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Instructions for Use

**CYPHER® Sirolimus-eluting Coronary Stent on RAPTOR™
Over-the-Wire Delivery System**

and

**CYPHER® Sirolimus-eluting Coronary Stent on RAPTORRAIL® Rapid
Exchange Delivery System**

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1. CYPHER® Sirolimus-eluting Coronary Stent System

The **CYPHER** Sirolimus-eluting Coronary Stent (**CYPHER** Stent) is a device/drug combination product comprised of two regulated components: a device (a **BX VELOCITY**® Stent System) and a drug product (a formulation of sirolimus in a polymer coating). The characteristics of the **CYPHER** Stent are described in Table 1-1.

Table 1-1: Device Component Description

| | CYPHER Stent on RAPTOR™ Over-the-Wire (OTW) Stent Delivery System | CYPHER Stent on RAPTORRAIL® Rapid Exchange (RX) Stent Delivery System |
|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Available Stent Lengths, unexpanded (mm): | 8, 13, 18, 23, 28, 33 | 8, 13, 18, 23, 28, 33 |
| Available Stent Diameters (mm): | 2.50, 2.75, 3.00, 3.50 | 2.50, 2.75, 3.00, 3.50 |
| Stent Material & Geometry: | A 316L stainless steel BX VELOCITY Stent; Six circumferential cells (2.50 - 3.00 mm) stents or seven circumferential cells (3.50 mm stents) | |
| Drug Component: | A coating of non-erodible polymers loaded with sirolimus in a formulation applied to the entire surface (i.e., luminal and abluminal) of the stent with a maximum nominal drug content of 314 µg on the largest stent (3.50 x 33 mm) | |
| Nominal Stent Foreshortening: | ≤ 1 mm | |
| 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 ≤ 0.014" (0.36 mm). |
| Stent Delivery Balloon: | Single-layer nylon, nominally 2 mm longer than stent with 2 platinum-iridium radiopaque marker bands. | |
| Balloon Inflation Pressure: | Nominal pressure: 11 atm (1115 kPa) Rated burst pressure: 16 atm (1621 kPa) | |
| Guiding Catheter Inner Diameter: | ≥ 0.067" (1.7 mm) | ≥ 0.056" (1.4 mm) for 2.50 – 3.00 mm ≥ 0.067" (1.7 mm) for 3.50 mm |
| Catheter Shaft Outer Diameter: | 3.3F (1.10 mm) proximally, 2.7F (0.90 mm) distally. | 2.3F (0.75 mm) proximally; 2.6F (0.85 mm) distally (Ø up to 3.00 mm); 2.9F (0.95 mm) distally (Ø > 3.00 mm). |

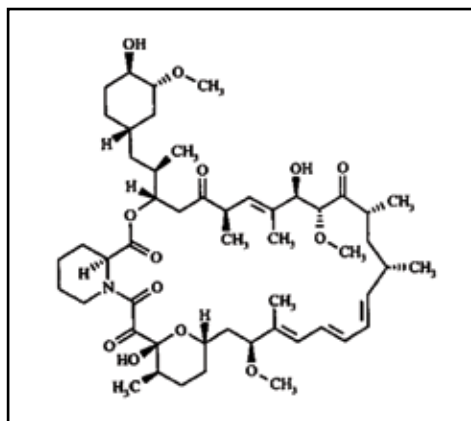
1.1. Device Component Description

The device component consists of the **BX VELOCITY** Balloon-Expandable Coronary Stent (**BX VELOCITY** Stent) premounted onto a stent delivery system (SDS), either the **RAPTOR** Over-the Wire (OTW) or the **RAPTORRAIL** Rapid Exchange (RX). The range of stent diameters is made possible by varying the number of circumferential "cells" on the stent. The 2.50, 2.75 and 3.00 mm diameter 316L stainless steel stents have six circumferential cells, whereas, the 3.50 mm diameter 316L stainless steel stents have seven circumferential cells. The stent is crimped on various size delivery catheter balloons, which are sized from 2.50 to 3.50 mm.

1.2. Drug Component Description

1.2.1. Sirolimus

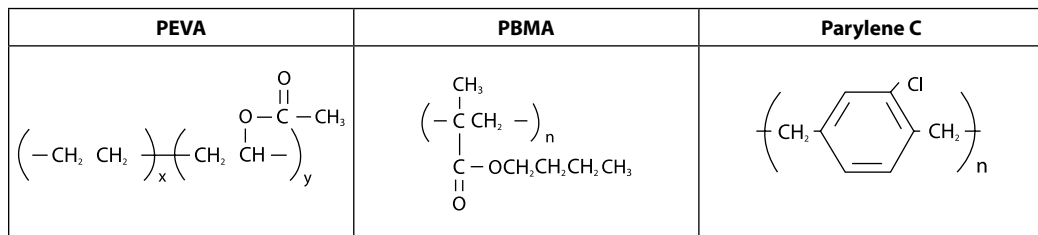
The active pharmaceutical ingredient in the **CYPHER** Stent is sirolimus (also known as rapamycin). Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. The chemical name of sirolimus is (3S,6R,7E,9R,10R,12R,14S,15E,17E,19E, 21S,23S,26R,27R, 34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentacontine-1,5,11,28,29 (4H,6H,31H)-pentone. Its molecular formula is C₅₁H₇₉NO₁₃ and its molecular weight is 914.2. The chemical structure of sirolimus is shown below:



Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile. Please refer to Table 1-2 for the nominal dosages of sirolimus on the **CYPHER** Stents.

1.2.2. Inactive Ingredients

The inactive ingredients in the CYPHER® Stent contain parylene C and the following two non-erodible polymers: polyethylene-co-vinyl acetate (PEVA) and poly n-butyl methacrylate (PBMA). A combination of the two polymers mixed with sirolimus (67%/33%) makes up the basecoat formulation which is applied to a parylene C treated stent. A drug-free topcoat solution of PBMA polymer is applied to the stent surface. The drug/polymer coating is adhered to the entire surface (i.e., luminal and abluminal) of the stent. The structural formulae of the polymer subunits are shown below:



1.2.3. Product Matrix and Sirolimus Content

Table 1-2: CYPHER Sirolimus-eluting Coronary Stent System Product Matrix & Nominal Sirolimus Dosages

| Product Code | | Nominal Expanded Stent ID (mm) | Nominal Unexpanded Stent Length (mm) | Nominal Sirolimus Content (µg) | Product Code | | Nominal Expanded Stent ID (mm) | Nominal Unexpanded Stent Length (mm) | Nominal Sirolimus Content (µg) |
|--------------|----------|--------------------------------|--------------------------------------|--------------------------------|--------------|----------|--------------------------------|--------------------------------------|--------------------------------|
| OTW | RX | | | | OTW | RX | | | |
| CWS08250 | CXS08250 | 2.50 | 8 | 71 | CWS23250 | CXS23250 | 2.50 | 23 | 190 |
| CWS08275 | CXS08275 | 2.75 | 8 | 71 | CWS23275 | CXS23275 | 2.75 | 23 | 190 |
| CWS08300 | CXS08300 | 3.00 | 8 | 71 | CWS23300 | CXS23300 | 3.00 | 23 | 190 |
| CWS08350 | CXS08350 | 3.50 | 8 | 83 | CWS23350 | CXS23350 | 3.50 | 23 | 221 |
| CWS13250 | CXS13250 | 2.50 | 13 | 111 | CWS28250 | CXS28250 | 2.50 | 28 | 229 |
| CWS13275 | CXS13275 | 2.75 | 13 | 111 | CWS28275 | CXS28275 | 2.75 | 28 | 229 |
| CWS13300 | CXS13300 | 3.00 | 13 | 111 | CWS28300 | CXS28300 | 3.00 | 28 | 229 |
| CWS13350 | CXS13350 | 3.50 | 13 | 129 | CWS28350 | CXS28350 | 3.50 | 28 | 268 |
| CWS18250 | CXS18250 | 2.50 | 18 | 150 | CWS33250 | CXS33250 | 2.50 | 33 | 268 |
| CWS18275 | CXS18275 | 2.75 | 18 | 150 | CWS33275 | CXS33275 | 2.75 | 33 | 268 |
| CWS18300 | CXS18300 | 3.00 | 18 | 150 | CWS33300 | CXS33300 | 3.00 | 33 | 268 |
| CWS18350 | CXS18350 | 3.50 | 18 | 175 | CWS33350 | CXS33350 | 3.50 | 33 | 314 |

2. Indications

The CYPHER Stent is indicated for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete *de novo* lesions of length ≤ 30 mm in native coronary arteries with a reference vessel diameter of ≥ 2.50 to ≤ 3.50 mm.

3. Contraindications

Use of the CYPHER Stent is contraindicated in the following patient types:

- Patients with a hypersensitivity to sirolimus or its structurally related compounds.
- Patients with a known hypersensitivity to polymethacrylates or polyolefin copolymers. See 1.2.2. – Inactive Ingredients for details.

Coronary artery stenting is contraindicated for use in:

- Patients who cannot receive recommended antiplatelet and/or anticoagulation therapy.
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery catheter.

4. Warnings

- Please ensure that the inner package has not been opened or damaged as this may indicate the sterile barrier has been breached.
- The use of this product carries the risks associated with coronary artery stenting, including sub thrombosis, vascular complications, and/or bleeding events.
- Patients with a known hypersensitivity to 316L stainless steel may suffer an allergic reaction to this implant.
- Patients who are unlikely to comply with recommended antiplatelet therapy should not receive this product.

5. Precautions

5.1. General Precautions

- 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.
- 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.
- Do not use Ethiodol or Lipiodol¹ contrast media.

¹ Ethiodol and Lipiodol are trademarks of Guerbet S.A.

- Do not expose the delivery system to organic solvents, such as alcohol, or detergents.
- Stent thrombosis is a low frequency event that current drug-eluting stent (DES) clinical trials are not adequately powered to fully characterize. Stent thrombosis is frequently associated with MI or death. Data from **CYPHER**® Stent randomized clinical trials (RAVEL and SIRIUS) have been prospectively evaluated and adjudicated using both the protocol definition of stent thrombosis and the definition developed by the Academic Research Consortium (ARC), and demonstrate specific patterns of stent thrombosis that vary depending on the definition used (See Section 9.4.1). In the **CYPHER** Stent clinical trials analyzed to date, differences in the incidence of stent thrombosis observed with the **CYPHER** Stent when compared to bare-metal stents have not been associated with an increased risk of cardiac death, myocardial infarction, or all-cause mortality. Additional data from longer-term follow-up in the randomized clinical trials on the **CYPHER** Stent (See Section 9.4.1) and analyses of DES-related stent thrombosis are expected and should be considered in making treatment decisions as data become available.
- When drug-eluting stents are used outside the specified Indications for Use, patient outcomes may differ from the results observed in the pivotal trials.
- Compared to use within the specified Indications for Use, the use of drug-eluting stents in patients and lesions outside the labeled indications may have an increased risk of adverse events, including stent thrombosis, stent embolization, myocardial infarction, or death.

5.2. Pre- and Post-Procedure Antiplatelet Regimen

- In the pivotal clinical trial of the **CYPHER** Stent, clopidogrel or ticlopidine was administered pre-procedure and for a period of three months post-procedure. Aspirin was administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce the risk of thrombosis. The use of aspirin together with clopidogrel or ticlopidine is referred to as “dual antiplatelet therapy.” Please refer to Section 9, Clinical Studies, for more specific information.
- The optimal duration of dual antiplatelet therapy, specifically clopidogrel, is unknown and DES thrombosis may still occur despite continued therapy. Data from several studies suggest that a longer duration of clopidogrel than was recommended post procedurally in drug-eluting stent pivotal trials (including SIRIUS) may be beneficial. Based upon consensus opinion, practice guidelines recommend that patients receive aspirin indefinitely plus a minimum of 3 months of clopidogrel, with clopidogrel therapy extended to 12 months in patients at low risk of bleeding (ref: ACC/AHA/SCAI PCI Practice Guidelines^{1,2,3}).

It is very important that the patient is compliant with the post-procedural antiplatelet recommendations. Early discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, myocardial infarction or death. Prior to Percutaneous Coronary Intervention (PCI), if a surgical or dental procedure is anticipated that requires early discontinuation of antiplatelet therapy, the interventional cardiologist and patient should carefully consider whether a drug-eluting stent and its associated recommended antiplatelet therapy is the appropriate PCI treatment choice. Following PCI, should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risk associated with early discontinuation of antiplatelet therapy.

Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient's treating physicians, the antiplatelet therapy should be restarted as soon as possible.

5.3. Use of Multiple Stents

The extent of the patient's exposure to drug and polymer is directly related to the number of stents implanted. Use of more than two **CYPHER** Stents has not received adequate clinical evaluation. Use of more than two **CYPHER** Stents with total length > 36 mm will result in the patient receiving larger amounts of drug and polymer than the experience reflected in the clinical studies.

To avoid the possibility of dissimilar metal corrosion, do not implant stents of different materials in tandem where overlap or contact is possible. Potential interactions of the **CYPHER** Stent with other drug-eluting or coated stents have not been evaluated and should be avoided whenever possible.

In the SIRIUS trial, 30.7% (158/515) of patients in the **CYPHER** Stent arm had overlapping stents to treat lesions < 30 mm in length (See Section 9.1).

5.4. Brachytherapy

The safety and effectiveness of the **CYPHER** Stent in patients with prior brachytherapy of the target lesion have not been established. The safety and effectiveness of use of brachytherapy to treat in-stent restenosis in a **CYPHER** Stent have not been established. Both vascular brachytherapy and the **CYPHER** Stent alter arterial biology, and the combined vascular responses of these two treatments have not been determined.

5.5. Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with **CYPHER** Stent implantation have not been established.

5.6. Use in Special Populations

5.6.1. Pregnancy: Pregnancy Category C. See Drug Information – 6.6. Pregnancy.

There are no adequate and well controlled studies in pregnant women or men intending to father children. Effective contraception should be initiated before implanting a **CYPHER** Stent and for 12 weeks after implantation. The **CYPHER** Stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus.

5.6.2. Use during lactation: See Drug Information – 6.7. Lactation. A decision should be made whether to discontinue nursing or to implant the stent, taking into account the importance of the stent to the mother.

5.6.3. Gender: Clinical studies of the **CYPHER** Stent did not find any significant differences in safety and effectiveness for male and female patients.

5.6.4. Ethnicity: Clinical studies of the **CYPHER** Stent did not include sufficient numbers of patients to assess for differences in safety and effectiveness due to ethnicity, either by individual category or when grouped by Caucasian and non-Caucasian.

5.6.5. Pediatric use: The safety and efficacy of the **CYPHER** Stent in pediatric patients below the age of 18 years have not been established.

5.6.6. Geriatric use: Clinical studies of the **CYPHER** Stent did not find that patients age 65 years and over differed with regard to safety and efficacy compared to younger patients.

5.6.7. Non-Coronary use: The safety and effectiveness of this product has not been established in the cerebral, carotid, or peripheral vasculature.

5.7. Lesion/Vessel Characteristics

The safety and effectiveness of the **CYPHER** Stent have not been established in these noted patient groups:

- Patients with vessel thrombus at the lesion site.
- Patients with coronary artery reference vessel diameter < 2.5 mm or > 3.5 mm.
- Patients with lesions located in saphenous vein grafts, in the unprotected left main coronary artery, ostial lesions, or lesions located at a bifurcation.

Footnote:

¹ Grines CL, Bonow RO, Casey DE, Gardner TJ, Lockhart PB, Moliterno DJ, O'Gara P, Whitlow P. Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients with Coronary Artery Stents. *Circulation*. 2007; 115:1-6.

² www.cardiosource.com/guidelines/clinicalalerts/thienopyridines.pdf

³ J. Am. Coll. Cardiology. 2006;47:216-235

- Patients with diffuse disease or poor flow distal to the identified lesions.
- Patients with multi-vessel disease.
- Patients with tortuous vessels in the region of the obstruction or proximal to the lesion.
- Patients with a recent acute myocardial infarction.
- Patients with lesions longer than 30 mm and requiring more than one **CYPHER® Stent**.
- Patients with chronic total occlusions.
- Patients with in-stent restenotic lesions.

The safety and effectiveness of the **CYPHER Stent** have not been established in the cerebral, carotid, or peripheral vasculature.

While not observed in pivotal clinical trials (First-in-Man, RAVEL, and SIRIUS) that supported the **CYPHER Stent PMA**, stent fractures are uncommon events but have been observed in long stented segments including those in which overlapping stents have been used. They have been observed in coronary segments that undergo significant motion, particularly in areas with severe angulation, tortuosity, and calcification. In the **CYPHER Stent**, they have been reported most often in certain lesion subgroups in which safety and effectiveness have not been established. The clinical implications of stent fracture are not well characterized.

5.8. Drug Interactions

Several drugs are known to affect the metabolism of sirolimus, and other drug interactions may be inferred from known metabolic effects. Sirolimus is known to be a substrate for both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein. See **Drug Information – 6.4. Drug Interactions Following Oral Administration of Sirolimus** for more specific information.

Consideration should be given to the potential for drug interaction when deciding to place a **CYPHER Stent** in a patient who is taking a drug that could interact with sirolimus, or when deciding to initiate therapy with such a drug in a patient who had recently received a **CYPHER Stent**. The effect of drug interactions on the safety or efficacy of the **CYPHER Stent** has not been determined.

5.9. Coronary Artery Surgery – Effect on Anastomoses

There have been rare reports of bronchial anastomotic dehiscence of transplant anastomoses in lung transplant patients who were receiving oral sirolimus therapy. In a vessel that has recently been implanted with a **CYPHER Stent**, the sirolimus concentrations are expected to be several fold higher than systemic sirolimus concentrations. Therefore, consideration should be given to the possibility that the presence of a **CYPHER Stent** may compromise the healing of coronary artery vascular anastomoses. No such event was observed in the very limited experience from clinical trials.

5.10. Immune Suppression Potential

Sirolimus, the active ingredient of the **CYPHER Stent**, is an immunosuppressive agent that is also available in oral formulations. The mean peak systemic blood concentration of sirolimus following placement of up to two **CYPHER Stents** (1.05 ng/ml) is substantially lower than the therapeutic concentrations usually obtained when sirolimus oral formulations are used as prophylaxis for renal transplant rejection (see **Drug Information – Pharmacokinetics (6.2)**). In clinical studies of **CYPHER Stents** when used according to its intended use, there were no reports of immune suppression. However, for patients who receive several **CYPHER Stents** simultaneously, it may be possible for systemic concentrations of sirolimus to approach immunosuppressive levels temporarily, especially in patients who also have hepatic insufficiency or who are taking drugs that inhibit CYP3A4 or P-glycoprotein. This possibility should be considered for such patients, particularly if they are also taking oral sirolimus (or rapamycin), other immunosuppressive agents, or are otherwise at risk for immune suppression.

