

## **2 Summary of Safety and Effectiveness**

## 2.1 Summary of Safety and Effectiveness

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### Summary of Safety and Effectiveness

The Summary of Safety and Effectiveness (SS&E) is based upon information available at the time of this submission.

Included in the SS&E are:

1. General Information
  2. Indications for Use
  3. Contraindications
  4. Warnings
  5. Precautions
  6. Device Description
  7. Alternative Practices and Procedures
  8. Marketing History
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### 1. General Information

Device Generic Name	Drug Eluting Stent
Device Trade Name	CYPHER™ Sirolimus-eluting Stent mounted on either RAPTOR™ Over-the-Wire or RAPTORRAIL™ Rapid Exchange delivery system
Applicant's Name and Address	Cordis Corporation 7 Powder Horn Drive Warren, NJ 07059
PMA Number	P0200026
Date of Panel Recommendation	10/22/02
Date of Notice of Approval to Applicant	TBD

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**2. Indications for Use**

The CYPHER? Sirolimus-eluting Stent is indicated for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete de novo lesions (?30mm in length) in native coronary arteries with reference vessel diameter of 2.25 mm to 5.00 mm.

The CYPHER™ Sirolimus-eluting Stent has been shown to significantly reduce binary restenosis, angiographic late loss at 8 months and repeat target lesion revascularization and target vessel failure at 9 months. Long-term outcome (beyond 24 months) for this permanent implant is unknown at present.

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**3. Contra-indications**

CYPHER? Sirolimus-eluting Stent is generally contraindicated in the following patient types:

- ?? Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.
  - ?? Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon.
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**4. Warnings**

CYPHER? Sirolimus-eluting Stent warnings are as follows:

- ?? Do not use if the inner package is opened or damaged.
  - ?? The use of this device carries the associated risks of subacute thrombosis, vascular complications, and/or bleeding events.
  - ?? The device should not be used in patients with a known hypersensitivity to sirolimus, 316L stainless steel, polymethacrylates or polyolefin copolymers.
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**5. Precautions**

CYPHER? Sirolimus-eluting Stent precautions are as follows:

- ?? Only physicians who have received adequate training should perform implantation of the stent.
  - ?? Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
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**5. Precautions,**  
continued

- ?? Subsequent stent blockage may require repeat dilatation of the arterial segment containing the stent. The long-term outcome following repeat dilatation of endothelialized stents is not well characterized.
- ?? To avoid the possibility of dissimilar metal corrosion, do not implant stents of different materials in tandem where overlap or contact is possible.
- ?? Do not use Ethiodol<sup>1</sup> or Lipiodol contrast media.
- ?? Do not expose the delivery system to organic solvents, such as alcohol or detergents.

**Stent Handling – Precautions**

- ?? **For single use only.** Do not resterilize or reuse this device. Note the “Use By” date on the product label.
- ?? **Do not remove the stent from the delivery balloon – removal may damage the stent and/or lead to stent embolization.**
- ?? **Do not induce a vacuum on the delivery system prior to reaching the target lesion.**
- ?? Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important while removing the catheter from the packaging, placing it over the guidewire, and advancing it through the large-bore rotating hemostatic valve and guiding catheter hub.
- ?? Stent manipulation (e.g., rolling the mounted stent with your fingers) may loosen the stent from the delivery system balloon and cause dislodgment.
- ?? Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.

**Stent Placement – Precautions**

- ?? **Do not prepare or pre-inflate the balloon prior to stent deployment other than as directed. Use the balloon purging technique described in the Operator’s Manual Section included in this document.**
- ?? Guiding catheters used must have lumen sizes that are suitable to accommodate the stent delivery system, see Device Description section.
- ?? Do not induce a negative pressure on the delivery catheter prior to placement of the stent across the lesion. This may cause premature dislodgment of the stent from the balloon.

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<sup>1</sup> Ethiodol is a trademark of Guerbet S.A.

**5. Precautions,**  
continued

**Stent Placement – Precautions (continued)**

- ?? Although the stent delivery balloon catheter is strong enough to expand the stent without rupture, a circumferential tear of the carrier balloon distal to the stent and prior to complete expansion of the stent could cause the balloon to become tethered to the stent, requiring surgical removal. In case of rupture of the balloon, it should be withdrawn and, if necessary, a new balloon catheter exchanged over the guidewire to complete the expansion of the stent.
- ?? Implanting a stent may lead to a dissection of the vessel distal and/or proximal to the stented portion and may cause acute closure of the vessel requiring additional intervention (CABG, further dilatation, placement of additional stents, or other intervention).
- ?? Do not expand the stent if it is not properly positioned in the vessel. (See Stent/System Removal – Precautions.)
- ?? Placement of the stent has the potential to compromise side branch patency.
- ?? Balloon pressures should be monitored during inflation. **Do not exceed rated burst pressure as indicated on the product label.** Use of pressures higher than those specified on the product label may result in a ruptured balloon with possible intimal damage and dissection.
- ?? **Do not attempt to pull an unexpanded stent back through the guiding catheter, as dislodgment of the stent from the balloon may occur. Remove as a single unit per instructions in Stent/System Removal – Precautions.**
- ?? Stent retrieval methods (use of additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.
- ?? Ensure full coverage of the entire lesion/dissection site so that there are no gaps between stents.

**Stent System Removal – Precautions**

Should **unusual resistance** be felt **at any time** during either lesion access or removal of the stent delivery system before stent implantation, the entire system **should be removed as a single unit.**

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**5. Precautions,**  
continued

**When removing the Delivery System as a single unit:**

- ?? Do not retract the delivery system into the guiding catheter.
- ?? Advance the guidewire into the coronary anatomy as far distally as safely possible.
- ?? Tighten the rotating hemostatic valve to secure the stent delivery system to the guiding catheter; then remove the guiding catheter and stent delivery system as a **single unit**.

