to late failure because of guide catheter or guidewire trauma or progression of disease remote from the treatment site. The target vessel revascularization definition required that: target vessel revascularization was clinically driven (as defined for the target lesion revascularization, see above). The angiographic core laboratory determined that the target lesion had a diameter stenosis of $\geq 50\%$ by QCA or the clinical site reported a narrowing of another site in the target vessel with diameter stenosis $\geq 50\%$.
- MACE-free at 6 months = MACE was defined as target vessel revascularization, Q wave myocardial infarction or cardiac death that could not be clearly attributed to a non-target vessel. Therefore, target vessel failure included any revascularization or adverse endpoints due to re-narrowing of any segment of the target vessel. Target vessel failure was reported when: target vessel revascularization occurred (defined below); myocardial infarction occurred and the territory was not clearly other than that of the target vessel; or cardiac death occurred and could not be clearly attributed to a non-target vessel.
- In-Hospital MACE = In-hospital MACE (Major Adverse Cardiac Events) were defined as cardiac death, target Q wave MI, and target vessel revascularization (CABG or PTCA of the target vessel) as determined by the independent Clinical Events Committee from index procedure through the hospital discharge.
- Out-of-Hospital MACE = Out-of-hospital MACE (Major Adverse Cardiac Events) were defined as death, Q wave MI, and target vessel revascularization (CABG or PTCA of the target vessel) as determined by the independent Clinical Events Committee from discharge through the 6 month contact.
- MACE to 30 days (cumulative) = The occurrence of any major adverse cardiac event including cardiac death, QWMI, CABG, or repeat PTCA within 30 days of the index procedure. One event should be reported per patient.
- MACE to 6 months (cumulative) = The occurrence of any major adverse cardiac event including cardiac death, QWMI and target vessel revascularization that occurred from the index procedure to the 6 month follow-up. One event should be reported per patient.
- Abrupt Closure = Abrupt closure is defined as the occurrence of new reduced flow (TIMI 0 or 1) of the target vessel and required rescue by another device or emergency surgery or resulted in myocardial infarction or death. Abrupt closure is related to the mechanical dissection (of the treatment site or other instrumental site), coronary thrombus, or severe spasm. Abrupt closure does not connote no re-flow in which the artery was patent but reduced flow persisted. Abrupt closure also does not connote transient closure unless a Class 2 or 3 MI or death occurred. Threatened abrupt closure was defined as a NHLBI dissection Grade B with a 50% diameter stenosis or any Grade C dissection or higher. Threatened closure was not used as a primary endpoint but was used to adjudicate the use of other devices.
- Subacute Closure to 30 days = Subacute closure was defined as abrupt closure that had occurred after the index procedure was completed and the patient had left the catheterization laboratory and was within 30 days of the index procedure.
- Stent Thrombosis = Cardiac death, Q wave MI, angiographic total occlusion at follow-up or evidence of angiographic thrombus (core laboratory and investigator), reported at 30 days. In the absence of the QCA, total occlusion was adjudicated by the Clinical Events Committee.
- CVA to 30 days = The occurrence of a new permanent stroke following the procedure within 30 days of the index procedure.
- In-Hospital Vascular Complications = In-hospital vascular complications were defined as the occurrence of any of the following: hematoma at the access site of > 4 cm in maximum diameter, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, procedure-related blood transfusion, or vascular surgical repair between index procedure to discharge date of hospital stay.
- Vascular Complications to 6 months (cumulative) = Vascular complications were defined as the occurrence of any of the following: hematoma at the access site of > 4 cm in maximum diameter, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, procedure related blood transfusion, or vascular surgical repair both in hospital from index procedure to discharge and out of hospital.
- Late Thrombosis = Myocardial infarction attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and in a newly implanted bypass graft at the target site > 30 days after the index procedure in the absence of an intervening revascularization of the target vessel.
- Late Total Occlusion = Consists of Late Thrombosis and Total Occlusion.

* Additionally, the rates of late thrombosis and late total occlusion for the crossover group are 5.1% (2/39) and 12.8% (5/39), respectively.

**11.6 Additional
Late
Thrombosis
Information**

Summarized in Table 11.4 is the late thrombosis information based on data collected from the GAMMA-I, SCRIPPS-I and WRIST trials up to June 2000, which is beyond the primary study endpoints (See Table 11.4 for further details).

	Radiation	Placebo
GAMMA-I	5.3% (7/131)	0.8% (1/121)
SCRIPPS-I	0.0% (0/29)	0.0% (0/31)
WRIST	6.2% (4/65)	1.5% (1/65)
WRIST (Crossover)	5.1% (2/39)	-
TOTAL	4.9% (13/264)	0.9% (2/217)

GAMMA-I: Results in this table represent data at 1.5 years. Patients with new stents received 8 weeks of antiplatelet therapy.
 SCRIPPS-I: Results in this table represent data at 3 years. Patients with new stent received 2 weeks of antiplatelet therapy.
 WRIST: Results in this table represent data at 2 years. All patients received 4 weeks of antiplatelet therapy.
 Late Thrombosis = Myocardial infarction attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and in a newly implanted bypass graft at the target site > 30 days after the index procedure in the absence of an intervening revascularization of the target vessel.