5.11. Lipid Elevation Potential

The use of oral sirolimus in renal transplant patients was associated with increased serum cholesterol and triglycerides that in some cases required treatment. The effect was seen with both low and high dose prolonged oral therapy in a dose related manner. When used according to the indications for use, the systemic sirolimus concentrations from the **CYPHER Stent** are expected to be lower than the concentrations usually obtained in transplant patients, but the magnitude and duration of any effect of those concentrations on lipids is not known.

5.12. Magnetic Resonance (MR) Imaging

Non-clinical testing has demonstrated that single and two overlapping **CYPHER Stents** are MR-conditional. They can be scanned safely, immediately post implantation, under the following conditions:

- Static magnetic field of 3 Tesla
- Spatial gradient field of 500 Gauss/cm
- Maximum whole-body-averaged specific absorption rate (SAR) of 4.0 W/kg for 15 minutes of scanning

In non-clinical testing, a single **CYPHER Stent** up to 33 mm in length produced a temperature rise of less than 1°C and two overlapping **CYPHER Stents** up to 33 mm in length produced a net temperature rise of less than 2°C at a maximum whole body averaged SAR of 4.0 W/kg for 15 minutes of MR scanning in a 3 Tesla Siemens Whole Body MR Scanner serial 20514, Software NUMARIS/4, version Syngo MR 2003T DHHS, VX22A. The maximum whole body averaged SAR was determined by calorimetry following ASTM F2182-02.

The image artifact extends approximately 1 mm from the device, both inside and outside of the device lumen when scanned in non-clinical testing using a pulse sequence generating a whole body SAR of 4.0 W/kg in a Siemens Whole Body MR Scanner, serial 20514, Software NUMARIS/4, version Syngo MR 2003T DHHS, VX22A with 3 Tesla coil.

5.13. Stent Handling Precautions

- **For single use only.** Do not resterilize or reuse this product. Note the “Use By” date on the product label.
- **Do not remove the stent from the delivery balloon – removal may damage the stent and coating and/or lead to stent embolization.** The stent system is intended to perform as a system.
- **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 cause coating damage, contamination or dislodgement of the stent from the delivery system balloon.
- 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.

5.14. Stent Placement Precautions

- **The vessel should be pre-dilated with an appropriate sized balloon.**
- **Do not prepare or pre-inflate the balloon prior to stent deployment other than as directed. Use the balloon purging technique described in Section 13 – Operator’s Manual.**
- Guiding catheters used must have lumen sizes that are suitable to accommodate the stent delivery system (see **CYPHER Stent** system product description in **Table 1-1**).
- Do not induce a negative pressure on the delivery catheter prior to placement of the stent across the lesion. This may cause premature dislodgement of the stent from the balloon.

- 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 **Precautions – 5.15. Stent/System Removal Precautions.**)
- Placement of the stent has the potential to compromise side branch patency.
- When treating multiple lesions, the distal lesion should be initially stented, followed by stenting of the more proximal lesion(s). Stenting in this order minimizes the need to cross the proximal stent in the placement of the distal stent and may reduce the chances of dislodging the proximal stent, or disrupting stent coating.
- Balloon pressures should be monitored during inflation. **Do not exceed rated burst pressure as indicated on the product label.** (See **Inflation Pressure Recommendations in Table 13-1.**) 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 dislodgement of the stent from the balloon may occur. Remove as a single unit per instructions in Precautions – 5.15. 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.

5.15. 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**.

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.

5.16. Post-Procedure 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 placement, apposition, geometry, and/or coating.
- Through non-clinical testing, single and two overlapping **CYPHER®** Stents have been shown to be MRI safe at field strengths of 3 Tesla or less (see **Precautions – 5.12. Magnetic Resonance Imaging (MRI)**). MR imaging quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.
- In the pivotal clinical trial of the **CYPHER** Stent, clopidogrel or ticlopidine was administered pre-procedure and for a period of 3 months post-procedure. Aspirin was administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce the risk of thrombosis. Please refer to Section 9, **Clinical Studies**, for more specific information.
- Patients who require early discontinuation of antiplatelet therapy (e.g. secondary to active bleeding), should be monitored carefully for cardiac events. At the discretion of the patient's treating physician, the antiplatelet therapy should be restarted as soon as possible (see **Precautions - 5.2. Pre- and Post-Procedure Antiplatelet Regimen**).

6. Drug Information

6.1. Mechanism of Action

The mechanism (or mechanisms) by which a **CYPHER** Stent affects neointima production as seen in clinical studies has not been established. Sirolimus inhibits T-lymphocyte activation and smooth muscle and endothelial cell proliferation in response to cytokine and growth factor stimulation. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12). The sirolimus-FKBP-12 complex binds to and inhibits the activation of the mammalian Target of Rapamycin (mTOR), leading to inhibition of cell cycle progression from the G₁ to the S phase.

6.2. Pharmacokinetics of the CYPHER Stent

The pharmacokinetics of sirolimus as delivered by the **CYPHER** Stent has been determined in patients with coronary artery disease after implantation of 1 (n=10) or 2 (n=9) **CYPHER** Stents. The parameters determined from patients receiving one and two **CYPHER** Stents are provided in Table 6-1.

Table 6-1: Whole Sirolimus Pharmacokinetic Parameters in Patients After Implantation of CYPHER Sirolimus-eluting Coronary Stents

| Number of Stents | Statistic | Dose (µg) | t _{max} (h) | C _{max} (ng/ml) | t _{1/2} (h) | AUC (ng·h/ml) | CL (ml/h/kg) |
|------------------|-----------|-----------|----------------------|--------------------------|----------------------|---------------|--------------|
| 1 (n=10) | Mean | 161 | 3.90 | 0.57 | 206 | 127 | 17.7 |
| | SD | 15 | 2.38 | 0.12 | 92 | 51 | 7.5 |
| | %CV | 9.09 | 61.0 | 20.5 | 44.8 | 40.3 | 42.2 |
| | Range | 149-178 | 1-6 | 0.43-0.77 | 111-354 | 58-225 | 6.22-29.2 |
| 2 (n=9) | Mean | 315 | 3.24 | 1.05 | 220 | 227 | 17.1 |
| | SD | 25 | 3.59 | 0.39 | 106 | 58 | 5.3 |
| | %CV | 7.84 | 111 | 37.4 | 48.3 | 25.7 | 31.2 |
| | Range | 299-355 | 1.05-12.2 | 0.51-1.66 | 131-486 | 149-307 | 9.31-24.5 |

t_{max}=time peak concentration occurs; C_{max}=peak blood concentration; t_{1/2}=terminal-phase half-life; AUC=area under the concentration-time curve; CL=total blood clearance

The results in Table 6-1 show that C_{max} and AUC were closely dose-proportional over a 2-fold range in doses. The blood levels after stent implantation were 10 to 20 fold lower than what was observed after oral administration of sirolimus in either healthy volunteers or transplanted patients. The mean ± SD sirolimus terminal half-life (t_{1/2}) after stent implantation for the combined groups (n=19) was 213 ± 97 h. By comparison, the mean ± SD sirolimus t_{1/2} values after single dose administration of sirolimus by oral solution in healthy subjects (n=305) and renal transplant patients (n=81) were 72.9 ± 19.3 h and 58.2 ± 19.2 h, respectively. The apparent discrepancy in half-lives after stent implantation and oral administration is due to the fact that the decline in terminal sirolimus concentrations reflects the release of sirolimus from the stent and not elimination of sirolimus from the body.

6.3. Pharmacokinetics Following Oral Administration of Sirolimus

Sirolimus pharmacokinetic activity has been determined following oral administration in healthy subjects, pediatric dialysis patients, hepatically-impaired patients, and renal transplant patients. Table 6-2 provides a summary of the descriptive statistics for the maximum whole blood sirolimus pharmacokinetic exposure, based on t_{max} , C_{max} and AUC.

Table 6-2: Pharmacokinetic Parameters (mean \pm SD) in Healthy Subjects, Renal Transplant Patients and Patients with Hepatic Impairment Following Oral Administration of Sirolimus

| Patient Status (n) | Dose | t_{max} (hours) | C_{max} (ng/ml) | AUC (ng-h/ml) |
|---------------------------|--------------------------------------|-------------------|-------------------|----------------|
| Healthy (n=18) | 15 mg single dose oral solution | 0.82 \pm 0.17 | 78.2 \pm 18.3 | 970 \pm 272 |
| Renal Transplant (n=19) | 2 mg/day multiple dose oral solution | 3.01 \pm 2.4 | 12.2 \pm 6.2 | 158 \pm 70 |
| Renal Transplant (n=23) | 5 mg/day multiple dose oral solution | 1.84 \pm 1.3 | 37.4 \pm 21 | 396 \pm 193 |
| Renal Transplant (n=13) | 2 mg/day multiple dose tablets | 3.46 \pm 2.4 | 15.0 \pm 4.9 | 230 \pm 67 |
| Hepatic Impairment (n=18) | 15 mg single dose oral solution | 0.84 \pm 0.17 | 77.9 \pm 23.1 | 1567 \pm 616 |

6.3.1. Distribution

The mean (\pm SD) blood to plasma ratio of sirolimus was 36 (\pm 18) in stable renal allograft patients, indicating that sirolimus is extensively partitioned into formed blood elements. Sirolimus is extensively bound (approximately 92%) to human plasma proteins. In man the binding of sirolimus was shown mainly to be associated with serum albumin (97%), alpha-1 acid glycoprotein and lipoproteins.

6.3.2. Metabolism

Sirolimus is a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein. Sirolimus is extensively metabolized by O-demethylation and/or hydroxylation. Seven major metabolites, including sirolimus, demethyl, and hydroxydemethyl are identifiable in blood. Some of these metabolites are also detectable in plasma, fecal and urine samples. Sirolimus is the major component in human whole blood and contributes to more than 90% of the immunosuppressive activity.

6.3.3. Special Populations

Hepatic impairment: Sirolimus (15 mg) was administered as a single oral dose to 18 subjects with normal hepatic function and 18 patients with Child-Pugh classification A or B hepatic impairment, in which hepatic impairment was primary and not related to an underlying systemic disease. Compared with the values in the normal hepatic group, the hepatic impairment had higher mean AUC (61%) and $t_{1/2}$ (43%) and had lower mean clearance values (33%). The mean $t_{1/2}$ increased from 79 \pm 12 hours in subjects with normal hepatic function to 113 \pm 41 hours in patients with impaired hepatic function. However, hepatic diseases with varying etiologies may show different effects and the pharmacokinetics of sirolimus in patients with severe hepatic dysfunction is unknown.

Renal impairment: The effect of renal impairment on the pharmacokinetics of sirolimus is not known. However, there is minimal (2.2%) renal excretion of the drug or its metabolites.

Demographics: After oral administration of sirolimus there was no effect of gender, race and age (> 65 years) on the pharmacokinetics of sirolimus.

6.4. Drug Interactions Following Oral Administration of Sirolimus

Drug interaction studies have not been conducted with the CYPHER[®] Stent. Sirolimus is extensively metabolized by cytochrome P450 3A4 (CYP3A4) in the gut wall and liver and undergoes efflux from enterocytes of the small intestine by P-glycoprotein (P-gp). Therefore, absorption and the subsequent elimination of systemically absorbed sirolimus may be influenced by drugs that affect these proteins. Inhibitors of CYP3A4 and P-gp may increase sirolimus levels, while inducers of CYP3A4 and P-gp may decrease sirolimus levels. The pharmacokinetic interaction between orally administered sirolimus and concomitantly administered drugs is discussed below. Drug interaction studies have not been conducted with drugs other than those described below.

6.4.1. Ketoconazole

Multiple-dose ketoconazole administration significantly affected the rate and extent of absorption and sirolimus exposure after administration of a sirolimus oral formulation, as reflected by increases in sirolimus C_{max} , t_{max} , and AUC of 4.3-fold, 38%, and 10.9-fold, respectively. However, the terminal $t_{1/2}$ of sirolimus was not changed. Single-dose sirolimus did not affect steady-state 12-hour plasma ketoconazole concentrations. It is recommended that sirolimus oral solution and oral tablets should not be administered with ketoconazole.

6.4.2. Rifampin

Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg daily for 14 days, followed by a single 20-mg dose of sirolimus, greatly increased sirolimus oral-dose clearance by 5.5-fold (range = 2.8 to 10), which represents mean decreases in AUC and C_{max} of about 82% and 71%, respectively. In patients where rifampin is indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

6.4.3. Diltiazem

The simultaneous oral administration of 10 mg of a sirolimus oral solution and 120 mg of diltiazem to 18 healthy volunteers significantly affected the bioavailability of sirolimus. Sirolimus C_{max} , t_{max} , and AUC were increased 1.4-, 1.3-, and 1.6-fold, respectively. Sirolimus did not affect the pharmacokinetics of either diltiazem or its metabolites desacetyldiltiazem and desmethyldiltiazem.

6.4.4. Cyclosporine

Single-dose pharmacokinetic interactions between cyclosporine and sirolimus were investigated for two sirolimus oral formulations in studies using 24 healthy volunteers. Compared to results obtained when oral sirolimus was administered alone, the oral administration of 10 mg sirolimus 4 hours after a single dose of 300 mg cyclosporine soft gelatin capsules increased mean sirolimus AUC by 33% to 80% and increased mean sirolimus C_{max} by 33% to 58%, depending on the sirolimus formulation. The half-life of sirolimus was not significantly affected. The cyclosporine mean AUC and mean C_{max} were not significantly affected.

In a single-dose cross-over drug-drug interaction study, 33 healthy volunteers received 5 mg sirolimus alone, 2 hours before, and 2 hours after a 300 mg dose of cyclosporine soft gelatin capsules. When given 2 hours before the cyclosporine administration, sirolimus C_{max} and AUC were comparable to those with administration of sirolimus alone. However, when given 2 hours after, the mean C_{max} and AUC of sirolimus were increased by 126% and 141%, respectively, relative to administration of sirolimus alone.

6.4.5. Erythromycin

The simultaneous oral administration of 2 mg daily of sirolimus oral solution and 800 mg q 8h of erythromycin as erythromycin ethylsuccinate tablets at steady state to 24 healthy volunteers significantly affected the bioavailability of sirolimus and erythromycin. Sirolimus C_{max} and AUC were increased 4.4- and 4.2-fold, respectively, and t_{max} was increased by 0.4 hr. Erythromycin C_{max} and AUC were increased 1.6- and 1.7-fold, respectively, and t_{max} was increased by 0.3 hr.

6.4.6. Verapamil

The simultaneous oral administration of 2 mg daily of sirolimus oral solution and 180 mg q 12h of verapamil at steady state to 26 healthy volunteers significantly affected the bioavailability of sirolimus and verapamil. Sirolimus C_{max} and AUC were increased 2.3- and 2.2-fold, respectively, without substantial change in t_{max} . The C_{max} and AUC of the pharmacologically active S(-) enantiomer of verapamil were both increased 1.5-fold and t_{max} was decreased by 1.2 hr.

6.4.7. Drugs which may be coadministered without dose adjustment

Clinically significant pharmacokinetic drug-drug interactions were not observed in studies of drugs listed below in conjunction with orally administered sirolimus. Sirolimus and these drugs may be coadministered without dose adjustments.

- Acyclovir
- Digoxin
- Glyburide
- Nifedipine
- Norgestrel/ethinyl estradiol
- Prednisolone
- Sulfamethoxazole/trimethoprim

6.4.8. Other drug interactions

Drugs that may increase sirolimus blood concentrations include:

- **Calcium channel blockers:** nicardipine.
- **Antifungal agents:** clotrimazole, fluconazole, itraconazole.
- **Macrolide antibiotics:** clarithromycin, troleandomycin.
- **Gastrointestinal prokinetic agents:** cisapride, metoclopramide.
- **Other drugs:** bromocriptine, cimetidine, danazol, HIV-protease inhibitors (e.g., ritonavir, indinavir).

Drugs that may decrease sirolimus levels include:

- **Anticonvulsants:** carbamazepine, phenobarbital, phenytoin.
- **Antibiotics:** rifabutin, rifapentine.

These lists are not all inclusive.

Care should be exercised when drugs or other substances that are metabolized by CYP3A4 are administered concomitantly with implantation of **CYPHER**® Stents.

6.4.9. Grapefruit juice:

Grapefruit juice reduces CYP3A4-mediated metabolism of sirolimus.

6.4.10. Herbal Preparations:

St. John's Wort (*Hypericum perforatum*) induces CYP3A4 and P-glycoprotein. Because sirolimus is a substrate for both cytochrome CYP3A4 and P-glycoprotein, there is the potential that the use of St. John's Wort in patients receiving **CYPHER** Stents could result in reduced sirolimus levels.

6.4.11. Vaccination

Immunosuppressants may affect response to vaccination. Therefore, for some period after receiving a **CYPHER** Stent, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid.

6.4.12. Drug-laboratory test interactions

There are no studies on the interactions of sirolimus in commonly employed clinical laboratory tests.

6.5. Mutagenesis, Carcinogenicity and Reproductive Toxicology

The genotoxicity, carcinogenicity, and reproductive toxicity of **CYPHER** Stents have not been evaluated. However, the genotoxicity, carcinogenicity, and reproductive toxicity of sirolimus have been investigated in bacterial and mammalian cells *in vitro* and in laboratory animals *in vivo*.

Sirolimus was not genotoxic in the *in vitro* bacterial reverse mutation assay, the Chinese hamster ovary cell chromosomal aberration assay, the mouse lymphoma cell forward mutation assay, or the *in vivo* mouse micronucleus assay.

Carcinogenicity studies in mouse showed hepatocellular adenoma and carcinoma at dosages of 1, 3 and 6 mg/kg/day orally (approximately 15 to 94 times the dosage provided by a stent coated with 314 µg sirolimus, adjusted for body surface area). In the 104-week rat study at dosage of 0.2 mg/kg/day (approximately 6 times the dosage provided by a stent coated with 314 µg sirolimus adjusted for body surface area), there was a significant increase in the incidence of testicular adenoma.

There was no effect on fertility in female rats following the administration of sirolimus at dosages up to 0.5 mg/kg/day (approximately 15 times the dosage provided by a stent coated with 314 µg sirolimus adjusted for body surface area). In male rats, there was no significant difference in fertility rate compared to controls at a dosage of 2 mg/kg/day (approximately 60 times the dosage provided by a stent coated with 314 µg sirolimus adjusted for body surface area). Reduction in testicular weights and/or histological lesions (e.g., tubular atrophy and tubular giant cells) were observed in rats following dosages of ≥ 0.65 mg/kg/day (approximately 20 times the dosage provided by a stent coated with 314 µg sirolimus adjusted for body surface area).