Failure to follow these steps or applying excessive force to the stent delivery system can potentially result in loss or damage to the stent or stent delivery system.

If it is necessary to retain the guidewire in position for subsequent artery/lesion access, leave the guidewire in place and remove all other system components.

**Post Implant – Precautions**

- ?? Great care must be exercised **when crossing a newly deployed stent** with an intravascular ultrasound (IVUS) catheter, a coronary guidewire or balloon catheter to avoid disrupting the stent geometry.
  - ?? Do not perform a **magnetic resonance imaging** (MRI) scan on a patient after stent implantation until the stent has completely endothelialized (eight weeks) to minimize the potential for migration. The stent may cause artifacts in MRI scans due to distortion of the magnetic field.
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**6. Device Description**      The device description is provided in tabular format.

<b>Description</b>	<b>CYPHER? Sirolimus-eluting Stent on Raptor Over-the-Wire SDS</b>	<b>CYPHER? Sirolimus-eluting Stent on RaptorRail Rapid Exchange SDS</b>
Available Stent Lengths, unexpanded (mm):	8, 13, 18, 23, 28 & 33	8, 13, 18, 23, 28 & 33
Available Stent Diameters (mm):	2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50 and 5.00	2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50 and 5.00
Stent Material:	Electropolished stainless steel (316L), laser-cut from seamless tubing in a sinusoidal pattern coated with a polymer and Sirolimus mixture.	
Stent Geometry:	Six circumferential cells (2.25 mm – 3.00 mm stents), Seven circumferential cells (3.50 – 4.00 mm stents) or Nine circumferential cells (4.50 – 5.00 mm stents).	
Nominal Stent Foreshortening:	1 mm or less for stents <4.00mm in diameter or <18 mm in length 2 mm or less for stents ≥ 4.00mm in diameter and ≥ 18mm in length	
Delivery System Usable Length:	145 cm	137 cm
Delivery System Y-Adapter Ports:	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen – designed for guidewire ≤ 0.014" (0.36 mm).)	Single access port to the inflation lumen. A guidewire exit port is located at 28 cm from the tip. Designed for guidewire guidewire ≤ 0.014" (0.36 mm).
Stent Delivery Balloon:	Single-layer nylon, nominally 2 mm longer than stent. Mounted stent length and location is defined by 2 platinum-iridium radiopaque marker bands.	
Balloon Inflation Pressure:	Nominal pressure for diameters 2.25 – 4.00mm: 11 atm (1115kPa) Nominal pressure for diameters 4.50 – 5.00mm: 10 atm (1031kPa) Rated Burst Pressure: 16 atm (1621 kPa)	
Guiding Catheter Inner Diameter:	? 0.067" (1.7 mm) for 2.25 – 4.00 mm ? 0.078" (1.98mm) for 4.00 – 5.00 mm	≥ 0.056" (1.4 mm) for 2.25 – 3.00 mm ? 0.067" (1.7 mm) for 3.50 – 4.00 mm ? 0.078" (1.98mm) for 4.50 – 5.00 mm
Catheter Shaft Outer Diameter:	3.3F proximally, 2.7F distally.	2.3F proximally, 2.6F distally (? up to 3.00 mm), 2.9F distally (? >3.00 mm).

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**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.

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**8. Marketing History**

The CYPHER<sup>?</sup> Sirolimus-eluting Stent is approved in Argentina, Australia, Brazil, Czech & Slovak Republic, the European Community, Hong Kong, India, Malaysia, Mexico, Pakistan, Peru, Philippines, Russia, Singapore, South Africa, Thailand, Uruguay, Venezuela, and Vietnam.

As of September 1, 2002, approximately 20,000 CYPHER<sup>?</sup> Sirolimus-eluting Stents have been distributed outside the United States. No products have been withdrawn from the market in any country for any reason.

**9. Adverse Events****Observed Adverse Events**

A total of 1058 patients were enrolled in a multi-center, double-blind, randomized clinical trial (SIRIUS trial) to evaluate the use of the Cordis CYPHER Sirolimus-eluting Stent for treatment of symptomatic ischemic coronary artery disease.

Additionally, data are provided on the RAVEL trial (multi-center, double-blind, randomized, 238 patients).