Additionally, the use of prolonged antiplatelet therapy was evaluated during the SCRIPPS-III and WRIST Plus registry trials. During the SCRIPPS-III trial, patients who received a new stent are placed on 12 months of antiplatelet medication and 6 months if no new stent is placed. During the WRIST Plus trial all patients received 6 months of antiplatelet medication. A summary of late thrombosis events through August 18, 2000 can be found in Table 11.5. Note: The follow-up in these two trials is not yet complete, since the studies are still on-going.

Time After Initial Procedure (days)	0	30	60	90	120	150	180	210
Effective Sample Size	508.5	481.5	447.5	413.5	379.0	333.5	269.5	206.0
Number Censored	19	35	31	35	34	57	71	54
Number of Events	0	1	1	0	0	0	1	0
% Survival	100%	100%	99.79%	99.56%	99.56%	99.56%	99.56%	99.17%
% Failure	0.00%	0.00%	0.21%	0.44%	0.44%	0.44%	0.44%	0.83%
% Peto Survival SE	0.00%	0.00%	0.21%	0.32%	0.33%	0.35%	0.38%	0.57%
% Failure 95% Lower Conf. Limit	0.00%	0.00%	0.03%	0.10%	0.10%	0.09%	0.08%	0.22%
% Failure 95% Upper Conf. Limit	0.00%	0.00%	1.53%	1.81%	1.92%	2.05%	2.36%	3.18%

11.7 Device Failures and Replacements

There were no device failures or replacements during the GAMMA-I, SCRIPPS-I or WRIST trials.

12. Conclusions Drawn from Studies

Summary of GAMMA-I Results: In suitable patients with restenotic coronary lesions, an interventional procedure (IP) followed by intravascular brachytherapy (Radiation) resulted in a statistically significant improvement in late angiographic and intravascular ultrasound (IVUS) results, a lower six-month angiographic restenosis rate, and lower major adverse cardiac events (MACE) at 9 months when compared to IP and Placebo intravascular brachytherapy. The rate of late stent thrombosis was higher in the Radiation arm.

Summary of SCRIPPS-I results: In suitable patients, an interventional procedure followed by intravascular brachytherapy (Radiation) in restenotic coronary artery lesions resulted in statistically significant improvement in 6-month intravascular ultrasound result, lower 6-month angiographic restenosis rate, and a trend for lower major adverse cardiac events (MACE) at 3 years.

Summary of WRIST results: In suitable patients, an interventional procedure (IP) followed by intravascular brachytherapy (Radiation) in restenotic coronary artery lesions resulted in statistically significant improvement in late angiographic and intravascular ultrasound (IVUS) results, lower six-month angiographic restenosis rate, and lower major adverse cardiac events (MACE) at six months compared to IP and Placebo intravascular brachytherapy.

12.1 Risk Benefit Analysis

Based on the clinical studies presented, it is reasonable to conclude that the benefits of this device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the instructions for use.

12.2 Safety

See Tables 11.1 – 11.5.

12.3 Effectiveness

See Tables 11.1 – 11.5.

**13. Panel
Recommendation**

At an advisory meeting held on June 19, 2000, the Circulatory System Devices Panel recommended that Cordis Corporation's PMA for the Cordis Checkmate™ 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 several changes to the labeling for the Cordis Checkmate™ System.
2. The panel recommended items to be incorporated into the training program.
3. The panel recommended that 5-year follow-up data be gathered for patients enrolled in the clinical investigations contained in the PMA.

**14. FDA
Decision**

CDRH concurred with the Circulatory System Devices Panel recommendation of June 19, 2000, and conveyed the Conditions of Approval in a facsimile dated November 1, 2000. In an amendment received by FDA on November 2, 2000, Cordis Corporation submitted the required information.

1. The panel recommended several changes to the labeling for the Cordis Checkmate™ System. These recommendations have been incorporated into the final draft labeling of the device.
2. The panel recommended items to be incorporated into the training program. A revised training program that incorporates the panel recommendations is provided in the October 16, 2000 submission.
3. The panel recommended that 5-year follow-up data be gathered for patients enrolled in the clinical investigations contained in the PMA. Cordis Corporation has agreed to this post-approval requirement, and an outline of the investigational plan for this study is provided in the August 31, 2000, amendment.

FDA issued an approval order on _____ . The applicant's manufacturing facility was inspected on February 10, 2000, and was found to be in compliance with the device Good Manufacturing Practice regulations.

The Cordis Checkmate™ System was granted expedited review status on September 22, 1998, 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.

**15. 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.