6.6. Pregnancy

Pregnancy Category C: There are no adequate and well controlled studies in pregnant women of sirolimus or **CYPHER** Stents. Sirolimus was embryo/feto toxic in rats at dosages of ≥ 0.1 mg/kg/day (approximately 3 times the dose provided by a stent coated with 314 µg sirolimus adjusted for body surface area). Embryo/feto toxicity was manifested as mortality and reduced fetal weights, with associated delays in skeletal ossification. No teratogenic effect of sirolimus was evident. There was no effect of sirolimus on rabbit development at the maternally toxic dosage of 0.05 mg/kg/day (approximately 3 times the dose provided by a stent coated with 314 µg sirolimus adjusted for body surface area).

Effective contraception should be initiated before implanting a **CYPHER** Stent and for 12 weeks after implantation. The **CYPHER** Stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus.

6.7. Lactation

Sirolimus is excreted in trace amounts in milk of lactating rats. It is not known whether sirolimus is excreted in human milk. The pharmacokinetic and safety profiles of sirolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from sirolimus, a decision should be made whether to discontinue nursing or to implant the stent, taking into account the importance of the stent to the mother.

7. Overview of Clinical Studies

SIRIUS was a multi-center, prospective, randomized, double-blind trial conducted at 53 sites in the U.S. The primary efficacy endpoint was TVF at 9 months, defined as cardiac death, myocardial infarction, or target vessel revascularization. To be eligible, a patient was required to have a *de novo* ischemic lesion of length 15 mm to 30 mm in a native coronary artery of diameter 2.5 mm to 3.5 mm (using visual estimates). Patients could be treated with up to two overlapping stents to cover the lesion. Patients were randomized 1:1 to either the **CYPHER**® Stent or the control **BX VELOCITY**® bare metal stent. A total of 1101 patients were randomized, and 1058 patients were included in the study results; 533 with **CYPHER** Stent and 525 with Control. A subset of 826 was pre-assigned to have angiographic follow-up at 8 months. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 3 months. Clinical follow-up through the 60-month (± 4 weeks) endpoint was available on 996 (94.1%) patients. Angiographic follow-up was obtained on 703 patients. A total of 209 patients had both baseline and follow-up IVUS studies. Yearly follow-up for clinical parameters through 6 years is ongoing.

RAVEL was a multi-center, prospective, randomized, double-blind trial conducted at 19 sites in Europe, Brazil and Mexico. The primary efficacy endpoint was in-stent late loss at 6 months. To be eligible a patient was required to have a *de novo* ischemic lesion of a length that could be covered by a single 18 mm stent in a native coronary artery of diameter 2.5 mm to 3.5 mm (using visual estimates). Patients were randomized 1:1 to either the **CYPHER** Stent or the control **BX VELOCITY** bare metal stent. A total of 238 patients were randomized: 120 to **CYPHER** Stent and 118 to Control. After the procedure patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 2 months. Angiographic follow-up at 6 months was obtained on 218 patients. IVUS follow-up (but without baseline studies) was obtained on 110 patients. The final 5-year clinical follow-up is available in 82.8% of patients.

FIM was a non-randomized, open-label study conducted at two sites, one in The Netherlands and one in Brazil. To be eligible, a patient was required to have a *de novo* ischemic lesion of a length that could be covered by a single 18 mm stent in a native coronary artery of diameter 3.0 mm to 3.5 mm (using visual estimates). A total of 45 patients were treated, of which 30 received the **CYPHER** Stent and 15 received an alternative formulation sirolimus-eluting stent. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel for 2 months. Angiographic follow-up was performed at 4, 12, 24 and 48 months, or at 6, 18 and 48 months, depending on the site. Angiographic follow-up at 48 months is available for 22 of 30 **CYPHER** patients, and IVUS follow-up is available for 21 patients. The final 5-year clinical follow-up is available.

The purpose of the US e-**CYPHER** Stent Registry was to collect post marketing surveillance data on the **CYPHER** Sirolimus-eluting Coronary Stent following marketing approval, tracking clinical outcomes when the **CYPHER** Stent was used in normal clinical practice. Data were collected using electronic data capture and 100% monitored both remotely and by visits to a subset of randomly selected sites. An independent clinical events committee adjudicated deaths as cardiac or non-cardiac, MIs as Q-wave or non-Q wave, and revascularizations as target lesion, target vessel, or non-target vessel and as clinically driven or non-clinically driven. Stent thrombosis was adjudicated using source documents, originally using the protocol definition and later using the ARC definition. Follow-up in all of the patients was at 30 days, 6 months, and one year.

Table 7-1: Clinical Study Comparison

| | SIRIUS Trial | RAVEL Trial | First-in-Man Study | US e-CYPHER |
|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| Study Type | Pivotal Study Multi-center (N=53), prospective, Randomized | Supportive Study Multi-center (N=19), prospective, Randomized | Feasibility Study Multi-center (N=2) Non-randomized | Open Enrollment Registry Multi-center (N=38) Non-randomized |
| Number of Patients | 1058 (533 CYPHER , 525 Bare Metal) | 238 (120 CYPHER , 118 Bare Metal) | 45 (30 CYPHER , 15 other) | 2067 (2067 CYPHER) |
| Lesion Criteria | Single <i>de novo</i> lesion in native coronary artery ≥ 2.5 to ≤ 3.5 mm in diameter, lesion 15 to 30 mm in length and coverable with 2 stents | Single <i>de novo</i> lesion in native coronary artery ≥ 2.5 to ≤ 3.5 mm in diameter, lesion coverable by one 18 mm stent | Single <i>de novo</i> lesion in native coronary artery ≥ 3.0 to ≤ 3.5 mm diameter, lesion coverable by one 18 mm stent | Open Enrollment |
| Products Used | CYPHER Sirolimus-Eluting Coronary Stent on RAPTOR ™ Over-the-Wire Stent Delivery System | CYPHER Sirolimus-Eluting Coronary Stent on RAPTORRAIL ® Rapid Exchange Stent Delivery System | CYPHER Sirolimus-Eluting Coronary Stent on RAPTOR Over-the-Wire Stent Delivery System | CYPHER Sirolimus-Eluting Coronary Stent RAPTORRAIL Over-the-Wire & Rapid Exchange Stent Delivery System |
| Primary Endpoint | Target vessel failure at 9 months | In-stent late loss at 6 months | Not applicable | Not applicable |
| Countries | United States | Europe, Latin America | Brazil, The Netherlands | United States |
| Antiplatelet Therapy | Aspirin indefinitely and ticlopidine or clopidogrel for 3 months | Aspirin indefinitely and ticlopidine or clopidogrel for 2 months | Aspirin indefinitely and ticlopidine or clopidogrel for 2 months | Aspirin indefinitely and ticlopidine or clopidogrel for 3 months |
| Follow-up | 8 months angiographic | 6 months angiographic | Brazil: 4, 12, 24, 48 months angio & IVUS | Not applicable |
| | 9 months clinical | 1 and 6 month clinical | Clinical follow-up at same times as angio follow-up | 12 months clinical |
| | 1, 3, 6, 12 months and 2, 3, 4, and 5 years telephone F/U | 12 months and 2, 3, 4, and 5 years telephone F/U | The Netherlands: 6 & 18, 48 months angio & IVUS | Not applicable |

8. Adverse Events

8.1. Observed Adverse Events

Observed adverse event experience comes from three clinical studies, the SIRIUS Trial, the RAVEL Trial, and the First-In-Man. See **Section 9 – Clinical Studies** for more complete descriptions of the study designs and results.

The SIRIUS Trial and the RAVEL Trial were multi-center, double-blind, randomized clinical trials in patients with symptomatic ischemic coronary artery disease due to *de novo* lesions in native coronary arteries. Patients were randomized to the **CYPHER® Stent** (a sirolimus-eluting **BX VELOCITY® Stent**) or to a Control stent (**BX VELOCITY Stent**, an uncoated 316L stainless steel stent). Eligibility was based on visual estimates of vessel diameter and lesion length. Following treatment, patients were treated with aspirin indefinitely and either clopidogrel or ticlopidine for 2 or 3 months, depending on the trial. Evaluations included clinical and angiographic outcomes. The First-In-Man Study was a small, non-randomized, two-center study that used the **CYPHER Stent** in 30 of its 45 patients. Major study characteristics are summarized in Table 7-1. Principal adverse events are shown in Table 8-1.

Table 8-1: Principal Adverse Events Observed in Clinical Studies In-Hospital and Out-of-Hospital

| | SIRIUS Trial to 1800 Days | | RAVEL Trial to 1825 Days | | First-in-Man to 1800 Days |
|--------------------------------------------------|---------------------------|---------------------|--------------------------|---------------------|---------------------------|
| | CYPHER Stent % (n) | Control Stent % (n) | CYPHER Stent % (n) | Control Stent % (n) | CYPHER Stent % (n) |
| In-Hospital | N=533* | N=525* | N=120* | N=118* | N=30* |
| MACE ¹ | 2.4% (13) | 1.5% (8) | 2.5% (3) | 2.5% (3) | 6.7% (2) |
| Death | 0.2% (1) | 0.0% (0) | 0.0% (0) | 0.0% (0) | 3.3% (1) |
| Cardiac Death | 0.2% (1) | 0.0% (0) | 0.0% (0) | 0.0% (0) | 3.3% (1) |
| Non-Cardiac Death | 0.0% (0) | 0.0% (0) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Myocardial Infarction | 2.3% (12) | 1.5% (8) | 2.5% (3) | 2.5% (3) | 3.3% (1) |
| Q-Wave | 0.4% (2) | 0.0% (0) | 1.7% (2) | 0.8% (1) | 0.0% (0) |
| Non Q-Wave | 1.9% (10) | 1.5% (8) | 0.8% (1) | 1.7% (2) | 3.3% (1) |
| Emergent CABG | 0.0% (0) | 0.0% (0) | -- | -- | 0.0% (0) |
| Target Lesion Revascularization (TLR) | 0.2% (1) | 0.0% (0) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Cardiac Death+ MI | 2.4% (13) | 1.5% (8) | 2.5% (3) | 2.5% (3) | 6.7% (2) |
| TVR not Target Lesion | 0.0% (0) | 0.0% (0) | 0.8% (1) | 0.8% (1) | 3.3% (1) |
| Target Vessel Failure ² | 2.4% (13) | 1.5% (8) | 2.5% (3) | 2.5% (3) | 6.7% (2) |
| All Target Vessel Revascularization | 0.2 (1) | 0.0% (0) | 0.8% (1) | 0.8% (1) | 3.3% (1) |
| Stent Thrombosis | 0.0% (0) | 0.0% (0) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Sub-abrupt Closure ⁴ | 0.2% (1) | 0.0% (0) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Out-of-Hospital to 30 days | N=533* | N=525* | N=120* | N=118* | N=30* |
| | % (n) | % (n) | % (n) | % (n) | % (n) |
| MACE ¹ | 0.2% (1) | 0.6% (3) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Death | 0.0% (0) | 0.2% (1) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Cardiac Death | 0.0% (0) | 0.2% (1) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Non-Cardiac Death | 0.0% (0) | 0.0% (0) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Myocardial Infarction | 0.2% (1) | 0.4% (2) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Q-Wave | 0.2% (1) | 0.0% (0) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Non Q-Wave | 0.0% (0) | 0.4% (2) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Emergent CABG | 0.0% (0) | 0.0% (0) | -- | -- | 0.0% (0) |
| Target Lesion Revascularization (TLR) | 0.2% (1) | 0.0% (0) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Cardiac Death+ MI | 0.2% (1) | 0.6% (3) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| TVR not Target Lesion | 0.2% (1) | 0.2% (1) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Target Vessel Failure ² | 0.4% (2) | 0.8% (4) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| All Target Vessel Revascularization | 0.4% (2) | 0.2% (1) | 0.8% (1) | 0.8% (1) | 3.3% (1) |
| Stent Thrombosis (0-30 days) | 0.2% (1) | 0.2% (1) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Sub-abrupt Closure ⁴ | 0.2% (1) | 0.0% (0) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Out-of-Hospital to 270 days | N=529* | N=524* | N=120* | N=118* | N=29* |
| | % (n) | % (n) | % (n) | % (n) | % (n) |
| MACE ¹ | 4.9% (26) | 18.1% (95) | 0.8% (1) | 16.1% (19) | 0.0% (0) |
| Death | 0.8% (4) | 0.6% (3) | 0.0% (0) | 1.7% (2) | 0.0% (0) |
| Cardiac Death | 0.2% (1) | 0.4% (2) | 0.0% (0) | 0.8% (1) | 0.0% (0) |
| Non-Cardiac Death | 0.6% (3) | 0.2% (1) | 0.0% (0) | 0.8% (1) | 0.0% (0) |
| Myocardial Infarction | 0.6% (3) | 2.1% (11) | 0.0% (0) | 1.7% (2) | 0.0% (0) |
| Q-Wave | 0.4% (2) | 0.8% (4) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Non Q-Wave | 0.2% (1) | 1.3% (7) | 0.0% (0) | 1.7% (2) | 0.0% (0) |
| Emergent CABG | 0.0% (0) | 0.0% (0) | -- | -- | 0.0% (0) |
| Target Lesion Revascularization (TLR) | 4.0% (21) | 16.6% (87) | 0.8% (1) | 13.6% (16) | 0.0% (0) |
| Cardiac Death+ MI | 0.8% (4) | 2.5% (13) | 0.0% (0) | 2.5% (3) | 0.0% (0) |
| Target Vessel Revascularization not Involving TL | 3.4% (18) | 4.8% (25) | 0.0% (0) | 0.8% (1) | 0.0% (0) |

continued on next page

| | | | | | |
|--------------------------------------------------|---------------|---------------|--------------|--------------|--------------|
| Target Vessel Failure ³ | 6.6% (35) | 19.7% (103) | 0.8% (1) | 16.9% (20) | 0.0% (0) |
| All Target Vessel Revascularization | 6.2% (33) | 18.9% (99) | 0.8% (1) | 14.4% (17) | 0.0% (0) |
| Stent Thrombosis (0-30 days) | 0.2% (1) | 0.2% (1) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Late Thrombosis (31-1800/1825 days) | 0.2% (1) | 0.6% (3) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Sub-abrupt Closure ⁴ | 0.2% (1) | 0.0% (0) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Out-of-Hospital to 5 years | N=516* | N=498* | N=97* | N=94* | N=28* |
| | % (n) | % (n) | % (n) | % (n) | % (n) |
| MACE ¹ | 18.8% (96) | 34.7% (173) | 26.8% (26) | 28.7% (27) | 10.7% (3) |
| Death | 8.7% (44) | 8.9% (44) | 15.1% (14) | 8.9% (8) | 7.1% (2) |
| Cardiac Death | 4.2% (21) | 3.9% (19) | 3.2% (3) | 6.7% (6) | 3.7% (1) |
| Non-Cardiac Death | 4.6% (23) | 5.1% (25) | 11.8% (11) | 2.2% (2) | 3.7% (1) |
| Myocardial Infarction | 4.1% (21) | 5.3% (26) | 8.5% (7) | 5.8% (5) | 0.0% (0) |
| Q-Wave | 1.2% (6) | 1.2% (6) | 3.8% (3) | 2.4% (2) | 0.0% (0) |
| Non Q-Wave | 3.2% (16) | 4.1% (20) | 4.9% (4) | 3.6% (3) | 0.0% (0) |
| Emergent CABG | 0.0% (0) | 0.0% (0) | -- | -- | 0.0% (0) |
| Target Lesion Revascularization (TLR) | 9.6% (49) | 25.5% (127) | 12.0% (10) | 20.9% (18) | 10.7% (3) |
| Cardiac Death+ MI | 7.7% (39) | 8.3% (41) | 10.6% (10) | 9.9% (9) | 3.7% (1) |
| Target Vessel Revascularization not Involving TL | 10.9% (55) | 13.8% (68) | 2.5% (2) | 2.4% (2) | 3.7% (1) |
| Target Vessel Failure ² | 21.2% (108) | 35.5% (177) | 18.4% (16) | 30.1% (28) | 10.7% (3) |
| All Target Vessel Revascularization | 17.1% (87) | 32.1% (160) | 12.2% (12) | 21.3% (20) | 10.7% (3) |
| Stent Thrombosis (0-30 days) | 0.2% (1) | 0.2% (1) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Late Thrombosis (31-1800/1825 days) | 0.8% (4) | 0.6% (3) | 0.0% (0) | 0.0% (0) | 0.0% (0) |
| Sub-abrupt Closure ⁴ | 0.2% (1) | 0.0% (0) | 0.0% (0) | 0.0% (0) | 0.0% (0) |

Numbers are % (Count/Sample Size). * Note: Sample size is defined as N at the top of each column for In-hospital and Out-of-Hospital measures. 1 MACE is defined as Death, Q-wave or non Q-wave MI, Emergent CABG, or Target Lesion Revascularization. 2 Target Vessel Failure is defined as Target Vessel Revascularization, MI or cardiac death that could not be clearly attributed to a vessel other than the target vessel. 3 TVF at 270 days is the primary endpoint for the SIRIUS study. 4 Sub-abrupt Closure. Sub-abrupt closure was defined as abrupt closure that occurs after the index procedure is completed (and the patient left the catheterization laboratory) and before the 30-day follow-up endpoint.

Table 8-2: Frequency of Incomplete Stent Apposition

| | SIRIUS Trial | | RAVEL Trial | |
|-----------------------------------------------|----------------|---------------|---------------|---------------|
| | CYPHER® Stent | Control Stent | CYPHER Stent | Control Stent |
| Incomplete Stent Apposition Rate at Follow-up | 17.8% (18/101) | 9.0% (7/78) | 20.8% (10/48) | 4.3% (2/47) |
| Resolved | 10.0% (8/80) | 4.9% (3/61) | Not available | Not available |
| Persistent | 7.5% (6/80) | 9.8% (6/61) | Not available | Not available |
| Late Acquired Incomplete Stent Apposition | 8.8% (7/80) | 0.0% (0/61) | Not available | Not available |

In the SIRIUS Trial, a subset of patients underwent intravascular ultrasound (IVUS) evaluation of the treated lesion immediately after treatment and as part of a scheduled angiographic evaluation at 8 months. In the RAVEL Trial, a subset of patients underwent an IVUS study as part of the follow-up angiographic evaluation at 6 months, but there was no baseline IVUS evaluation. In both studies, patients who received the CYPHER Stent had a greater frequency of incomplete stent apposition at follow-up than patients who received the control stent (BX VELOCITY® Stent, an uncoated 316L stainless steel stent). From the SIRIUS Trial, it appeared that in about half of the cases, the incomplete stent apposition had not been observed immediately after stenting (late incomplete stent apposition). Late incomplete stent apposition was not observed in the control group. There were no clinical adverse events that were related to the occurrence of incomplete stent apposition. Frequencies of incomplete stent apposition are shown in Table 8-2.