Major Adverse Cardiac Events, In-Hospital vs. Out-of-Hospital						
	SIRIUS (N=1058) to 270 Days			RAVEL (N=238) to 365 Days		
	Sirolimus-eluting Bx VELOCITY™ (N=533 Patients N=533 Lesions)	BX VELOCITY™ (N=525 Patients N=531 Lesions)	All Patients (N=1058 Patients N=1064 Lesions)	Sirolimus-eluting Bx VELOCITY™ (N=120)	BX VELOCITY™ (N=118)	All Patients (N=238)
<b>In-Hospital Complication</b>						
MACE (Death, Q wave or non-Q wave MI, Em CABG, TLR)*	13 (2.4%)	8 (1.5%)	21 (2.0%)	3 (2.5%)	3 (2.5%)	6 (2.5%)
Death	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Myocardial Infarction	12 (2.3%)	8 (1.5%)	20 (1.9%)	3 (2.5%)	3 (2.5%)	6 (2.5%)
- Q-wave	2 (0.4%)	0 (0.0%)	2 (0.2%)	2 (1.7%)	1 (0.8%)	3 (1.3%)
- Non Q-wave	10 (1.9%)	8 (1.5%)	18 (1.7%)	1 (0.8%)	2 (1.7%)	3 (1.3%)
Emergent CABG	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Target Lesion Revascularization	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- TL CABG	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- TL RPTCA	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MACE				3 (2.5%)	3 (2.5%)	6 (2.5%)
Target Vessel Revascularization not involving Target Lesion	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
- TV/non-TL-CABG	0 (0.0%)	0 (0.0%)	0 (0.0%)			
- TV/non-TL-PTCA	0 (0.0%)	0 (0.0%)	0 (0.0%)			
Target Vessel Failure	13 (2.4%)	8 (1.5%)	21 (2.0%)	3 (2.5%)	3 (2.5%)	6 (2.5%)
Stent Thrombosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sub-acute Closure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CVA	1 (0.2%)	4 (0.8%)	5 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Out-of-Hospital Complications</b>						
MACE (Death, Q wave or non-Q wave MI, Em CABG, TLR)*	26 (4.9%)	93 (17.7%)	119 (11.2%)	4 (3.3%)	20 (16.9%)	24 (10.1%)
Death	4 (0.8%)	3 (0.6%)	7 (0.7%)	2 (1.7%)	2 (1.7%)	4 (1.7%)
Myocardial Infarction	3 (0.6%)	9 (1.7%)	12 (1.1%)	1 (0.8%)	3 (2.5%)	4 (1.7%)
- Q-wave	2 (0.4%)	2 (0.4%)	4 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Non Q-wave	1 (0.2%)	7 (1.3%)	8 (0.8%)	1 (0.8%)	3 (2.5%)	4 (1.7%)
Emergent CABG	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Target Lesion Revascularization	21 (3.9%)	87 (16.6%)	108 (10.2%)	1 (0.8%)	16 (13.6%)	17 (7.1%)
- TL CABG	3 (0.6%)	8 (1.5%)	11 (1.0%)	1 (0.8%)	0 (0.0%)	1 (0.4%)
- TL RPTCA	19 (3.6%)	83 (15.8%)	102 (9.6%)	0 (0.0%)	16 (13.6%)	16 (6.7%)
Target Vessel Revascularization not involving Target Lesion	17 (3.2%)	25 (4.8%)	42 (4.0%)	0 (0.0%)	1 (0.8%)	1 (0.4%)
- TV/non-TL-CABG	3 (0.6%)	7 (1.3%)	10 (0.9%)			
- TV/non-TL-PTCA	15 (2.8%)	19 (3.6%)	34 (3.2%)			
Target Vessel Failure (Primary Endpoint*)	34 (6.4%)	103 (19.6%)	137 (12.9%)	2 (1.7%)	21 (17.8%)	23 (9.7%)
Stent Thrombosis	1 (0.2%)	1 (0.2%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sub-acute Closure	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Late Thrombosis	1 (0.2%)	3 (0.6%)	4 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CVA	4 (0.8%)	5 (1.0%)	9 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CI - Confidence Interval						
Difference = Sirolimus - Bx VELOCITY™	SE = sqrt(p1*q1/n1+p2*q2/n2)		CI = Diff ± 1.96*SE			
* Primary endpoint for SIRIUS trial.						

<b>Table First-in-Man: Clinical Events</b>	
<b>All Patients Treated with Slow Release Formulation (N = 30)</b>	
<b>Parameters</b>	<b>Counts (%)</b>
In Hospital	
Any MACE <sup>1</sup>	2/30 (6.7%)
Death	1/30 (3.3%)
MI <sup>2</sup>	1/30 (3.3%)
Target Lesion Revascularization	0/30 (0.0%)
CABG	0/30 (0.0%)
PTCA	0/30 (0.0%)
Target Vessel Revascularization not involving the TL	1/30 (3.3%)
Out of Hospital (1 month)	
Any MACE <sup>1</sup>	0/30 (0.0%)
Death	0/30 (0.0%)
MI <sup>2</sup>	0/30 (0.0%)
Target Lesion Revascularization	0/30 (0.0%)
CABG	0/30 (0.0%)
PTCA	0/30 (0.0%)
Target Vessel Revascularization not involving the TL	0/30 (0.0%)
Out of Hospital (24 months)	
Any MACE <sup>1</sup>	1/30 (3.3%)
Death	0/30 (0.0%)
MI <sup>2</sup>	0/30 (0.0%)
Target Lesion Revascularization	1/30 (3.3%)
CABG	0/30 (0.0%)
PTCA	1/30 (3.3%)
Target Vessel Revascularization not involving the TL	1/30 (3.3%)
Combined (24 months)	
Any MACE <sup>1</sup>	3/30 (10.0%)
Death	1/30 (3.3%)
MI <sup>2</sup>	1/30 (3.3%)
Target Lesion Revascularization	1/30 (3.3%)
CABG	0/30 (0.0%)
PTCA	1/30 (3.3%)
Target Vessel Revascularization not involving the TL	2/30 (6.7%)
<sup>1</sup> MACE is a composite endpoint comprised of deaths, WHO defined non-Q wave myocardial infarction, Q-wave myocardial infarction, or target lesion revascularization.	
<sup>2</sup> MI includes WHO defined non-Q wave myocardial infarction and Q-wave myocardial infarction.	

**Potential Adverse Events**

Adverse events (in alphabetical order) which may be associated with the implantation of a coronary stent in coronary arteries:

- Allergic reaction
- Aneurysm
- Arrhythmias
- Cardiac tamponade
- Death
- Dissection
- Drug reactions to antiplatelet agents / anticoagulation agents / contrast media
- Emboli, distal (tissue, air, or thrombotic emboli)
- Embolization, stent
- Emergency CABG
- Failure to deliver the stent to the intended site
- Fever
- Fistulization
- Hemorrhage
- Hypotension/Hypertension
- Infection and pain at the intended site
- Myocardial infarction
- Myocardial ischemia
- Occlusion
- Prolonged angina
- Pseudoaneurysm
- Renal failure
- Restenosis of stented segment (greater than 50% obstruction)
- Rupture of native and bypass graft
- Stent compression
- Stent migration
- Stroke
- Thrombosis (acute, subacute, or late)
- Ventricular fibrillation
- Vessel spasm
- Vessel perforation

Although systemic effects of sirolimus are not anticipated, see Physicians' Desk Reference<sup>2</sup> for more information concerning potential adverse effects observed with RAPAMUNE<sup>3</sup>

<sup>2</sup> Physicians' Desk Reference, published by Medical Economics Company, Inc. at Montvale, NJ.