8.2. Potential Adverse Events

Adverse events (in alphabetical order) which may be associated with the implantation of a coronary stent in coronary arteries (including those listed in Table 8-1 and Table 8-2):

8.2.1. Potential Adverse Events Associated with Coronary Stent Placement

- 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
- Incomplete stent apposition
- 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 migration
- Stroke
- Thrombosis (acute, sub-acute, late, or very late)
- Ventricular fibrillation
- Vessel spasm
- Vessel perforation

8.2.2. Potential Adverse Events Related to Sirolimus (Following Oral Administration):

- Abnormal liver function tests
- Anemia
- Arthralgias
- Diarrhea
- Hypercholesterolemia
- Hypersensitivity, including anaphylactic/anaphylactoid type reactions
- Hypertriglyceridemia (see section 5.11)
- Hypokalemia
- Infections
- Interstitial lung disease
- Leukopenia
- Lymphoma and other malignancies
- Thrombocytopenia

9. Clinical Studies

9.1. SIRIUS Trial (Pivotal Study)

Purpose: The purpose of the trial was to evaluate the safety and effectiveness of the **CYPHER**[®] Stent in reducing target vessel failure in *de novo* native coronary artery lesions.

Conclusions: In selected patients, use of the **CYPHER** Stent significantly reduced the rate of target vessel failure (TVF) at 9 months compared to the Control (**BX VELOCITY**[®] Stent, an uncoated 316L stainless steel stent). Angiographic lesion characteristics at 8 months were also significantly improved.

Design: This was a multi-center, prospective, randomized, double-blind trial conducted at 53 sites in the U.S. Patients were randomized with equal probability to receive either the **CYPHER** Stent or the Control. The primary efficacy endpoint was pre-specified to be TVF at 9 months, defined as cardiac death, myocardial infarction, or target vessel revascularization. To be eligible, a patient was required to have a *de novo* ischemic lesion of length 15 mm to 30 mm in a native coronary artery of diameter 2.5 mm to 3.5 mm (using visual estimates). Patients could be treated with up to two overlapping stents to cover the lesion. 32.5% (173/533) of the SIRIUS **CYPHER** patients received overlapping stents.

A total of 1101 patients were randomized, and 1058 patients were included in the study results; 533 with **CYPHER** Stent and 525 with Control. A subset of 826 was pre-assigned to have angiographic follow-up at 8 months. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 3 months.

Clinical follow-up through the 60-month (± 4 weeks) endpoint was available on 996 (94.1%) patients. Angiographic follow-up was obtained on 703 patients. A total of 209 patients had both baseline and follow-up IVUS studies. Clinical follow-up currently is available through five years.

Demography: Baseline characteristics were similar for both treatment arms; factors evaluated included age (mean 62 years), gender (29% female), race (90% Caucasian, 4.3% African American, 3.4% Hispanic, 1.7% Asian, and approximately 0.6% other), diabetes (26%), prior MI (31%), hypertension (68%), hyperlipidemia (74%), ejection fraction (mean 54%), CSS Angina Class (44% III or IV), and IIb/IIIa inhibitor use (60%), LAD (44%), LCX (25%), RCA (31%), reference vessel diameter (mean 2.8 mm), minimum lumen diameter (mean 0.97 mm), percent diameter stenosis (mean 65%), and lesion length (mean 14.4 mm). The overall fraction with a smoking history was 23%, but it was slightly lower in the **CYPHER** Stent arm (20%) than in the control arm (26%); smoking history was not found to be a significant predictor of outcome in the trial.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by clinical coordinators at the clinical sites. Angiographic and IVUS outcomes were assessed in a blinded fashion by quantitative analysis at designated central laboratories. An independent Clinical Events Committee adjudicated clinical events, and the trial was monitored by an independent Data and Safety Monitoring Committee.

Results: In selected patients, elective **CYPHER** Stent placement in native coronary *de novo* lesions resulted in a reduction in the incidence of TVF at 9 months compared to Control (8.9% vs. 21.0%, $p < 0.001$). By follow-up angiography at 8 months, there was significantly lower in-stent late loss (0.17 mm vs. 1.00 mm, $p < 0.001$) and mean in-lesion % diameter stenosis was significantly reduced (23.6% vs. 43.2%, $p < 0.001$). There was no evidence of an edge-effect 5 mm proximal or distal to the stent. Examination by IVUS at 8 months showed that neointimal hyperplasia (NIH) volume was significantly reduced in the **CYPHER** Stent arm (4.4 mm³ vs. 57.6 mm³, $p < 0.001$), but there was a higher rate of incomplete stent apposition (18% vs. 9%, $p = 0.123$). There were no clinical events related to the occurrence of incomplete stent apposition. Clinical outcomes through 5 years were consistent with the 9-month outcomes. The incidence of major adverse cardiac events in these patients was statistically lower than the patients who received an uncoated stent.

Table 9-1-1: summarizes the principal effectiveness and safety results of the SIRIUS Trial through 1800 days. Figure 9-1-1 provides the freedom from TVF rates through 1800 days.

Table 9-1-1: SIRIUS Trial Principal Effectiveness and Safety Results (to 1800 Days) All Patients Treated (N=1058)

| | CYPHER® Stent (N=533 Patients N=533 Lesions) | Control (N=525 Patients N=531 Lesions) | Difference [95% CI] ‡ | P-Value ‡ |
|--------------------------------------------------|-----------------------------------------------------|-----------------------------------------------|------------------------------|------------------|
| Effectiveness Measures | | | | |
| Product Success | 97.9% (522/533) | 98.7% (524/531) | -0.7% [-2.3, 0.8] | 0.477 |
| Procedure Success | 97.4% (519/533) | 98.5% (517/525) | -1.1% [-2.8%, 0.6%] | 0.281 |
| TVF to 9 Months (Primary Endpoint) | 8.9% (47/529) | 21.0% (110/524) | -12.2% [-16.4%, -7.9%] | <0.001 |
| Clinical Endpoints to 270 Days | | | | |
| TLR-Free† | 95.8% | 83.2% | 12.6% [8.5%, 16.7%] | <0.001 |
| TVR-Free† | 93.5% | 81.1% | 12.4% [8.0%, 16.8%] | <0.001 |
| TVF-Free† | 91.1% | 78.9% | 12.2% [7.5%, 16.8%] | <0.001 |
| MACE-Free† | 92.8% | 81.0% | 11.8% [7.4%, 16.3%] | <0.001 |
| Clinical Endpoints to 1800 Days | | | | |
| TLR-Free† | 90.0% | 75.1% | 15.0% [9.8%, 20.2%] | <0.001 |
| TVR-Free† | 82.6% | 69.1% | 13.5% [7.8%, 19.2%] | <0.001 |
| TVF-Free† | 76.7% | 64.7% | 12.0% [6.0%, 18.0%] | <0.001 |
| MACE-Free† | 79.3% | 66.1% | 13.2% [7.5%, 19.0%] | <0.001 |
| Safety Measures¹ | | | | |
| In-Hospital MACE* | 2.4% (13/533) | 1.5% (8/525) | 0.9% [-0.8%, 2.6%] | 0.379 |
| Safety Endpoint to 270 days | | | | |
| Out-of-Hospital MACE* | 4.9% (26/529) | 18.1% (95/524) | -13.2% [-17.0%, -9.4%] | < 0.001 |
| In- and Out-of-Hospital MACE* | 7.2% (38/529) | 19.3% (101/524) | -12.1% [-16.1%, -8.1%] | < 0.001 |
| Death | 0.9% (5/529) | 0.6% (3/524) | 0.4% [-0.7%, 1.4%] | 0.726 |
| Cardiac Death | 0.4% (2/529) | 0.4% (2/524) | 0.0% [-0.7%, 0.7%] | 1.000 |
| Non-Cardiac Death | 0.6% (3/529) | 0.2% (1/524) | 0.4% [-0.4%, 1.1%] | 0.634 |
| Myocardial Infarction | 2.8% (15/529) | 3.6% (19/524) | -0.8% [-2.9%, 1.3%] | 0.491 |
| Q-Wave | 0.8% (4/529) | 0.8% (4/524) | 0.0% [-1.1%, 1.0%] | 1.000 |
| Non Q-Wave | 2.1% (11/529) | 2.9% (15/524) | -0.8% [-2.7%, 1.1%] | 0.434 |
| Emergent CABG | 0.0% (0/529) | 0.0% (0/524) | -- | -- |
| Target Lesion Revascularization (TLR) | 4.2% (22/529) | 16.6% (87/524) | -12.4% [-16.1%, -8.8%] | <0.001 |
| In- and Out-of-Hospital Cardiac Death+ MI | 3.2% (17/529) | 4.0% (21/524) | -0.8% [-3.0%, 1.5%] | 0.513 |
| In- and Out-of-Hospital TVR-Non TL | 3.4% (18/529) | 4.8% (25/524) | -1.4% [-3.8%, 1.0%] | 0.279 |
| In- and Out-of-Hospital TVF* (Primary End point) | 8.9% (47/529) | 21.0% (110/524) | -12.1% [-16.4%, -7.9%] | <0.001 |
| In- and Out-of-Hospital All TVR | 6.4% (34/529) | 18.9% (99/524) | -12.5% [-16.4%, -8.5%] | <0.001 |
| Stent thrombosis (0-30 days) | 0.2% (1/529) | 0.2% (1/524) | -0.0% [-0.5%, 0.5%] | 1.000 |
| Late Thrombosis (31-270 days) | 0.2% (1/529) | 0.6% (3/524) | -0.4% [-1.1%, 0.4%] | 0.372 |
| In- and Out-of-Hospital Sub-abrupt Closure | 0.2% (1/529) | 0.0% (0/524) | 0.2% [-0.2%, 0.6%] | 1.000 |
| Safety Endpoint to 1800 days | | | | |
| Out-of-Hospital MACE* | 18.8% (96/510) | 34.7% (173/498) | -15.9% [-21.3%, -10.5%] | <0.001 |
| In- and Out-of-Hospital MACE* | 21.2% (108/510) | 35.3% (176/498) | -14.2% [-19.7%, -8.7%] | <0.001 |
| Death | 8.9% (45/504) | 8.9% (44/492) | -0.0% [-3.6%, 3.5%] | 1.000 |
| Cardiac Death | 4.4% (22/504) | 3.9% (19/492) | 0.5% [-2.0%, 3.0%] | 0.751 |
| Non-Cardiac Death | 4.6% (23/504) | 5.1% (25/492) | -0.5% [-3.2%, 2.1%] | 0.768 |
| Myocardial Infarction | 6.5% (33/507) | 6.9% (34/492) | -0.4% [-3.5%, 2.7%] | 0.802 |
| Q-Wave | 1.6% (8/505) | 1.2% (6/492) | 0.4% [-1.1%, 1.8%] | 0.789 |
| Non Q-Wave | 5.1% (26/506) | 5.7% (28/492) | -0.6% [-3.4%, 2.3%] | 0.780 |
| Emergent CABG | 0.0% (0/504) | 0.0% (0/492) | 0.0% [--, --] | N/A |
| Target Lesion Revascularization (TLR) | 9.8% (50/509) | 25.5% (127/498) | -15.7% [-20.3%, -11.1%] | <0.001 |
| In- and Out-of-Hospital Cardiac Death+ MI | 10.3% (52/507) | 10.0% (49/492) | 0.3% [-3.4%, 4.0%] | 0.917 |
| In- and Out-of-Hospital TVR-Non TL | 10.9% (55/506) | 13.8% (68/494) | -2.9% [-7.0%, 1.2%] | 0.178 |
| In- and Out-of-Hospital TVF* | 23.6% (120/509) | 36.5% (182/499) | -12.9% [-18.5%, -7.3%] | <0.001 |
| In- and Out-of-Hospital All TVR | 17.3% (88/509) | 32.1% (160/499) | -14.8% [-20.0%, -9.5%] | <0.001 |
| Stent Thrombosis (0-30 days) | 0.2% (1/505) | 0.2% (1/492) | -0.0% [-0.6%, 0.6%] | 1.000 |
| Late Thrombosis (31-1800 days) | 0.8% (4/504) | 0.6% (3/492) | 0.2% [-0.9%, 1.2%] | 1.000 |
| In- and Out-of-Hospital Sub-abrupt Closure | 0.2% (1/505) | 0.0% (0/492) | 0.2% [-0.2%, 0.6%] | 1.000 |

Numbers are % (counts/sample size) or Mean \pm SD. CI = Confidence Interval SE = Calculated in SAS² software (SAS is a trademark of SAS Institute, Inc) using Mantel-Haenszel Method.

‡ For the endpoints other than the primary endpoint, the p-values and confidence intervals are unadjusted for multiple comparisons.

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.

Product Success (Lesion Based) – Achievement of a final residual diameter stenosis of <50% (by QCA) using the assigned stent 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).

MLD = Minimum Lumen Diameter

DS = Diameter Stenosis

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

* Event rates in this table included the WHO definition of non Q-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.

¹The 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.

¹ For each parameter in the safety measures, the denominator is the number of patients randomized to each treatment arm (excluding de-registered patients) who had sufficient follow up (at least 240 days for 9 month visit and at least 1770 days for 5 year visit) plus any patients who had an event prior to the milestone visit.

Major Adverse Cardiac Events (MACE) – A composite endpoint comprised of death, Q-wave or WHO-defined non Q-wave MI, emergent CABG, or target lesion 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.

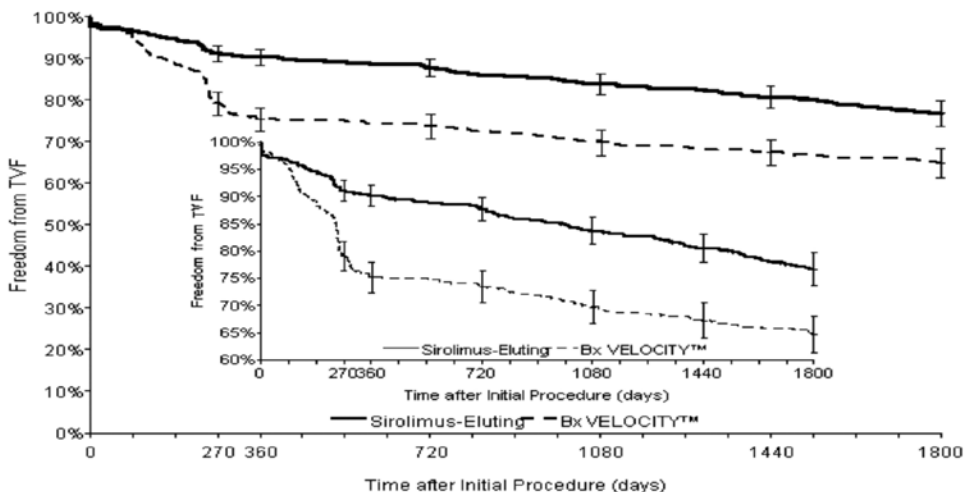
Stent Thrombosis – A 30-day endpoint including sub-abrupt closure or unexplained death or Q-wave MI.

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.

Sub-abrupt Closure. Sub-abrupt closure was defined as abrupt closure that occurs after the index procedure is completed (and the patient left the catheterization laboratory) and before the 30-day follow-up endpoint.

Figure 9-1-1:

Kaplan-Meier Graph and Life Table to 1800 Days SIRIUS Trial Freedom from Target Vessel Failure



Error Bars indicate 1.5 Standard Error

| Measurement | Time after initial procedure (days) | | | | | | |
|---------------------------------------|-------------------------------------|------------|----------|---------|-------|-------|-------|
| | 0 | 270 | 360 | 720 | 1080 | 1440 | 1800 |
| Sirolimus-Eluting Bx VELOCITY™ | | | | | | | |
| # Entered | 533 | 530 | 479 | 473 | 453 | 427 | 406 |
| # Censored | 0 | 7 | 1 | 7 | 6 | 5 | 51 |
| # Incomplete | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| # at risk | 533.0 | 526.5 | 478.5 | 469.5 | 450.0 | 424.5 | 380.5 |
| # Events | 3 | 44 | 5 | 13 | 20 | 16 | 19 |
| # Events/Month | - | 4.9 | 1.7 | 1.1 | 1.7 | 1.3 | 1.6 |
| % Survived | 99.4% | 91.1% | 90.2% | 87.7% | 83.7% | 80.6% | 76.7% |
| SE | 0.3% | 1.2% | 1.3% | 1.4% | 1.6% | 1.8% | 2.0% |
| Bx VELOCITY™ | | | | | | | |
| # Entered | 525 | 525 | 413 | 391 | 377 | 354 | 330 |
| # Censored | 0 | 2 | 2 | 5 | 4 | 12 | 42 |
| # Incomplete | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| # at risk | 525.0 | 524.0 | 412.0 | 388.5 | 375.0 | 348.0 | 309.0 |
| # Events | 0 | 110 | 20 | 9 | 19 | 12 | 12 |
| # Events/Month | - | 12.2 | 6.7 | 0.8 | 1.6 | 1.0 | 1.0 |
| % Survived | 100.0% | 79.0% | 75.2% | 73.4% | 69.7% | 67.3% | 64.7% |
| SE | 0.0% | 1.8% | 1.9% | 1.9% | 2.0% | 2.1% | 2.3% |
| Tests Between Groups | | | | | | | |
| | Test | Chi-Square | Deg Frdm | P-value | | | |
| | WILCOXON | 23.89 | 1 | <.0001 | | | |
| | LOGRANK | 21.65 | 1 | <.0001 | | | |

Standard error estimates by Peto formula.

Table 9-1-2 summarizes angiographic and IVUS results through 8 months.

Table 9-1-2: SIRIUS Trial - Angiographic and IVUS Results (to 8 months) All Patients Treated (N=1058)

| | CYPHER® Stent (N=533 Patients N=533 Lesions) | Control (N=525 Patients N=531 Lesions) | Difference [95% CI] ‡ | P-Value ‡ |
|---------------------------------------|-----------------------------------------------------|-----------------------------------------------|------------------------------|------------------|
| Angiographic Measures | | | | |
| Pre-Procedure | | | | |
| Reference Vessel Diameter RVD (mm) | 2.79 ± 0.45 (531) | 2.81 ± 0.49 (527) | -0.03 [-0.08, 0.03] | 0.362 |
| MLD (mm) | 0.97 ± 0.40 (531) | 0.97 ± 0.38 (526) | 0.01 [-0.04, 0.06] | 0.705 |
| % DS | 65.1% ± 12.6% (531) | 65.6% ± 12.1% (526) | -0.5% [-2.0%, 1.0%] | 0.487 |
| Lesion Length (mm) | 14.4 ± 5.8 (527) | 14.4 ± 5.8 (524) | 0.0 [-0.7, 0.7] | 0.978 |
| Post-Procedure MLD (mm) | | | | |
| In-Stent | 2.67 ± 0.40 (529) | 2.68 ± 0.42 (526) | 0.00 [-0.05, 0.05] | 0.985 |
| In-Lesion | 2.38 ± 0.45 (530) | 2.40 ± 0.46 (526) | -0.01 [-0.07, 0.04] | 0.643 |
| Post-Procedure % DS | | | | |
| In-Stent | 5.4% ± 8.2% (529) | 6.0% ± 7.9% (526) | -0.6% [-1.6%, 0.4%] | 0.229 |
| In-Lesion | 16.1% ± 9.7% (530) | 16.2% ± 8.5% (526) | -0.1% [-1.2%, 1.0%] | 0.792 |
| Eight-Month Follow-up MLD (mm) | | | | |
| In-Stent | 2.50 ± 0.58 (349) | 1.69 ± 0.79 (353) | 0.82 [0.71, 0.92] | <0.001 |
| In-Lesion | 2.15 ± 0.61 (350) | 1.60 ± 0.72 (353) | 0.55 [0.45, 0.65] | <0.001 |
| Eight-Month Follow-up % DS | | | | |
| In-Stent | 10.4% ± 16.5% (349) | 40.1% ± 25.3% (353) | -29.7% [-32.9%, -26.5%] | <0.001 |
| In-Lesion | 23.6% ± 16.4% (350) | 43.2% ± 22.4% (353) | -19.7% [-22.6%, -16.8%] | <0.001 |
| Eight-Month Late Loss (mm) | | | | |
| In-Stent | 0.17 ± 0.44 (347) | 1.00 ± 0.70 (350) | -0.83 [-0.92, -0.74] | <0.001 |
| In-Lesion | 0.24 ± 0.47 (348) | 0.81 ± 0.67 (350) | -0.57 [-0.66, -0.49] | <0.001 |
| Eight-Month Binary Restenosis (%) | | | | |
| In-Stent | 3.2% (11/349) | 35.4% (125/353) | -32.3% [-37.6%, -26.9%] | <0.001 |
| In-Lesion | 8.9% (31/350) | 36.3% (128/353) | -27.4% [-33.2%, -21.6%] | <0.001 |
| IVUS Measures | | | | |
| Post-Procedure | | | | |
| EEM Area (mm ²) | 13.7 ± 4.1 (108) | 14.3 ± 4.9 (93) | -0.6 [-1.9, 0.6] | 0.346 |
| EEM Volume (mm ³) | 305.8 ± 149.2 (56) | 342.2 ± 146.8 (112) | -36.4 [-91.2, 18.4] | 0.134 |
| Mean Stent Area (mm ²) | 6.8 ± 1.8 (57) | 7.1 ± 2.4 (57) | -0.3 [-1.1, 0.5] | 0.452 |
| Stent Volume (mm ³) | 146.2 ± 75.0 (56) | 161.3 ± 63.3 (57) | -15.1 [-41.0, 10.7] | 0.250 |
| Mean Lumen Area (mm ²) | 6.8 ± 1.8 (57) | 7.1 ± 2.4 (57) | -0.3 [-1.1, 0.5] | 0.452 |
| Minimal Lumen Area (mm ²) | 5.9 ± 1.9 (108) | 5.9 ± 2.3 (94) | 0.0 [-0.5, 0.6] | 1.000 |
| Lumen Volume (mm ³) | 146.2 ± 75.0 (56) | 161.3 ± 63.3 (57) | -15.1 [-41.0, 10.7] | 0.250 |
| Plaque Volume (mm ³) | 159.6 ± 78.9 (56) | 181.9 ± 87.2 (56) | -22.3 [-53.4, 8.8] | 0.159 |
| Incomplete Stent Apposition (ISA) | 14.7% (16/109) | 14.0% (14/100) | 0.7% [-8.8%, 10.2%] | 1.000 |
| Eight-Month Follow-up | | | | |
| EEM Area (mm ²) | 14.1 ± 4.1 (99) | 15.3 ± 4.5 (69) | -1.2 [-2.6, 0.1] | 0.075 |
| EEM Volume (mm ³) | 313.5 ± 130.4 (50) | 336.7 ± 114.4 (39) | -23.2 [-75.7, 29.3] | 0.382 |
| Mean Stent Area (mm ²) | 6.8 ± 2.1 (101) | 7.7 ± 2.4 (75) | -0.9 [-1.6, -0.2] | 0.009 |
| Stent Volume (mm ³) | 147.2 ± 64.3 (51) | 165.6 ± 62.7 (44) | -18.4 [-44.3, 7.6] | 0.163 |
| Mean Lumen Area (mm ²) | 6.7 ± 2.0 (51) | 5.0 ± 1.8 (45) | 1.7 [0.9, 2.4] | <0.001 |
| Minimal Lumen Area (mm ²) | 5.4 ± 2.1 (101) | 3.9 ± 1.9 (75) | 1.5 [0.9, 2.1] | <0.001 |
| Lumen Volume (mm ³) | 142.6 ± 63.3 (51) | 109.7 ± 43.9 (45) | 32.9 [10.6, 55.3] | 0.004 |
| Mean NIH Area (mm ²) | 0.5 ± 0.8 (101) | 2.7 ± 1.5 (75) | -2.3 [-2.6, -1.9] | <0.001 |
| NIH Volume (mm ³) | 4.4 ± 6.5 (51) | 57.6 ± 32.7 (45) | -53.2 [-62.5, -43.9] | <0.001 |
| Plaque Volume (mm ³) | 172.9 ± 73.8 (50) | 226.2 ± 79.3 (39) | -53.3 [-85.7, -20.9] | <0.001 |
| Volumetric Plaque Burden (%) | 3.1% ± 5.3% (51) | 33.4% ± 14.3% (44) | -30.3% [-34.6%, -26.0%] | <0.001 |
| Incomplete Stent Apposition (ISA) | 17.8% (18/101) | 9.0% (7/78) | 8.8% [-0.9%, 18.6%] | 0.123 |

EEM=External Elastic Membrane.

Plaque Burden (%) = 100*NIH Area / Stent Area.

Volumetric Plaque Burden (%) = 100*NIH Volume / Stent Volume.

Plaque Volume = EEM volume - Lumen volume.

NIH = Neointimal Hyperplasia.

"Plaque" (volume, or area) measured/analyzed at follow-up reflects the sum of atherosclerotic tissue in the vessel wall (original plaque plus Neointimal Hyperplasia).

‡ For the endpoints other than the primary endpoint, the p-values and confidence intervals are unadjusted for multiple comparisons

Table 9-1-3 summarizes stent thrombosis (ST) based on protocol definition.

Table 9-1-3: SIRIUS Trial - Summary of Stent Thrombosis Based on Protocol Definition

| | CYPHER* | Control |
|--------------------------------------|----------------|----------------|
| Cumulative ST through 5 years | 1.0% (5) | 0.8% (4) |
| Acute ST (≤24 hrs) | 0.0% (0) | 0.0% (0) |
| Subacute ST (>24 hrs and ≤ 30days) | 0.2% (1) | 0.2% (1) |
| Late ST (>30 days and ≤12 months) | 0.2% (1) | 0.6% (3) |
| Very Late ST (>12 months to 5 years) | 0.6% (3) | 0.0% (0) |

For all calculations, event rates are cumulative incidences using Kaplan-Meier method.

Protocol Thrombosis is defined as the composite of Stent Thrombosis and Late Thrombosis, where, Stent Thrombosis is defined as a 30-day endpoint including sub-abrupt closure or unexplained death or Q-wave MI; Late Thrombosis is defined as 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.

9.2. RAVEL Trial

Purpose: The purpose of the trial was to evaluate the safety and effectiveness of the **CYPHER** Stent for reducing late loss in *de novo* native coronary artery lesions.

Conclusions: In selected patients, use of the **CYPHER** Stent significantly reduced in-stent late loss at 6 months compared to the Control (**BX VELOCITY** Stent, an uncoated 316L stainless steel stent). Clinical outcomes at 5 years were also significantly improved.

Design: This was a multi-center, prospective, randomized, double-blind trial conducted at 19 sites in Europe, Brazil and Mexico. The primary efficacy endpoint was pre-specified to be in-stent late loss at 6 months. To be eligible a patient was required to have a *de novo* ischemic lesion of a length that could be covered by a single 18 mm stent in a native coronary artery of diameter 2.5 mm to 3.5 mm (using visual estimates).

Patients were randomized with equal probability to receive either the **CYPHER** Stent or the Control stent. A total of 238 patients were randomized; 120 to **CYPHER** Stent and 118 to Control. After the procedure patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 2 months.

Angiographic follow-up at 6 months was obtained on 218 patients. IVUS follow-up (but without baseline studies) was obtained on 110 patients. The final 5 year clinical follow-up is currently available in 82.8% of patients.

Demography: Baseline characteristics were similar for both treatment arms; factors evaluated included age (mean 61 years), diabetes (18%), prior MI (36%), hypertension (49%), hyperlipidemia (52%), current smoking (30%), CSS Angina Class (12% III or IV), IIb/IIIa inhibitor use (10%), LAD (50%), LCX (23%), RCA (27%), reference vessel diameter (mean 2.6 mm), minimum lumen diameter (mean 0.95 mm), percent diameter stenosis (mean 64%), and lesion length (mean 9.6 mm). Overall 24% were female, but there were more women in the **CYPHER** Stent arm (30%) than in the Control arm (19%); gender was not a significant predictor of outcome in the trial.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by clinical coordinators at the clinical sites. Angiographic and IVUS outcomes were assessed in a blinded fashion by quantitative analysis at designated central laboratories. An independent review committee adjudicated clinical events, and the trial was monitored by an independent Data and Safety Monitoring Committee.

Results: In selected patients, elective **CYPHER** Stent placement in native coronary *de novo* lesions resulted in significantly lower in-stent late loss at 6 months compared to control (-0.01 mm vs. 0.80 mm, $p < 0.001$), and the mean in-lesion % diameter stenosis also was significantly reduced (25.3% vs. 38.7%, $p < 0.001$). There was no evidence of an edge-effect 5 mm proximal or distal to the stent. Examination by IVUS at 6 months showed that neointima volume was significantly reduced in the **CYPHER** Stent arm (1.5 mm³ vs. 34.3 mm³, $p < 0.001$), but there was a higher rate of incomplete stent apposition (21% vs. 4%, $p = 0.028$). The rate of target vessel failure by 1 year was lower (4% vs. 20%, $p < 0.001$).

Table 9-2-1 summarizes the principal effectiveness and safety results of the RAVEL Trial to 1825 days. Figure 9-2-1 provides the freedom from TVF rates to 1825 days.

Table 9-2-1: RAVEL Trial Principal Effectiveness and Safety Results (to 1825 days) All Patients Treated (N=238)

| | CYPHER® Stent (N=120 Patients) | Control (N=118 Patients) | Difference [95% CI]‡ | P-Value‡ |
|---------------------------------------------------|--------------------------------|--------------------------|-------------------------|----------|
| Effectiveness Measures | | | | |
| Product Success | 99.2% (119/120) | 95.7% (111/116) | 3.5% [-0.6%, 7.5%] | 0.115 |
| Procedure Success | 96.7% (116/120) | 93.1% (108/116) | 3.6% [-2.1%, 9.2%] | 0.248 |
| 6-Month Binary Restenosis Rate (Primary endpoint) | 0.0% (0/109) | 26.6% (29/109) | -26.6% [-34.9%, -18.3%] | <0.001 |
| Clinical Endpoints to 270 Days | | | | |
| TLR-Free† | 99.2% | 84.7% | 14.5% [7.4%,21.6%] | <0.001 |
| TVR-Free† | 98.3% | 84.5% | 13.8% [6.8%,20.8%] | <0.001 |
| TVF-Free† | 96.7% | 81.4% | 15.3% [7.6%,23.0%] | <0.001 |
| MACE-Free† | 96.7% | 82.2% | 14.5% [6.9%,22.1%] | <0.001 |
| Clinical Endpoints to 1825 Days | | | | |
| TLR-Free† | 90.6% | 84.4% | 6.3% [-6.2%, 18.8%] | 0.070 |
| TVR-Free† | 89.1% | 81.7% | 7.3% [-6.0%, 20.7%] | 0.060 |
| TVF-Free† | 82.8% | 74.1% | 8.7% [-6.4%, 23.8%] | 0.050 |
| MACE-Free† | 75.1% | 75.0% | 0.0% [-15.5%, 15.6%] | 0.690 |
| Safety Measures¹ | | | | |
| In-Hospital MACE* | 2.5% (3/120) | 2.5% (3/118) | 0.0% [-4.0%, 3.9%] | 1.000 |
| Safety Endpoint to 270 days | | | | |
| Out-of-Hospital MACE* | 0.8% (1/120) | 16.1% (19/118) | -15.3% [-22.1%, -8.4%] | <0.001 |
| In- and Out-of-Hospital MACE* | 3.3% (4/120) | 17.8% (21/118) | -14.5% [-22.1%, -6.9%] | <0.001 |
| Death | 0.0% (0/120) | 1.7% (2/118) | -1.7% [-4.0%, 0.6%] | 0.245 |
| Cardiac Death | 0.0% (0/120) | 0.8% (1/118) | -0.8% [-2.5%, 0.8%] | 0.496 |
| Non-Cardiac Death | 0.0% (0/120) | 0.8% (1/118) | -0.8% [-2.5%, 0.8%] | 0.496 |
| Myocardial Infarction | 2.5% (3/120) | 4.2% (5/118) | -1.7% [-6.3%, 2.8%] | 0.498 |
| Q-Wave | 1.7% (2/120) | 0.8% (1/118) | 0.8% [-2.0%, 3.6%] | 1.000 |
| Non Q-Wave | 0.8% (1/120) | 3.4% (4/118) | -2.6% [-6.2%, 1.1%] | 0.211 |
| Emergent CABG | -- | -- | -- | -- |
| Target Lesion Revascularization (TLR) | 0.8% (1/120) | 13.6% (16/118) | -12.7% [-19.1%, -6.3%] | <0.001 |
| In- and Out-of-Hospital Cardiac Death+ MI | 2.5% (3/120) | 4.2% (5/118) | -1.7% [-6.3%, 2.8%] | 0.498 |
| In- and Out-of-Hospital TVR-Non TL | 0.8% (1/120) | 1.7% (2/118) | -0.9% [-3.7%, 2.0%] | 0.620 |
| In- and Out-of-Hospital TVF* | 3.3% (4/120) | 18.6% (22/118) | -15.3% [-23.0%, -7.6%] | <0.001 |
| In- and Out-of-Hospital All TVR | 1.7% (2/120) | 15.3% (18/118) | -13.6% [-20.5%, -6.7%] | <0.001 |
| Stent thrombosis (0-30 days) | 0.0% (0/120) | 0.0% (0/118) | -- | -- |
| Late Thrombosis (31-270 days) | 0.0% (0/120) | 0.0% (0/118) | -- | -- |
| In- and Out-of-Hospital Sub-abrupt Closure | 0.0% (0/120) | 0.0% (0/118) | -- | -- |
| Safety Endpoint to 1825 days | | | | |
| Out-of-Hospital MACE* | 26.8% (26/97) | 28.7% (27/94) | -1.9% [-14.6%, 10.8%] | 0.872 |
| In- and Out-of-Hospital MACE* | 29.6% (29/98) | 30.5% (29/95) | -0.9% [-13.9%, 12.0%] | 1.000 |
| Death | 15.1% (14/93) | 8.9% (8/90) | 6.2% [-3.2%, 15.5%] | 0.257 |
| Cardiac Death | 3.2% (3/93) | 6.7% (6/90) | -3.4% [-9.7%, 2.8%] | 0.325 |
| Non-Cardiac Death | 11.8% (11/93) | 2.2% (2/90) | 9.6% [2.4%, 16.8%] | 0.018 |
| Myocardial Infarction | 12.0% (10/83) | 9.1% (8/88) | 3.0% [-6.3%, 12.2%] | 0.621 |
| Q-Wave | 6.3% (5/80) | 3.5% (3/85) | 2.7% [-3.9%, 9.3%] | 0.486 |
| Non Q-Wave | 6.1% (5/82) | 5.9% (5/85) | 0.2% [-7.0%, 7.4%] | 1.000 |
| Emergent CABG | -- | -- | -- | -- |
| Target Lesion Revascularization (TLR) | 12.0% (10/83) | 20.9% (18/86) | -8.9% [-20.0%, 2.2%] | 0.149 |
| In- and Out-of-Hospital Cardiac Death+ MI | 13.7% (13/95) | 12.0% (11/92) | 1.7% [-7.8%, 11.3%] | 0.828 |
| In- and Out-of-Hospital TVR-Non TL | 3.8% (3/80) | 3.7% (3/82) | 0.1% [-5.7%, 5.9%] | 1.000 |
| In- and Out-of-Hospital TVF* | 21.6% (19/88) | 31.9% (30/94) | -10.3% [-23.1%, 2.4%] | 0.134 |
| In- and Out-of-Hospital All TVR | 12.2% (12/98) | 21.3% (21/94) | -10.1% [-20.7%, 0.5%] | 0.085 |

continued on next page

| | | | | |
|--------------------------------------------|-------------|-------------|-------------|----|
| Stent Thrombosis (0-30 days) | 0.0% (0/79) | 0.0% (0/82) | 0.0% [—, —] | -- |
| Late Thrombosis to (31-1825 days) | 0.0% (0/79) | 0.0% (0/82) | 0.0% [—, —] | -- |
| In- and Out-of-Hospital Sub-abrupt Closure | 0.0% (0/79) | 0.0% (0/82) | 0.0% [—, —] | -- |

Numbers are % (counts/available field sample size) or mean + 1 standard deviation.

CI = Confidence Interval CI = Diff ± 1.96 • SE

SD = Standard Deviation SE = sqrt (p1•q1/n1 + p2•q2/n2)

Procedure success – Successful implantation of study stent, attainment of < 30% diameter stenosis by angiographic corelab. Quantitative Coronary Angiography (QCA) determination, and freedom from in-hospital MACE.

Product Success (Lesion Based) – Achievement of a final residual diameter stenosis of <50% (by QCA) using the assigned stent only (if QCA was not available, the visual estimate of diameter stenosis was used).

% DS – Percent diameter stenosis – value calculated as 100•(1-MLD/RVD) using the mean values from two orthogonal views (when possible) by Quantitative Coronary Angiography (QCA). A 100% DS was imputed for total occlusions if no RVD values were available.

Restenosis Rate – Percent lesions with a follow-up percent diameter stenosis is > 50%.

In-Lesion (Within Segment) - In-lesion measurement was defined as the measurements either within the stented segment or within side branch proximal or distal to the stent edges.

In-Stent (Within Stent) - In-stent measurement was defined as the measurement within the stented segment.

†The following survival estimates are by Kaplan-Meier methods. Standard Error estimates from Peto formula.

TLR-Free – No target lesion revascularization

TVR-Free – No target vessel revascularization

TVF-Free – No cardiac death, target vessel related myocardial infarction or target vessel revascularization

MACE-Free – No death, myocardial infarction, target lesion CABG or target lesion Re-PTCA

In-Hospital MACE – Death, myocardial infarction (Q-wave and non Q-wave), target lesion CABG or target lesion revascularization prior to hospital discharge as determined by the independent Clinical Events Committee.