<sup>3</sup> Rapamune is a registered trademark of Wyeth Pharmaceuticals.

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**10. Summary of Non-clinical Laboratory Studies – *In vitro* Testing**

*In vitro* studies were conducted to support the design and performance for the CYPHER Sirolimus-eluting Stent mounted on either the RAPTOR™ Over the Wire (OTW) stent delivery system or the RAPTORRAIL™ Rapid Exchange (RX) stent delivery system. All testing was performed in accordance with an established protocol. The results of the tests revealed that the CYPHER Sirolimus-eluting Stent mounted on either the RAPTOR™ Over the Wire stent delivery system or the RAPTORRAIL™ Rapid Exchange stent delivery system performed in accordance with established specifications. The details of the testing are included in the next section.

**Details of *in vitro* Tests**

The following are the details for the *in vitro* studies conducted to support the design and performance for the CYPHER Sirolimus-eluting Stent mounted on either the RAPTOR™ Over the Wire stent delivery system or the RAPTORRAIL™ Rapid Exchange stent delivery system.

Test	Description of Test	Results
Material Analysis	Material analysis and testing for surface impurities was conducted on the stainless steel tubing used to fabricate the stents.	Pass
Mechanical Properties	Testing was performed to characterize the tensile strength and percent elongation of the tubing sizes used to fabricate the stents.	Pass
Corrosion	Corrosion testing was performed as part of the fatigue testing on the stents to analyze the stent for resistance to corrosion.	Pass
Stent Free Area & dimensional changes (foreshortening)	The percent change in free or open area and stent foreshortening were tested for the stents.	Pass
Stent Uniformity Testing	The stent uniformity testing was conducted on the stent. It was calculated by subtracting the maximum outer diameter measurement of the stent from the minimum outer diameter measurement of the stent and dividing this result by the labeled inner diameter of the stent, then multiplying by 100%. This testing compares the stent diameter measurements along the expanded stent length.	Pass
Radial (hoop) Strength	The radial strength of the stent was tested to ensure it could withstand radial compression.	Pass
Fatigue Testing	An accelerated 10-year fatigue equivalent and finite element analysis (FEA) was conducted on the stent to demonstrate the ability of this stent design to maintain structural integrity.	Pass
Stent Recoil	The recoil of the stent was tested to quantify the amount of diameter reduction experienced after the inflated balloon no longer supports the stent. The recoil is calculated by subtracting the internal stent diameter after balloon deflation from the internal diameter on the inflated balloon. The foreshortening of the stent was tested to determine the amount of length reduction the stent may experience after it is expanded to the rated burst pressure. The foreshortening is calculated by subtracting the expanded length from the crimped length.	Pass

<b>Test</b>	<b>Description of Test</b>	<b>Results</b>
Magnetic Resonance Imaging	The interaction between the implanted stent and magnetic resonance imaging was evaluated.	Pass
Stent Expansion/ Crack Initiation	The stent expansion testing was conducted on the stent as part of fatigue testing. The test was conducted to determine whether the plastic deformation experienced by the stent in going from its initial to final position could give rise to crack initiation.	Pass
Dimensional Verification	Testing was conducted on the stent, delivery systems and stent/delivery systems to verify they meet their dimensional specifications.	Pass
Maximum Pressure (Burst: 95%, 99.9%)	Testing was conducted on the stent/delivery system to determine the burst pressure rating for the delivery systems. The results demonstrate statistically with 95% confidence at least 99.9% of the balloons will not experience loss of integrity at or below the rated burst pressure.	Pass
Stent Diameter vs. Balloon Inflation Pressure (Compliance)	Testing was performed on the stent/delivery systems to verify that the stent would expand to within ten percent of the labeled diameter in the working pressure range for the delivery system.	Pass
Bond Strength	The delivery systems were tested to quantify the tensile strength of each catheter joint (balloon distal seal/tip, balloon proximal seal, hub to catheter shaft bond and transition seal) and meets specifications.	Pass
Diameter and Profile	The delivery systems were tested to determine the diameter of the catheter shaft, profile of the balloons and inflated diameter of the balloons to ensure that the actual diameter matches the labeled diameters.	Pass
Balloon Deflatability	The delivery systems were tested to verify that the balloon could be withdrawn from the deployed stent within a specified time.	Pass
Balloon Inflation and Deflation Time	Testing was conducted on the stent/delivery systems to verify the device successfully deploys the stent and that the balloon deflates within a specified time.	Pass
Multiple Inflations	Testing was conducted on the stent/delivery systems to determine the ability of the delivery system to withstand multiple consecutive inflation cycles to the rated burst pressure without failure.	Pass
Catheter Body Maximum Pressure	Testing was conducted on the stent/delivery systems to determine the ability of the adhesive bond (hub/shaft), the catheter shaft and the transition seal to withstand the rated burst pressure.	Pass
Tip Pulling and Torquing	Testing was conducted on the delivery systems to verify that the force required to break the joints and/or materials in the distal end of the catheter is sufficiently large to assure the integrity of the tip during pulling, pushing or torquing maneuvers.	Pass
Stent Retention	Testing was conducted on the stent/delivery system to determine the tensile force required to move the crimped stent away from the original crimped position.	Pass
Crossing Profile	Testing was conducted on the stent/delivery systems to determine the crossing profile of the system.	Pass

Test	Description of Test	Results
Drug Content/ Impurities	Testing was conducted on the stent to verify the drug content meets specifications for both finished goods release and stability testing.	Pass
Residual Solvents	Testing was conducted on the stent to verify the residual levels of the solvents used in manufacturing meet specifications.	Pass
Elution	Testing was performed on the stent to evaluate the release performance of the stent meets specifications.	Pass
Particulate Testing	Testing was performed to evaluate the coating for particulates that could be generated by the coating or stent deployment.	Pass
Polymer Stability	Testing was conducted to establish the 10-year equivalent chemical and mechanical stability for CYPHER™ Sirolimus eluting Stent coating materials.	Pass

**10. Summary of  
Non-clinical  
Laboratory  
Studies –  
Biocompatibility**

SDS Components and Stent-contacting Packaging Materials

Tests were conducted to support the biocompatibility of the SDS systems and stent-contacting packaging materials. GLP biocompatibility tests and USP Enhanced Physicochemical Testing were performed in accordance with ISO 10993-1 on the SDS components and stent-contacting materials. In all of these tests systems, the materials were non-reactive and produced no greater response than the negative control employed in each test system.