Out-of-Hospital MACE - Death, myocardial infarction (Q-wave and non Q-wave), target lesion CABG or target lesion revascularization after hospital discharge through the 1825 days contact as determined by the independent Clinical Events Committee.

Late loss— Difference MLD after device— MLD at follow-up.

† For each parameter in the safety measures, the denominator is the number of patients randomized to each treatment arm who had sufficient follow up (at least 1795 days for the 5 year visit) plus any patients who had an event prior to the milestone visit.

*MACE – Major Adverse Cardiac Events: death, myocardial infarction (Q-wave and non Q-wave), target lesion CABG or target lesion revascularization.

MI – Myocardial Infarction: Necrosis of the myocardium, as a result of interruption of the blood supply to the area as in coronary thrombosis. For this study, myocardial infarction was categorized in Q-wave and non Q-wave.

Sub-abrupt closure – New reduced (TIMI 0 or 1) flow at the target vessel as a result of mechanical obstruction, such as dissection or luminal thrombus, occurring after completion of the index procedure but within thirty days of stent deployment.

Stent Thrombosis – Complete thirty-day ischemic endpoint including death, Q-wave MI or sub-abrupt closure requiring revascularization.

Late Thrombosis – Late Thrombosis was myocardial infarction attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site > 30 days after the index procedure in the absence of an intervening revascularization of the target vessel.

MLD – mean minimal luminal diameter (mm) from two orthogonal views using Quantitative Coronary Angiography (QCA).

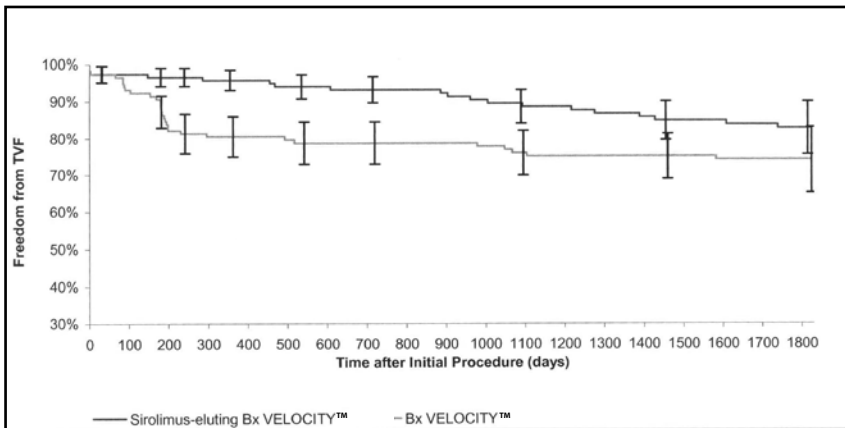
RVD – Reference Vessel Diameter: Average of normal segments proximal and distal to the target lesion from two orthogonal views (when available) using QCA.

TL = Target Lesion

TV = Target Vessel

‡ For the endpoints other than the primary endpoint, the p-values and confidence intervals are unadjusted for multiple comparisons.

Figure 9-2-1
Kaplan-Meier Graph and Life Table to 1825 Days RAVEL Trial Freedom from Target Vessel Failure



Error Bars indicate + 1.5 Standard Error 9.3. First-in-Man Study

Target Vessel Failure Life Table Analysis: All Patients Treated (N=238)

| Interval ending day | 0 | 2 | 180 | 240 | 300 | 360 | 420 | 480 | 540 | 600 | 660 | 720 | 1095 | 1460 | 1825 |
|-----------------------------------------------|-------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| Sirolimus-eluting Bx VELOCITY™ (N=120) | | | | | | | | | | | | | | | |
| # Entered | 120 | 120 | 117 | 116 | 116 | 115 | 113 | 111 | 109 | 107 | 106 | 105 | 104 | 96 | 88 |
| # Censored | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 2 | 1 | 0 | 1 | 3 | 4 | 36 |
| # At risk | 120 | 120 | 117 | 116 | 116 | 114 | 112 | 111 | 108 | 107 | 106 | 105 | 103 | 94 | 70 |
| # Events | 0 | 3 | 1 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 1 | 0 | 5 | 4 | 2 |
| # Events / Month | 0 | 45.0 | 0.5 | 0.0 | 0.5 | 0.0 | 0.0 | 1.0 | 0.0 | 0.0 | 0.5 | 0.0 | 0.4 | 0.3 | 0.2 |
| Cume. Survival rate (%) | 100.0 | 97.5 | 96.7 | 96.7 | 95.8 | 95.8 | 95.8 | 94.1 | 94.1 | 94.1 | 93.2 | 93.2 | 88.6 | 84.9 | 82.8 |
| Survival std. Err. (%) | 0.0 | 1.4 | 1.6 | 1.6 | 1.8 | 1.8 | 1.9 | 2.2 | 2.2 | 2.2 | 2.4 | 2.4 | 3.0 | 3.5 | 4.9 |
| Bx VELOCITY™ (N=118) | | | | | | | | | | | | | | | |
| # Entered | 118 | 118 | 109 | 105 | 96 | 94 | 93 | 91 | 91 | 88 | 88 | 88 | 88 | 84 | 82 |
| # Censored | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 41 |
| # At risk | 118 | 118 | 109 | 105 | 96 | 94 | 92 | 91 | 91 | 88 | 88 | 88 | 88 | 84 | 62 |
| # Events | 0 | 3 | 4 | 9 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 3 | 1 | 1 |
| # Events / Month | 0 | 45.0 | 2.0 | 4.5 | 0.5 | 0.0 | 0.0 | 0.0 | 1.0 | 0.0 | 0.0 | 0.0 | 0.2 | 0.1 | 0.1 |
| Cume. Survival rate (%) | 100.0 | 97.5 | 89.0 | 81.4 | 80.5 | 80.5 | 80.5 | 80.5 | 78.7 | 78.7 | 78.7 | 78.7 | 76.0 | 75.1 | 74.1 |
| Survival std. Err. (%) | 0.0 | 1.4 | 2.9 | 3.6 | 3.7 | 3.7 | 3.7 | 3.7 | 3.9 | 3.9 | 3.9 | 3.9 | 4.1 | 4.1 | 6.0 |

Survival Curves Comparison

| | Log-Rank P-value | Wilcoxon P-Value |
|-----------------------|------------------|------------------|
| Life-Table Analysis | 0.050 | 0.020 |
| Kaplan-Meier Analysis | 0.050 | 0.020 |

Standard error estimates by Peto formula.

Table 9-2-2 summarizes angiographic and IVUS results of the RAVEL Trial to 6 months.

Table 9-2-2: RAVEL Trial Angiographic and IVUS Results (to 6 months) All Patients Treated (N=238)

| | CYPHER® Stent (N=120 Patients N=120 Lesions) | Control (N=118 Patients N=118 Lesions) | Difference [95% CI]‡ | P-Value‡ |
|-------------------------------------|-----------------------------------------------------|-----------------------------------------------|-----------------------------|-----------------|
| Angiographic Measures | | | | |
| Pre-Procedure | | | | |
| Reference Vessel Diameter RVD (mm) | 2.60 ± 0.54 (116) | 2.64 ± 0.52 (114) | -0.04 [-0.17, 0.10] | 0.608 |
| MLD (mm) | 0.94 ± 0.31 (120) | 0.95 ± 0.35 (117) | -0.01 [-0.10, 0.07] | 0.746 |
| % DS | 63.6% ± 10.7% (120) | 64.0% ± 10.2% (117) | -0.4% [-3.1%, 2.2%] | 0.763 |
| Lesion Length (mm) | 9.56 ± 3.33 (116) | 9.58 ± 3.25 (114) | -0.05 [-0.89, 0.79] | 0.904 |
| Post-Procedure MLD (mm) | | | | |
| In-Stent | 2.43 ± 0.41 (N=120) | 2.41 ± 0.40 (N=116) | 0.01 [-0.09, 0.12] | 0.705 |
| In-Lesion | 1.97 ± 0.40 (N=120) | 2.01 ± 0.44 (N=116) | -0.04 [-0.14, 0.07] | 0.465 |
| Post-Procedure % DS | | | | |
| In-Stent | 11.9 ± 5.9 (N=120) | 14.0 ± 6.8 (N=116) | -2.1 [-3.7, -0.5] | 0.012 |
| In-Lesion | 24.5 ± 8.6 (N=120) | 24.7 ± 10.7 (N=116) | -0.2 [-2.7, 2.2] | 0.855 |
| Six-Month Follow-up MLD (mm) | | | | |
| In-Stent | 2.42 ± 0.49 (N=109) | 1.64 ± 0.59 (N=109) | 0.78 [0.64, 0.93] | <0.001 |
| In-Lesion | 2.01 ± 0.47 (N=109) | 1.57 ± 0.53 (N=109) | 0.45 [0.31, 0.58] | <0.001 |
| Six-Month Follow-up % DS | | | | |
| In-Stent | 14.7 ± 6.9 (N=109) | 36.7 ± 18.0 (N=109) | -22.0 [-25.6, -18.4] | <0.001 |
| In-Lesion | 25.3 ± 9.6 (N=109) | 38.7 ± 16.9 (N=109) | -13.5 [-17.1, -9.8] | <0.001 |
| Six-Month Late Loss (mm) | -0.01 ± 0.33 (N=109) | 0.80 ± 0.53 (N=108) | -0.81 [-0.93, -0.70] | <0.001 |
| Six-Month Binary Restenosis Rate | 0.0% (0/109) | 26.6% (29/109) | -26.6% [-34.9%, -18.3%] | <0.001 |
| IVUS Measures | | | | |
| Six-Month Follow-up | | | | |
| Mean EEM Area (mm ²) | 15.33 ± 3.97 (42) | 16.25 ± 4.19 (35) | -0.92 [-2.73, 0.89] | 0.327 |
| EEM Volume (mm ³) | 279.8 ± 70.5 (42) | 289.3 ± 77.4 (35) | -9.5 [-42.3, 23.2] | 0.575 |
| Mean Stent Area (mm ²) | 7.28 ± 2.04 (56) | 7.65 ± 2.02 (54) | -0.36 [-1.11, -0.39] | 0.341 |
| Stent Volume (mm ³) | 131.6 ± 34.8 (56) | 136.7 ± 37.4 (54) | -5.2 [-18.6, 8.2] | 0.461 |
| Mean Lumen Area (mm ²) | 7.2 ± 2.0 (56) | 5.7 ± 2.5 (54) | 1.5 [0.7, 2.3] | <0.001 |
| Mean Plaque Area (mm ²) | 8.25 ± 2.49 (42) | 10.17 ± 2.83 (35) | -1.92 [-3.10, -0.74] | 0.002 |
| Lumen Volume (mm ³) | 130.1 ± 34.2 (56) | 102.5 ± 45.0 (54) | 27.6 [12.8, 42.4] | <0.001 |
| Minimal Luminal Diameter (mm) | 2.52 ± 0.41 (56) | 2.03 ± 0.58 (54) | 0.50 [0.31, 0.68] | <0.001 |
| Mean NIH Area (mm ²) | 0.08 ± 0.25 (56) | 1.93 ± 1.61 (54) | -1.85 [-2.27, -1.42] | <0.001 |
| NIH Volume (mm ³) | 1.5 ± 4.2 (56) | 34.3 ± 28.3 (54) | -32.8 [-40.2, -25.3] | <0.001 |
| Plaque Volume (mm ³) | 150.8 ± 45.7 (42) | 181.0 ± 52.1 (35) | -30.2 [-51.8, -8.5] | 0.008 |
| Volume Obstruction In-Stent (%) | 1.1% ± 2.5% (56) | 26.1% ± 20.2% (54) | -25.0% [-30.3%, -19.7%] | <0.001 |

EEM=External Elastic Membrane.

Plaque Burden (%) = 100*NIH Area / Stent Area.

Volumetric Plaque Burden (%) = 100*NIH Volume / Stent Volume.

Plaque Volume = EEM volume – Lumen volume.

NIH = Neointimal Hyperplasia.

Plaque (volume, or area) measured/analyzed at follow-up reflects the sum of atherosclerotic tissue in the vessel wall (original plaque plus Neointimal Hyperplasia).

‡ For all of the endpoints in this table, the p-values and confidence intervals are unadjusted for multiple comparisons.

Table 9-2-3 summarizes stent thrombosis based on protocol definition.

Table 9-2-3: RAVEL Trial – Summary of Stent Thrombosis Based on Protocol Definition

| | CYPHER | Control |
|-------------------------------------------------------|---------------|----------------|
| Cumulative ST through 5 years | 0.0% (0) | 0.0% (0) |
| Acute ST (≤24 hrs) | 0.0% (0) | 0.0% (0) |
| Subacute ST (24 hrs to 30 days) | 0.0% (0) | 0.0% (0) |
| Late ST (31 to 12 Months (360 days)) | 0.0% (0) | 0.0% (0) |
| Very Late ST (12 Months (361) to 5 years (1800 days)) | 0.0% (0) | 0.0% (0) |

For all calculations, event rates are cumulative incidences using Kaplan-Meier method

Protocol Thrombosis is defined as the composite of Stent Thrombosis and Late Thrombosis, where, Stent Thrombosis is defined as a 30-day endpoint including sub-abrupt closure or unexplained death or Q-wave MI; Late Thrombosis is defined as 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.

9.3. First-in-Man Study

Purpose: The purpose of this early feasibility study was to evaluate the performance of the **CYPHER**[®] Stent and an alternate formulation sirolimus-eluting stent in *de novo* native coronary artery lesions. This study provides the longest follow-up experience available.

Conclusions: In selected patients, use of the **CYPHER** Stent provided favorable IVUS and angiographic results through 48 months and clinical results through 60 months of follow-up.

Design: This was a non-randomized, open-label study conducted at two sites, one in The Netherlands and one in Brazil. To be eligible, a patient was required to have a *de novo* ischemic lesion of a length that could be covered by a single 18 mm stent in a native coronary artery of diameter 3.0 mm to 3.5 mm (using visual estimates). A total of 45 patients were treated, of which 30 received the **CYPHER** Stent and 15 received an alternative formulation sirolimus-eluting stent. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel for 2 months. Angiographic follow-up was performed at 4, 12, 24, and 48 months, or at 6, 18 and 48 months, depending on the site. Angiographic follow-up at 48 months is available for 22 patients, and IVUS follow-up is available for 21 patients. The Final clinical follow-up is available through 5 years.

Demography: Patients had a mean age of 58 years, there were 36% females, and 13% had diabetes, 51% of the lesions treated were in LAD, 22% were in the LCX, 27% were in the RCA, mean reference vessel diameter was 2.9 mm, mean minimum lumen diameter was 0.95 mm, mean percent diameter stenosis was 67%, and 27% of patients had a lesion length < 10 mm and 73% of patients had a lesion length between 10 and 18 mm. **Note:** IIb/IIIa inhibitor usage was not monitored during this study.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms. Angiographic and IVUS outcomes were assessed by quantitative analysis at designated central laboratories. An independent Clinical Events Committee adjudicated clinical events.

Results: At 48 months following elective **CYPHER** Stent placement in native coronary *de novo* lesions, in-stent mean % diameter stenosis was 11%, and mean in-stent late loss was 0.19 mm. Mean obstructive volume by IVUS was 8%. The overall MACE rate at 60 months was 17%.

Table 9-3-1: First-in-Man Study: Effectiveness and Safety Results All Patients Treated with CYPHER Stent

| | CYPHER Stent (N=30 Patients, N=30 Lesions) |
|-------------------------------------------|---------------------------------------------------|
| Effectiveness Measures | |
| Procedure Success (QCA) | 100.0% (30/30) |
| 48 months* | |
| In-Stent % Diameter Stenosis | 11.1% ± 8.2% (22) |
| In-Lesion % Diameter Stenosis | 22.4% ± 20.6% (22) |
| In-Stent Late Loss (mm) | 0.19 ± 0.36 (22) |
| In-Lesion Late Loss (mm) | 0.26 ± 0.71 (22) |
| Obstruction Volume (%) ¹ | 8.1% ± 9.7% (21) |
| Clinical Endpoints to 270 Days | |
| TLR-Free† | 100.0% ± 0.0 |
| TVR-Free† | 96.7% ± 3.3 |
| TVF-Free† | 93.3% ± 4.6 |
| MACE-Free† | 93.3% ± 4.6 |
| Clinical Endpoints to 1800 Days | |
| TLR-Free† | 89.4% ± 5.8 |
| TVR-Free† | 86.0% ± 6.5 |
| TVF-Free† | 83.1% ± 6.9 |
| MACE-Free† | 83.1% ± 6.9 |
| Safety Measures² | % (n/N) |
| In-Hospital MACE Events | 6.7% (2/30) |
| Safety Endpoint to 270 days | |
| Out-of-Hospital MACE | 0.0% (0/30) |
| In- and Out-of-Hospital MACE | 6.7% (2/30) |
| Death | 3.3% (1/30) |
| Cardiac Death | 3.3% (1/30) |
| Non-Cardiac Death | 0.0% (0/29) |
| Myocardial Infarction | 3.4% (1/29) |
| Q-Wave | 0.0% (0/29) |
| Non Q-Wave | 3.4% (1/29) |
| Emergent CABG | 0.0% (0/29) |
| Target Lesion Revascularization (TLR) | 0.0% (0/29) |
| In- and Out-of-Hospital Cardiac Death+ MI | 6.7% (2/30) |
| In- and Out-of-Hospital TVR-Non TL | 3.4% (1/29) |
| In- and Out-of-Hospital TVF | 6.7% (2/30) |
| In- and Out-of-Hospital All TVR | 3.4% (1/29) |

continued on next page

| | |
|--------------------------------------------|--------------|
| Stent thrombosis (0-30 days) | 0.0% (0/29) |
| Late Thrombosis (31-270 days) | 0.0% (0/29) |
| In- and Out-of-Hospital Sub-abrupt Closure | 0.0% (0/29) |
| Safety Endpoint to 1800 days | |
| Out-of-Hospital MACE | 10.7% (3/28) |
| In and Out-of-Hospital MACE | 17.2% (5/29) |
| Death | 10.3% (3/29) |
| Cardiac Death | 7.1% (2/28) |
| Non-Cardiac Death | 3.7% (1/27) |
| Myocardial Infarction | 3.8% (1/26) |
| Q-Wave | 0.0% (0/26) |
| Non Q-Wave | 3.8% (1/26) |
| Emergent CABG | 0.0% (0/26) |
| Target Lesion Revascularization (TLR) | 10.7% (3/28) |
| In- and Out-of-Hospital Cardiac Death+ MI | 10.7% (3/28) |
| In- and Out-of-Hospital TVR-Non TL | 7.4% (2/27) |
| In- and Out-of-Hospital TVF | 17.2% (5/29) |
| In- and Out-of-Hospital All TVR | 14.3% (4/28) |
| Stent thrombosis (0-30 days) | 0.0% (0/26) |
| Late Thrombosis (31-270 days) | 0.0% (0/26) |
| In- and Out-of-Hospital Sub-abrupt Closure | 0.0% (0/26) |

Numbers are number of events (field sample size) or Mean ± Standard Deviation.