Polymer and Stent Materials

Tests were conducted to support the biocompatibility of the polymer and stent materials. Biocompatibility testing was conducted in accordance with ISO 10993-1 on ethylene oxide-sterilized, polymer-coated 316L stainless steel stents or polymer-coated 316L stainless steel coupons. In addition, thrombogenicity of polymer-coated stents was evaluated through a series of porcine feasibility implant studies. Complement activation, leukocyte migration (*in vitro* and *in vivo*), and muscle implant (3- and 30-day in rat, 7- and 14-day in rabbit) tests were also performed on polymer-coated stents. In all of these tests, the polymer-coated stainless steel was non-reactive and produced no greater response than the negative control employed in each test system.

CYPHER? Sirolimus-eluting Stents

Tests were conducted to support the biocompatibility of the sirolimus-eluting coronary stent. The safety and biocompatibility were assessed in conjunction with a series of feasibility studies evaluating the efficacy of sirolimus-eluting stents in porcine, rabbit and canine models of stent-mediated vascular injury. The intravascular safety and biocompatibility were also evaluated in a six-month GLP safety study in pigs. The results of these tests support the biocompatibility of the sirolimus-eluting stent.

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**10. Non-clinical Laboratory Studies – Shelf Life Studies** Shelf life testing was conducted to support a 12-month shelf life for the CYPHER Sirolimus-eluting Stent. In addition, an on-going stability program has been established that will generate site specific stability data.

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**10. Non-clinical Laboratory Studies – Animal Studies** Animal testing was conducted to support the safety and efficacy of the CYPHER Sirolimus-eluting Stent mounted on either the RAPTOR™ Over the Wire stent delivery system or the RAPTORRAIL™ Rapid Exchange stent delivery system.

#### GLP Efficacy Studies

The ability of sirolimus to reduce intimal hyperplasia in response to stent implantation was evaluated in a series of GLP studies in a porcine model of stent-mediated vascular injury. The studies included: a six-month biocompatibility study of the fast-eluting (1X) and slow-eluting (1XTC) formulations; a 30 day study of the 1XTC formulation produced under validated clinical manufacturing conditions; a 90 day re-endothelialization study of the 1XTC formulation and a 30 day study of the 1XTC formulation with varying doses of sirolimus. Collectively, these studies indicate that sirolimus consistently reduces neointimal hyperplasia following implantation in normal pig coronary arteries or rabbit iliac arteries and suggest that sirolimus may be useful in preventing restenosis in humans when delivered from a polymeric stent coating.

#### In Vivo Elution of Sirolimus

The *in vivo* elution rate of sirolimus from the polymer formulation was evaluated in several feasibility studies and in several GLP studies.

#### Feasibility Studies

Feasibility studies were conducted with sirolimus formulated at various concentrations in the polymer matrix and coated on Cordis coronary stents with or without a topcoat. These tests served as a basis for device design and dose selection for our clinical investigations.

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## 10. Summary of Studies – Clinical Investigations

### Conclusion SIRIUS study:

In suitable patients, elective Sirolimus-eluting Bx VELOCITY™ stent placement in native coronary *de novo* lesions resulted in significantly lower angiographic in-stent late loss (0.17 mm vs. 1.00 mm, difference [95% CI] -0.83 [-0.92, -0.74]) at 8 month follow-up and significantly lower cumulative incidence of the primary endpoint target vessel failure (TVF) (8.6% vs. 21.0%, difference [95% CI] -12.3% [-16.5%, -8.1%]) at 270 days post procedure as compared to uncoated Bx VELOCITY™ stent control. In the Sirolimus arm, 8-month follow-up angiography revealed: mean in-stent % diameter stenosis was significantly reduced (10.5% vs. 40.1%, difference [95% CI] -29.6% [-32.8%, -26.4%]), in-stent binary restenosis was significantly reduced (3.2% vs. 35.4%, difference [95% CI] -32.2% [-37.6%, -26.9%]); mean in-lesion % diameter stenosis was significantly reduced (23.6% vs. 43.3%, difference [95% CI] -19.6% [-22.5%, -16.7%]), in-lesion binary restenosis was significantly reduced (8.9% vs. 36.3%, difference [95% CI] -27.4% [-33.2%, -21.5%]); and there was no evidence of an edge-effect 5 mm proximal or distal to the stent. Neointimal hyperplasia (NIH) volume by intravascular ultrasound (IVUS) was also significantly reduced in the Sirolimus arm (4.1 mm<sup>3</sup> vs. 56.8 mm<sup>3</sup>, difference [95% CI] -52.7 [-62.3, -43.1]). The reductions described above lead to a highly significant reduction in incidence of target lesion revascularization (TLR) at 270 days (4.1 vs. 16.6%, difference [95% CI] -12.4% [-16.0%, -8.8%]).