Procedure Success – The attainment of a final in-stent diameter stenosis of <50% (by QCA) in the absence of death, emergent CABG, Myocardial Infarction, or TLR prior to hospital discharge.

QCA – Quantitative Coronary Angiography by Core lab.

In-Stent (Within Stent) – In-stent measurement was defined as the measurement within the stented segment.

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.

* Quantitative coronary angiography core lab data at 48 months.

¹ IVUS core lab data at 48 months.

² For each parameter in the safety measures, the denominator is the number of patients randomized to each treatment arm (excluding de-registered patients) who had sufficient follow up (at least 240 days for 9 month visit and at least 1770 days for 5 year visit) plus any patients who had an event prior to the milestone visit.

[†]The following survival estimates are by Kaplan-Meier methods. Standard Error estimates from Peto formula.

TLR-Free – No target lesion revascularization

TVR-Free – No target vessel revascularization

MACE-Free – No cardiac death, target vessel related myocardial infarction or target vessel revascularization

MACE-Free – No death, myocardial infarction, target lesion CABG or target lesion Re-PTCA

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 sub-abrupt 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.

Sub-abrupt 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.

9.4. SIRIUS and RAVEL Trials (Patient Level Pooled Results To 5-Years)

The trials described above were not powered to evaluate low frequency events such as death, myocardial infarction, or stent thrombosis.

Since the enrollment criteria were qualitatively similar, patient level data to 5 years of follow-up from the RAVEL and SIRIUS trials were combined for these and the target lesion revascularization endpoints to enhance the sample size for analysis. Table 9-4-1 details patient compliance to follow-up at 5 years for this pooled analysis and demonstrates greater than or equal to 92% overall follow-up for these patient cohorts. Kaplan-Meier analysis of the incidence of target lesion revascularization (TLR) (Figure 9-4-1) and target vessel failure (TVF) (Figure 9-4-2) demonstrates maintenance of the initial separation of the curves seen at 1 year to the 5-year follow-up time point (for CYPHER® vs. Control, TLR-Free: 90.3% vs. 77.0%, log rank p < 0.001; TVF-Free: 77.8% vs. 66.4%, p < 0.001). Kaplan-Meier curves of death or MI, death, cardiac death, non-cardiac death, MI, Q-wave MI, and Non Q-Wave MI are presented in Figures 9-4-3 through 9-4-9. No statistically significant difference were observed for these end points at significant level of 0.5, when comparing CYPHER Stent to bare metal stent control.

Table 9-4-1: Patient Disposition to 1800 Days – RAVEL and SIRIUS Pooled Patients

| | CYPHER Stent | | | Control | | |
|------------------------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | RAVEL | SIRIUS | Pooled | RAVEL | SIRIUS | Pooled |
| Number of Patients Randomized | 120 | 533 | 653 | 118 | 525 | 643 |
| Number of Patients who Died to 1770 days | 14 | 44 | 68 | 8 | 40 | 48 |
| Number of Patients who Survived and had Follow-up to ≥ 1770 Days | 93 | 460 | 553 | 95 | 452 | 547 |
| Number of Patients who Died Between 1771 and 1800 Days | 0 | 0 | 0 | 0 | 0 | 0 |
| Clinical Compliance Excluding Patients Who Died | 87.7% (93/106) | 94.1% (460/489) | 92.9% (553/595) | 86.4% (95/110) | 93.2% (452/485) | 91.9% (547/595) |
| Clinical Compliance with Patients Who Died Included | 89.2% (107/120) | 94.5% (504/533) | 93.6% (611/653) | 87.3% (103/118) | 93.7% (492/525) | 92.5% (595/643) |

Figure 9-4-1: Kaplan-Meier Graph to 1800 Days - Freedom from Target Lesion Revascularization RAVEL and SIRIUS Pooled Data

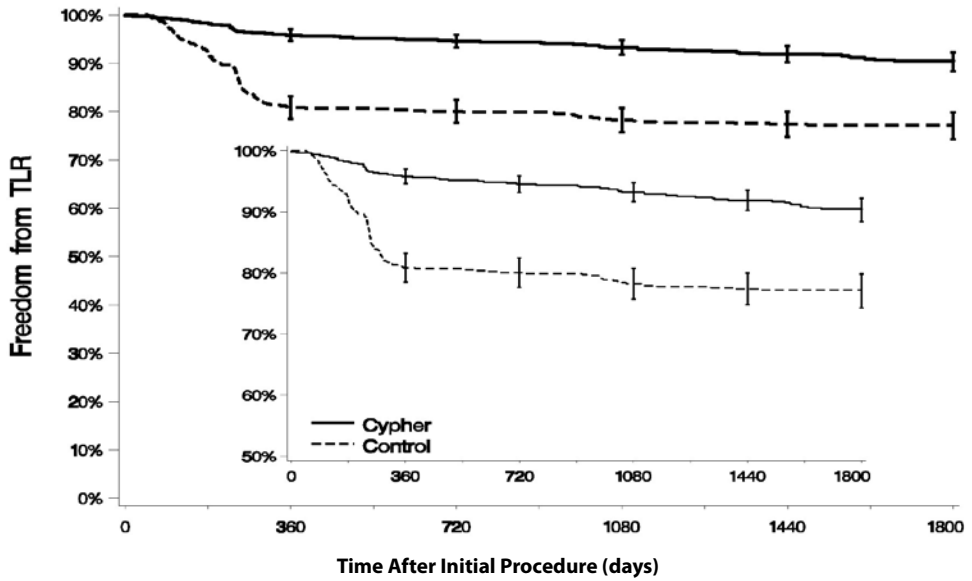


Figure 9-4-2: Kaplan-Meier Graph to 1800 Days - Freedom from Target Vessel Failure RAVEL and SIRIUS Pooled Data

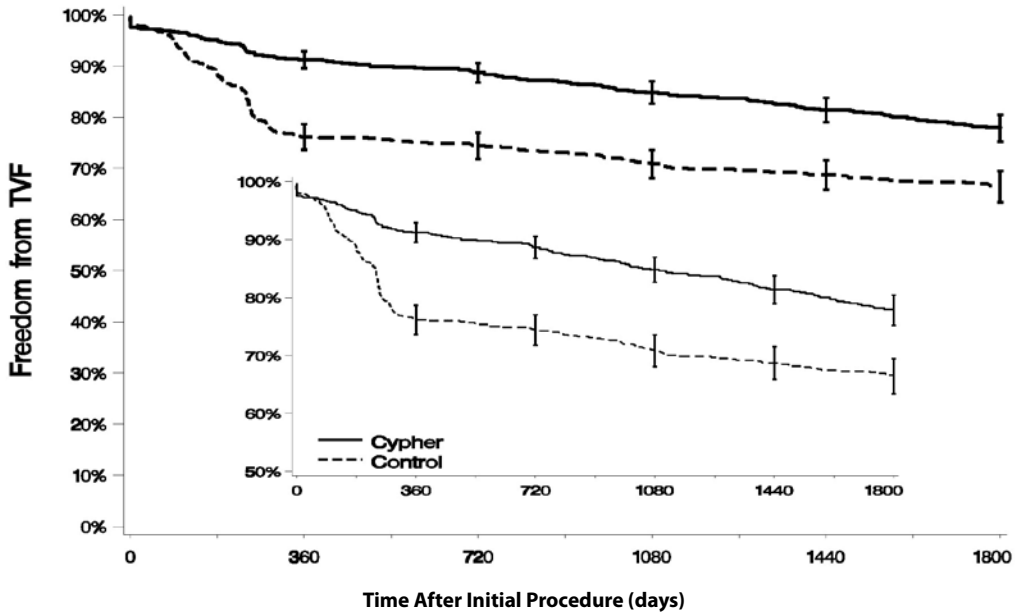


Figure 9-4-3: Kaplan-Meier Graph to 1800 Days - Freedom from Any Death or Any Myocardial Infarction RAVEL and SIRIUS Pooled Data

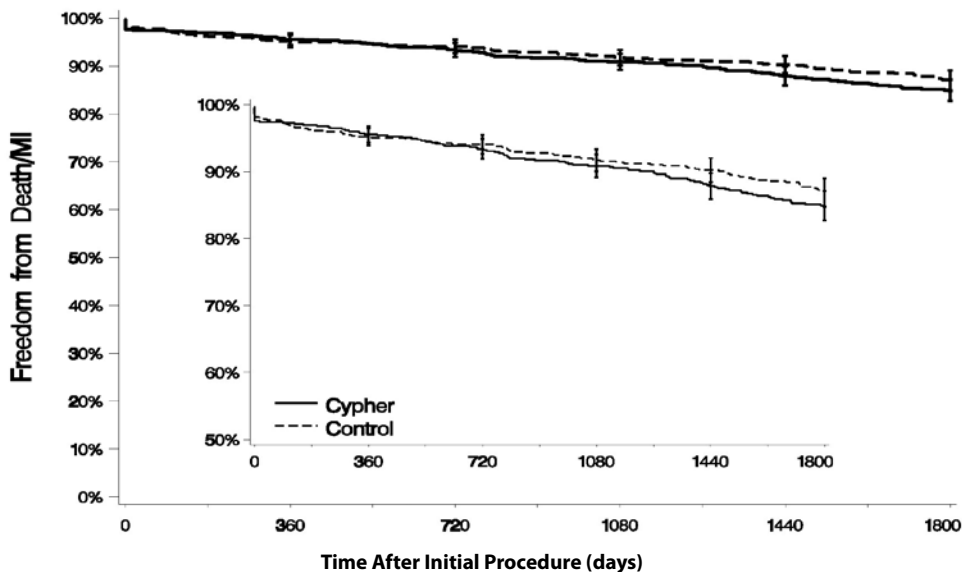


Figure 9-4-4: Kaplan-Meier Graph to 1800 Days - Freedom from Any Death RAVEL and SIRIUS Pooled Data

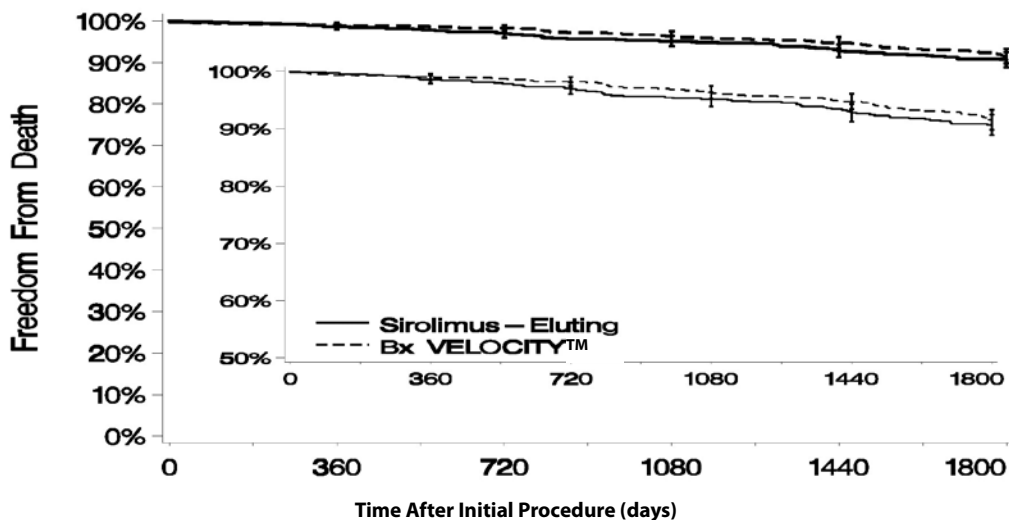


Figure 9-4-5: Kaplan-Meier Graph to 1800 Days - Freedom from Cardiac Death RAVEL and SIRIUS Pooled Data

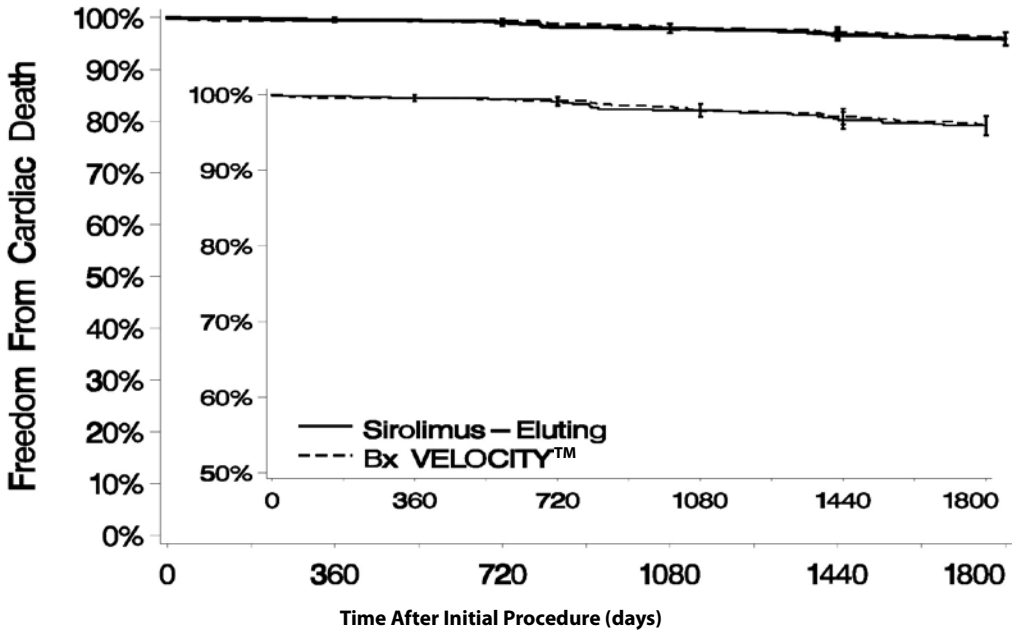


Figure 9-4-6: Kaplan-Meier Graph to 1800 Days - Freedom from Non-Cardiac Death RAVEL and SIRIUS Pooled Data

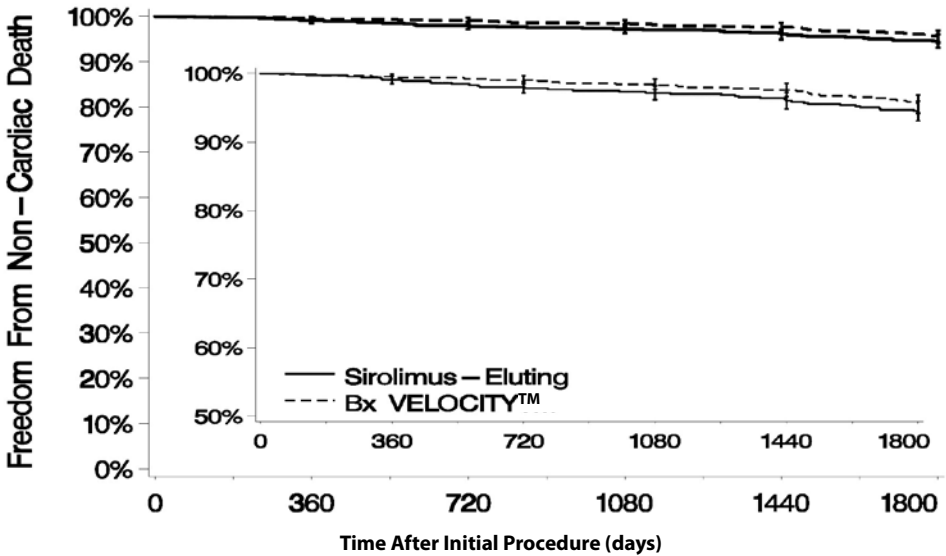


Figure 9-4-7: Kaplan-Meier Graph to 1800 Days - Freedom from Myocardial Infarction RAVEL and SIRIUS Pooled Data

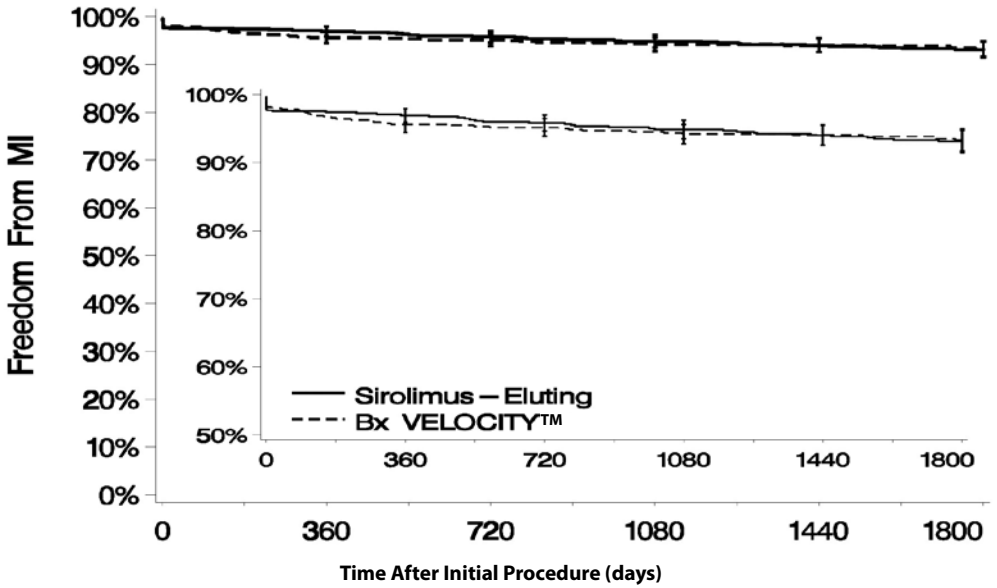


Figure 9-4-8: Kaplan-Meier Graph to 1800 Days - Freedom from Q Wave Myocardial Infarction RAVEL and SIRIUS Pooled Data