### Conclusion RAVEL study:

In suitable patients, elective Sirolimus-eluting Bx VELOCITY™ stent placement in native coronary *de novo* lesions resulted in significantly lower angiographic in-stent late loss (0.0mm vs. 0.8 mm, difference [95% CI] -0.8 [-0.9, -0.7]) at 6 month follow-up and significantly lower major adverse cardiac events (MACE) (5.8% vs. 18.6%, difference [95% CI] -12.8% [-21.0%, -4.6%]) at 365 days post-procedure as compared to uncoated Bx VELOCITY™ stent control. In the Sirolimus arm, 6-month follow-up angiography revealed: mean % diameter stenosis was significantly reduced (14.7 vs. 36.7, difference [95% CI] -22.0 [-25.6, -18.4]); there were no instances of binary restenosis [≥ 50% diameter stenosis] with observed rates of 0.0% vs. 26.6%, difference [95% CI] -26.6% [-34.9%, -18.3%]); and there was no evidence of an edge effect 5 mm proximal or distal to the stent. Percent volume obstruction in-stent by intravascular ultrasound (IVUS) was also significantly reduced in the Sirolimus arm (1.1 vs. 26.1, difference [95% CI] -25.0 [-30.3, -19.7]). The reductions in the Sirolimus arm led to a highly significant reduction in incidence of target lesion revascularization (TLR) at 365 days (0.8% vs. 13.6%, difference [95% CI] -12.7% [-19.1%, -6.3%]).

**Conclusion First-In-Man Study:**

In 45 suitable patients, elective sirolimus-eluting Bx VELOCITY™ stent placement in native coronary de novo lesions resulted in 100% procedure success. At 18 to 24 months, the in-stent mean percent diameter stenosis (%DS) ranged from 1.4% to 13.1% and mean in-stent late loss ranged from 0.09 mm to 0.28 mm. Loss of stent volume (obstruction volume) by neointima ranged from means of 2.27% to 7.53% by Intravascular Ultrasound (IVUS) at 18 to 24 months. The overall MACE rate at 24 months was 11.1% (5/45); 1 patient (2.2%) expired at 3 days, 3 patients (6.7%) had a target lesion revascularization, and 2 patients (4.4%) had a WHO defined non-Q wave myocardial infarction. Of the patients treated with the slow release formulation (n=30), the overall MACE rate at 24 months was 10.0% (3/30); 1 patient (3.3%) expired at 3 days, 1 patient (3.3%) had a target lesion revascularization, and 1 patient (3.3%) had a WHO defined non-Q wave myocardial infarction.

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Table SIRIUS: Principal Effectiveness and Safety Results (to 270 Days)

All Patients Treated						
Effectiveness Measures	Sirolimus-eluting Bx VELOCITY? (N=533 Patients N=533 Lesions)	Bx VELOCITY? (N=525 Patients N=531 Lesions)	All Patients (N=1058 Patients N=1064 Lesions)	Relative Risk [95% CI]	Difference [95% CI]	P-Value
Lesion Success	99.8% (532/533)	100.0% (531/531)	99.9% (1063/1064)	1.00 [0.99, 1.00]	-0.2% [-0.6%, 0.2%]	1.000
Device Success	97.9% (522/533)	98.7% (524/531)	98.3% (1046/1064)	0.99 [0.98, 1.01]	-0.7% [-2.3%, 0.8%]	0.477
Procedure Success*	97.4% (519/533)	98.5% (517/525)	97.9% (1036/1058)	0.99 [0.97, 1.01]	-1.1% [-2.8%, 0.6%]	0.281
Post-Procedure in-Stent Minimal Lumen Diameter (MLD, in mm)						
Mean $\pm$ SD (N)	2.67 $\pm$ 0.40 (528)	2.68 $\pm$ 0.42 (526)	2.68 $\pm$ 0.41 (1054)	N/A	0.00 [-0.05, 0.05]	0.978
Range (min, max)	(1.71, 4.22)	(1.41, 4.25)	(1.41, 4.25)			
Post-Procedure In-Stent Percent Diameter Stenosis (%DS)						
Mean $\pm$ SD (N)	5.4 $\pm$ 8.2% (528)	6.0 $\pm$ 7.9% (526)	5.7 $\pm$ 8.1% (1054)	N/A	-0.6% [-1.6%, 0.4%]	0.222
Range (min, max)	(-34.5%, 28.1%)	(-30.3%, 34.7%)	(-34.5%, 34.7%)			
Post-Procedure in-Lesion Minimal Lumen Diameter (MLD, in mm)						
Mean $\pm$ SD (N)	2.38 $\pm$ 0.45 (529)	2.40 $\pm$ 0.46 (526)	2.39 $\pm$ 0.46 (1055)	N/A	-0.01[-0.07, 0.04]	0.627
Range (min, max)	(0.00, 4.00)	(1.16, 3.75)	(0.00, 4.00)			
Post-Procedure In-Lesion Percent Diameter Stenosis (%DS)						
Mean $\pm$ SD (N)	16.1 $\pm$ 9.7% (529)	16.2 $\pm$ 8.5% (526)	16.2 $\pm$ 9.1% (1055)	N/A	-0.1% [-1.2%, 1.0%]	0.799
Range (min, max)	(-5.5%, 100.0%)	(-2.9%, 49.1%)	(-5.5%, 100.0%)			
Eight-Month Follow-up In-Stent Minimal Lumen Diameter (MLD, in mm)						
Mean $\pm$ SD (N)	2.50 $\pm$ 0.58 (348)	1.68 $\pm$ 0.80 (353)	2.09 $\pm$ 0.81 (701)	N/A	0.81 [0.71, 0.92]	<0.001
Range (min, max)	(0.00, 4.05)	(0.00, 3.70)	(0.00, 4.05)			
Eight-Month Follow-up In-Stent Percent Diameter Stenosis (%DS)						
Mean $\pm$ SD (N)	10.5 $\pm$ 16.7% (348)	40.1 $\pm$ 25.3% (353)	25.4 $\pm$ 26.1% (701)	N/A	-29.6% [-32.8%, -26.4%]	<0.001
Range (min, max)	(-33.2%, 100.0%)	(-10.3%, 100.0%)	(-33.2%, 100.0%)			
Eight-Month Follow-up In-Lesion Minimal Lumen Diameter (MLD, in mm)						
Mean $\pm$ SD (N)	2.15 $\pm$ 0.61 (349)	1.60 $\pm$ 0.72 (353)	1.87 $\pm$ 0.72 (702)	N/A	0.55 [0.45, 0.65]	<0.001
Range (min, max)	(0.00, 3.76)	(0.00, 3.45)	(0.00, 3.76)			
Eight-Month Follow-up In-Lesion Percent Diameter Stenosis (%DS)						
Mean $\pm$ SD (N)	23.6 $\pm$ 16.4% (349)	43.3 $\pm$ 22.4% (353)	33.5 $\pm$ 22.0% (702)	N/A	-19.6% [-22.5%, -16.7%]	<0.001
Range (min, max)	(-8.3%, 100.0%)	(4.3%, 100.0%)	(-8.3%, 100.0%)			
Eight-Month Late Loss In-Stent (mm)						
Mean $\pm$ SD (N)	0.17 $\pm$ 0.44 (346)	1.00 $\pm$ 0.70 (350)	0.59 $\pm$ 0.72 (696)	N/A	-0.83 [-0.92, -0.74]	<0.001
Range (min, max)	(-1.23, 2.65)	(-0.80, 3.12)	(-1.23, 3.12)			
Eight-Month Late Loss In-Lesion (mm)						
Mean $\pm$ SD (N)	0.24 $\pm$ 0.48 (347)	0.81 $\pm$ 0.67 (350)	0.52 $\pm$ 0.65 (697)	N/A	-0.57 [-0.66, -0.48]	<0.001
Range (min, max)	(-0.93, 2.24)	(-0.93, 2.78)	(-0.93, 2.78)			
Eight-Month In-Stent Binary Restenosis	3.2% (11/348)	35.4% (125/353)	19.4% (136/701)	0.09 [0.06, 0.14]	-32.2% [-37.6%, -26.9%]	<0.001
Eight-Month In-Lesion Binary Restenosis	8.9% (31/349)	36.3% (128/353)	22.6% (159/702)	0.24 [0.18, 0.34]	-27.4% [-33.2%, -21.5%]	<0.001
Eight-Month Minimum Lumen Area (mm <sup>2</sup> )						
Mean $\pm$ SD (N)	5.4 $\pm$ 2.1 (99)	3.9 $\pm$ 1.9 (76)	4.7 $\pm$ 2.2 (175)	N/A	1.6 [0.9, 2.2]	<0.001
Range (min, max)	(1, 13)	(1, 11)	(1, 13)			
Eight-Month NIH Volume (mm <sup>3</sup> )						
Mean $\pm$ SD (N)	4.1 $\pm$ 5.9 (45)	56.8 $\pm$ 31.7 (42)	29.5 $\pm$ 34.6 (87)	N/A	-52.7 [-62.3, -43.1]	<0.001
Range (min, max)	(0, 21)	(8, 124)	(0, 124)			
TLR-Free at 270 days <sup>†</sup>	95.7%	82.9%	89.3%	N/A	12.8% [8.7%, 16.9%]	<0.001
TVR-Free at 270 days <sup>†</sup>	93.6%	80.8%	87.1%	N/A	12.8% [8.4%, 17.2%]	<0.001
TVF-Free at 270 days <sup>†</sup>	91.1%	78.6%	84.9%	N/A	12.6% [7.9%, 17.3%]	<0.001
MACE-Free at 270 days <sup>†</sup>	92.7%	80.7%	86.7%	N/A	12.0% [7.6%, 16.5%]	<0.001
<b>Safety Measures</b>						
In-Hospital MACE*	2.4% (13/533)	1.5% (8/525)	2.0% (21/1058)	1.60 [0.67, 3.80]	0.9% [-0.8%, 2.6%]	0.379
Out-of-Hospital MACE to 270 days*	4.9% (26/533)	17.7% (93/525)	11.2% (119/1058)	0.28 [0.19, 0.40]	-12.8% [-16.6%, -9.1%]	<0.001
MACE to 270 days*	7.1% (38/533)	18.9% (99/525)	12.9% (137/1058)	0.38 [0.27, 0.53]	-11.7% [-15.7%, -7.7%]	<0.001
TVF to 270 days (Primary Endpoint)*	8.6% (46/533)	21.0% (110/525)	14.7% (156/1058)	0.41 [0.30, 0.56]	-12.3% [-16.5%, -8.1%]	<0.001
Stent Thrombosis to 30 days	0.2% (1/533)	0.2% (1/525)	0.2% (2/1058)	0.98 [0.06, 15.73]	0.0% [-0.5%, 0.5%]	1.000
Late Thrombosis to 270 days	0.2% (1/533)	0.6% (3/525)	0.4% (4/1058)	0.33 [0.04, 2.81]	-0.4% [-1.1%, 0.4%]	0.371
Subacute Closure	0.2% (1/533)	0.0% (0/525)	0.1% (1/1058)	-- [--, --]	0.2% [-0.2%, 0.6%]	1.000
Cerebrovascular Accident (CVA) to 270 days	0.9% (5/533)	1.7% (9/525)	1.3% (14/1058)	0.55 [0.19, 1.60]	-0.8% [-2.2%, 0.6%]	0.295
Major Bleeding Complications	3.4% (18/533)	3.4% (18/525)	3.4% (36/1058)	0.98 [0.52, 1.87]	-0.1% [-2.2%, 2.1%]	1.000
Major (Hemorrhagic) Vascular Complications	1.5% (8/533)	2.3% (12/525)	1.9% (20/1058)	0.66 [0.27, 1.58]	-0.8% [-2.4%, 0.9%]	0.376
Hematological Dyscrasia to 270 days	0.8% (4/533)	0.8% (4/525)	0.8% (8/1058)	0.98 [0.25, 3.92]	0.0% [-1.1%, 1.0%]	1.000
Numbers are % (counts/sample size) or Mean $\pm$ SD. CI = Confidence Interval Relative Risk = Sirolimus/Bx VELOCITY? SE = Calculated in SAS? Using Mantel-Haenszel Method CI = RR*exp( $\pm$ 1.96*SE)						
All event data were adjudicated by the independent Clinical Events Committee (CEC). All QCA data were assessed by the Angiographic Core Laboratory. All IVUS data were assessed by the IVUS Core Laboratory.						
Lesion Success (Lesion Based) – The attainment of <50% residual stenosis (by QCA), using any percutaneous method (if QCA was not available, the visual estimate of diameter stenosis was used).						
Device Success (Lesion Based) – Achievement of a final residual diameter stenosis of <50% (by QCA) using the assigned device only (if QCA was not available, the visual estimate of diameter stenosis was used).						
Procedure Success (Lesion Based) – Achievement of a final diameter stenosis of <50% (by QCA) using any percutaneous method, without the occurrence of death, Q wave or WHO-defined non-Q wave MI, or repeat revascularization of the target lesion during the hospital stay (if QCA was not available, the visual estimate of diameter stenosis was used).						
In-Lesion (Within Segment) – In-lesion measurement was defined as the measurements either within the stented segment or within 5 mm proximal or distal to the stent edges.						
In-Stent (Within Stent) – In-stent measurement was defined as the measurement within the stented segment.						
NIH = Neointimal Hyperplasia						
*Events rates in this table included the WHO definition of non-W wave MI.						
WHO-defined non-Q wave MI – Elevation of post-procedure CK levels to >2 times normal with elevated CKMB in the absence of new pathological Q waves.						
† The following survival estimates are by Kaplan-Meier Methods with standard error estimates by Peto formula:						
TLR-Free – No target lesion revascularization						
TVR-Free – No target vessel revascularization.						
TVF-Free – No cardiac death, Q-wave or WHO-defined non-Q wave MI, or target vessel revascularization.						
MACE-Free – No death, Q wave or WHO-defined non-Q wave MI, or target vessel revascularization.						
Major Adverse Cardiac Events (MACE) – A composite endpoint comprised of death, Q wave or WHO-defined non-Q wave MI, or target vessel revascularization.						
Target Vessel Failure (TVF) – A composite endpoint comprised of cardiac death, Q-wave or WHO-defined non-Q wave MI, or target vessel revascularization						
Stent Thrombosis – A 30-day endpoint including subacute closure or unexplained death or Q wave MI.						
Late Thrombosis – Myocardial infarction occurring >30 days after the index procedure and attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and freedom from an interim revascularization of the target vessel.						
Subacute (Subarupt) Closure – Abrupt closure that occurred after the index procedure was completed (and the patient left the catheterization laboratory) and before the 30-day follow-up endpoint.						
Cerebrovascular Accident (CVA) – Sudden onset of vertigo, numbness, aphasia, or dysarthria due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persisted >24 hours.						
Major Bleeding Complications – Bleeding requiring transfusions or associated with hemoglobin drop >5g.						
Major (hemorrhagic) Vascular Complication – Hematoma at access site >5 cm; false aneurysm; AV fistula; retroperitoneal bleed; peripheral ischemia/nerve injury; any transfusion required was reported as a vascular complication unless clinical indication clearly other than catheterization complication; and vascular surgical repair.						



<b>Table First-in-Man: Effectiveness and Safety Results</b>	
<b>All Patients Treated with Slow Release Formulation (N=30 Patients, 30 Lesions)</b>	
<b>Effectiveness Measures</b>	<b>Sirolimus-Eluting Bx VELOCITY? (N=30 Patients, N=30 Lesion)</b>
Procedure Success (QCA)	100.0% (30/30)
18-month In-Stent % DS – Slow Release Netherlands Mean ± SD (N)	3.2% ± 13.1% (10)
24-month In-Stent % DS – Slow Release Brazil Mean ± SD (N)	1.4% ± 5.9% (14)
18-Month In-Stent Late Loss (mm) – Slow Release Netherlands Mean ± SD (N)	0.20 ± 0.24 (10)
24-month In-Stent Late Loss (mm) – Slow Release Brazil Mean ± SD (N)	-0.09 ± 0.24 (14)
18-month Obstruction Volume (%) – Slow Release Netherlands Mean ± SD (N) Range (min, max)	2.27% ± 2.09% (7) (0.08%, 5.09%)
24-month Obstruction Volume (%) – Slow Release Brazil Mean ± SD (N) Range (min, max)	7.53% ± 7.27% (8) (0.01%, 18.29%)
24-month Target Lesion Revascularization (TLR)	3.3% (1/30)
<b>Safety Measures</b>	
In Hospital MACE Events	6.7% (2/30)
Out-of-Hospital MACE Events to 24 months	3.3% (1/30)
Combined (In and Out-of-Hospital) MACE Events to 24 months	10.0% (3/30)
<p>Numbers are % (counts available field sample size) or Mean ± Standard Deviation.            Procedure Success – The attainment of a final in-stent diameter stenosis of &lt;50% (by QCA) in the absence of death, emergent CABG, Myocardial Infarction, or TLR prior to hospital discharge.            QCA – Quantitative Coronary Angiography by Corelab            %DS – Percent Diameter Stenosis            MACE is a composite endpoint comprised of deaths, WHO defined non-Q wave myocardial infarction, Q-wave myocardial infarction, or target lesion revascularization.</p>	

**11. Conclusions Drawn from Studies**

Based on the non-clinical and clinical studies presented in this section, 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. Panel Recommendation**

TBD

**13. CDRH Decision**

TBD

**14. Approval Specifications**

TBD