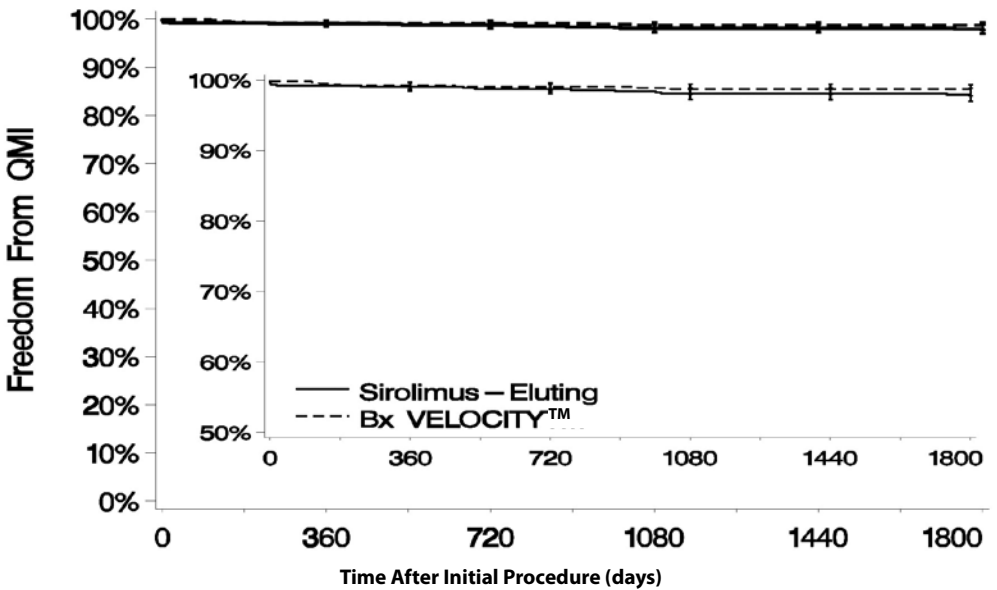
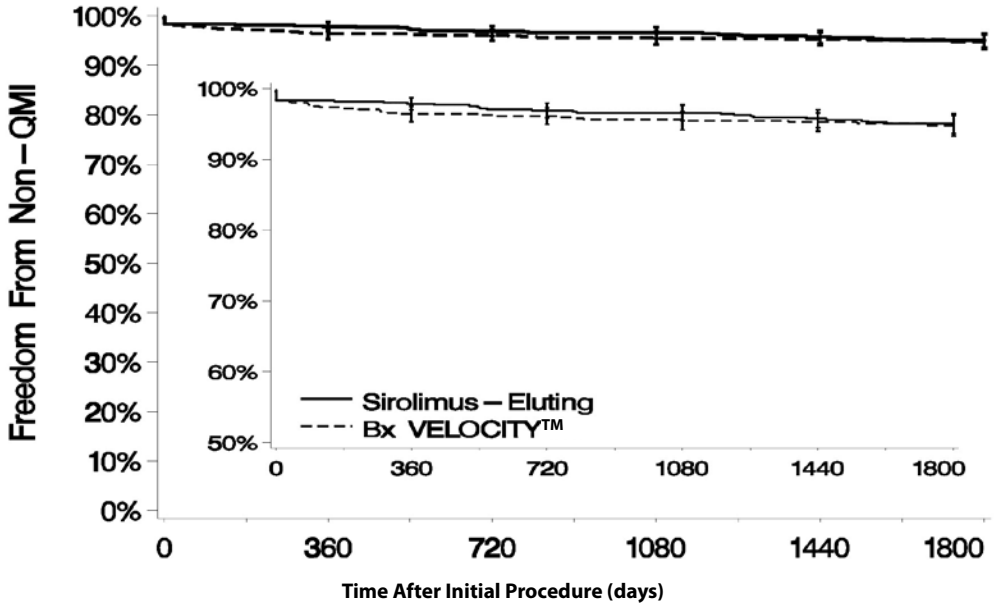


Figure 9-4-9: Kaplan-Meier Graph to 1800 Days - Freedom from Non-Q Wave Myocardial Infarction RAVEL and SIRIUS Pooled Data



9.4.1. Stent Thrombosis

Stent thrombosis (ST) is an uncommon adverse event associated with percutaneous stent placement that can have significant clinical consequences. Stent thrombosis is characterized as acute (within 24 hours of stent placement), sub (> 24 hours to 30 days), late (31 days to 1 year) and very late (> 1 year). Contributing factors to acute, sub, and late stent thrombosis are well described in the cardiology literature, and include procedural, patient, lesion, and adjunctive pharmacology variables. Determination of the true rates of late and very late stent thrombosis in any clinical study are dependent upon the definitions used and the clinical follow-up data available to identify possible stent thrombosis.

Protocol definitions of stent thrombosis were identical for the RAVEL and SIRIUS trials. Early stent thrombosis was defined as a thirty-day ischemic endpoint, which included death, Q-wave MI or sub-abrupt closure requiring revascularization. Late thrombosis was defined as myocardial infarction attributable to the target vessel with angiographic documentation of thrombus or total occlusion at the target site > 30 days after the index procedure in the absence of an intervening revascularization of the target vessel. A summary of the protocol-defined rates of stent thrombosis to 5 years is presented as a Kaplan-Meier analysis in Figure 9-4-1-1. A limitation of this analysis is that the protocol definition of late and very late stent thrombosis is conservative, requiring angiographic proof of thrombosis and excluding thrombosis with prior TLR. A broader definition that accounts for stent thrombosis related clinical events would provide additional insight into the assessment of the risk of stent thrombosis.

A consortium of academicians and institutions (HCRI, DCRI, Cardialysis and CRF⁴), all major stent manufacturers, and the FDA have proposed a new and more encompassing definition of stent thrombosis, referred to as the Academic Research Consortium or "ARC" definition of stent thrombosis, which includes clinical outcomes in addition to angiographic proof of thrombosis (See Table 9-4-1-1 for formal definitions). Given that limitations of available clinical data may lead to the inclusion of events that may not be stent thrombosis, this definition presents the data in three categories: a) definite stent thrombosis (angiographic or autopsy documentation); b) probable stent thrombosis (MI in region of stented vessel or unexplained death within the first 30 days); and c) possible (unexplained death after 30 days) stent thrombosis. Because ascertainment of the cause of death can be difficult in clinical studies (note that cardiac death is the default category when no information is available on any other cause), the data are presented in Kaplan-Meier format using the cumulative incidence of the "definite" and "probable" thromboses categories. The combination of "definite" and "probable" provide the optimal balance of sensitivity and specificity of estimating the stent thrombosis rates. Data are presented without and with censoring of patients with intercurrent target lesion revascularization (TLR) to differentiate intent-to-treat patient related outcomes (i.e., without censoring of TLR) (Figure 9-4-1-2) to outcomes limited to the stent initially implanted (i.e., with censoring of TLR) (Figure 9-4-1-3).

There is no statistical difference between the **CYPHER**[®] and the control in cumulative ST, according to any definition of ST, and in any time window. However, for very late ST (VLST, after 1 year), a small numerical excess can be seen with **CYPHER** versus BMS control that did not reach statistical significance using the protocol definition (Log Rank p-value=0.750), or using the Primary ARC Definite plus Probable definition (Log Rank p-value=0.812). The incidence/cumulative incidence of protocol thrombosis, ARC Definite and Probable thrombosis, ARC Definite and Probable thrombosis with prior TLR censored are summarized in Tables 9-4-1-2 and 9-4-1-3.

| Table 9-4-1-1 ARC Definitions of Stent Thrombosis⁵ | |
|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Level of probability: | <ul style="list-style-type: none"> • Definite Stent Thrombosis Definite ST is considered to have occurred by either angiographic or pathologic confirmation. • Probable ST Probable ST is considered to have occurred after intracoronary stenting in the following cases: <ol style="list-style-type: none"> 1. Any unexplained death within the first 30 days. 2. Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause. • Possible ST Possible ST is considered to have occurred with any unexplained death following 30 days after the intracoronary stenting until the end of trial follow-up. |
| Relation to original procedure | <ul style="list-style-type: none"> ARC ST Censored for prior TLR ARC ST Uncensored for prior TLR |

4 HCRI = Harvard Clinical Research Institute; DCRI = Duke Clinical Research Institute; CRF = Cardiovascular Research Foundation.
5 Circulation, 2007; 115: 2344 – 2351.

Table 9-4-1-2 - Summary of the Incidence of Stent Thrombosis in Yearly Time Intervals up to 5-years – RAVEL and SIRIUS Pooled Data

| | | | Protocol | ARC Definite+ Probable, TLR-Censored | ARC Definite + Probable, TLR-Uncensored |
|--------|---------------|--------------|-----------------|-------------------------------------------------|----------------------------------------------------|
| Year 1 | CYPHER® Stent | # Entered† | 653 | 653 | 653 |
| | | # Events‡ | 2 | 2 | 2 |
| | | Incidence %‡ | 0.3% | 0.3% | 0.3% |
| | BMS* | # Entered† | 643 | 643 | 643 |
| | | # Events‡ | 4 | 7 | 8 |
| | | Incidence %‡ | 0.6% | 1.1% | 1.2% |
| Year 2 | CYPHER Stent | # Entered† | 638 | 638 | 638 |
| | | # Events‡ | 1 | 1 | 1 |
| | | Incidence %‡ | 0.2% | 0.2% | 0.2% |
| | BMS | # Entered† | 629 | 627 | 626 |
| | | # Events‡ | 0 | 0 | 1 |
| | | Incidence %‡ | 0.0% | 0.0% | 0.2% |
| Year 3 | CYPHER Stent | # Entered† | 619 | 619 | 619 |
| | | # Events‡ | 1 | 2 | 2 |
| | | Incidence %‡ | 0.1% | 0.3% | 0.3% |
| | BMS | # Entered† | 619 | 618 | 616 |
| | | # Events‡ | 0 | 0 | 2 |
| | | Incidence %‡ | 0.0% | 0.0% | 0.3% |
| Year 4 | CYPHER Stent | # Entered† | 601 | 600 | 600 |
| | | # Events‡ | 1 | 2 | 2 |
| | | Incidence %‡ | 0.2% | 0.3% | 0.3% |
| | BMS | # Entered† | 603 | 602 | 599 |
| | | # Events‡ | 0 | 0 | 0 |
| | | Incidence %‡ | 0.0% | 0.0% | 0.0% |
| Year 5 | CYPHER Stent | # Entered† | 579 | 577 | 577 |
| | | # Events‡ | 0 | 1 | 1 |
| | | Incidence %‡ | 0.0% | 0.2% | 0.2% |
| | BMS | # Entered† | 582 | 582 | 579 |
| | | # Events‡ | 0 | 0 | 1 |
| | | Incidence %‡ | 0.0% | 0.0% | 0.2% |

† Life table method was used to calculate number of patients that entered into specified time interval and had event within that interval

‡ Incidence was calculated using Kaplan-Meier method

* BMS is bare metal stent control

Table 9-4-1-3 - Summary of the Cumulative Incidence of Stent Thrombosis up to 5-years – RAVEL and SIRIUS Pooled Data

| | | | Protocol | ARC Definite + Probable, TLR-censored | ARC Definite + Probable, TLR-uncensored |
|-------------|---------------|-------------------------|----------|---------------------------------------|-----------------------------------------|
| Year 1 | CYPHER® Stent | # Entered† | 653 | 653 | 653 |
| | | # Events† | 2 | 2 | 2 |
| | | Cumulative Incidence %‡ | 0.3% | 0.3% | 0.3% |
| | BMS | # Entered† | 643 | 643 | 643 |
| | | # Events† | 4 | 7 | 8 |
| | | Cumulative Incidence %‡ | 0.6% | 1.1% | 1.2% |
| Year 1 to 5 | CYPHER Stent | # Entered† | 638 | 638 | 638 |
| | | # Events† | 3 | 6 | 6 |
| | | Cumulative Incidence %‡ | 0.5% | 1.0% | 1.0% |
| | BMS | # Entered† | 629 | 627 | 626 |
| | | # Events† | 0 | 0 | 4 |
| | | Cumulative Incidence %‡ | 0.0% | 0.0% | 0.7% |
| Year 5 | CYPHER Stent | # Entered† | 579 | 577 | 577 |
| | | # Events† | 5 | 8 | 8 |
| | | Cumulative Incidence %‡ | 0.8% | 1.3% | 1.3% |
| | BMS | # Entered† | 582 | 582 | 579 |
| | | # Events† | 4 | 7 | 12 |
| | | Cumulative Incidence %‡ | 0.6% | 1.1% | 1.9% |

† Life table method was used to calculate number of patients that entered into specified time interval and had event within that interval

‡ Cumulative Incidence was calculated using Kaplan-Meier method

Figure 9-4-1-1: Kaplan-Meier Graph to 1800 Days – Cumulative Incidence of Protocol Thrombosis RAVEL and SIRIUS Pooled Data

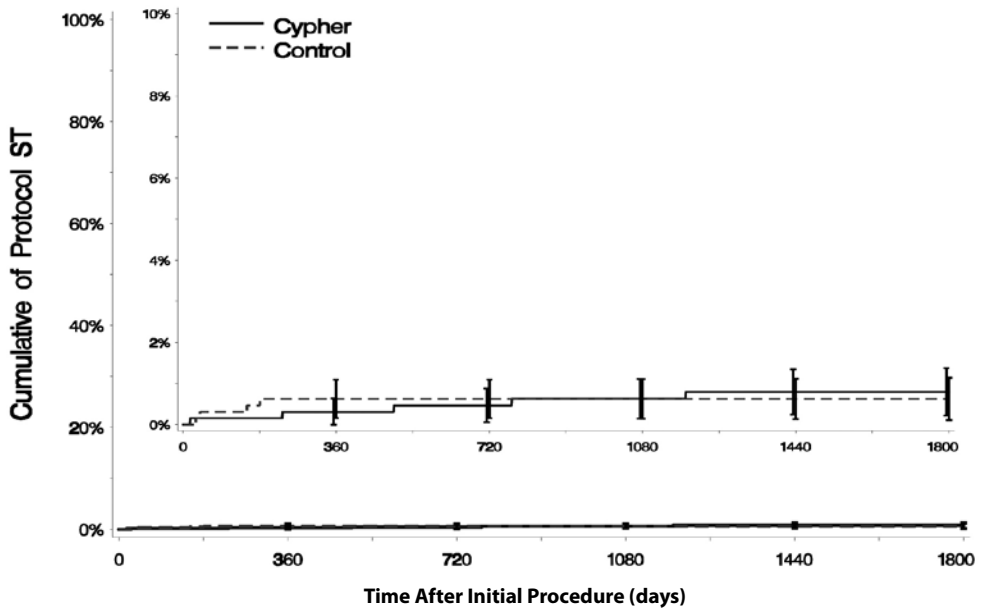


Figure 9-4-1-2: Kaplan-Meier Graph to 1800 Days –
Cumulative Incidence of ARC Definite/Probable Thrombosis – RAVEL and SIRIUS Pooled Data

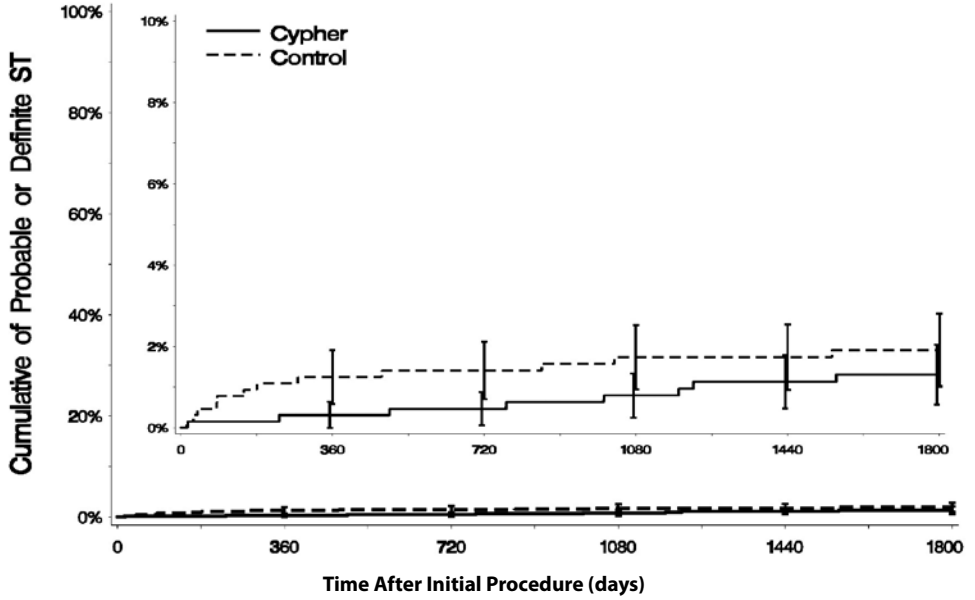
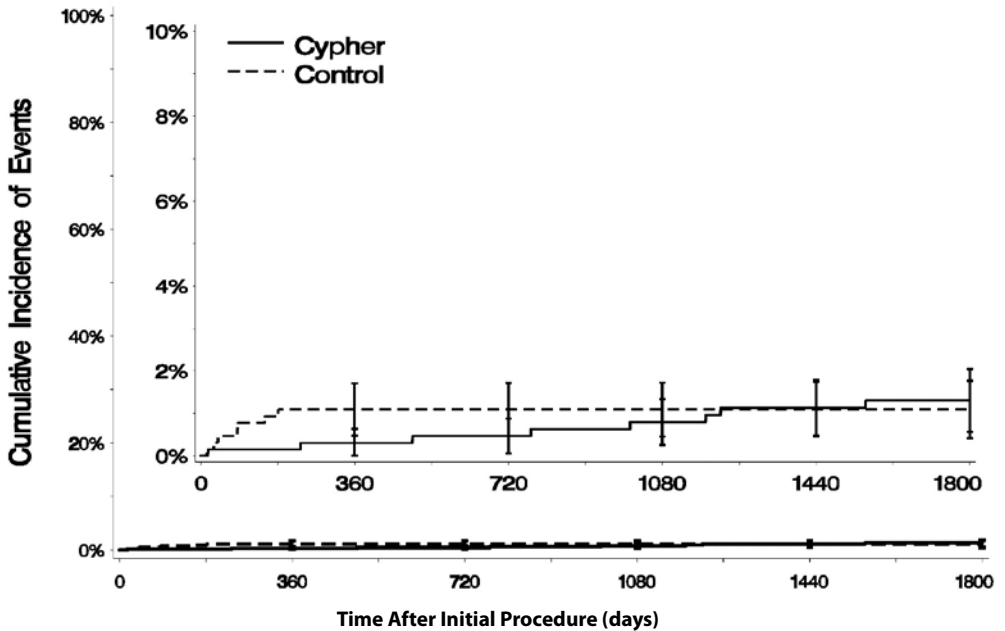


Figure 9-4-1-3: Kaplan-Meier Graph to 1800 Days –
Cumulative Incidence of ARC Definite/Probable Thrombosis Censored for Prior TLR – RAVEL and SIRIUS Pooled Data



9.4.2. Diabetes SIRIUS and RAVEL Trials (Pooled Results out to 5 Years)

Patients with diabetes mellitus represent a high risk group for clinical events following percutaneous coronary intervention. While diabetic status was captured, these trials were neither designed nor adequately powered to evaluate outcomes in diabetic patients, allow evaluation of the rate of low frequency events such as death or MI or stent thrombosis, or compare the incidence of these endpoints to a bare metal stent control group. Diabetic patients were identified by investigators and the presence of diabetes and medications received reported on case report forms. The clinical trials conducted on the **CYPHER**® Stent were not designed to specifically support an approval for use in diabetic patients. The data below is a post-hoc analysis of data on diabetic patients from the RAVEL and SIRIUS trials and presents data on 150 Diabetes Mellitus patients treated with the **CYPHER** stent and 173 patients treated with the control bare metal stent.

Figure 9-4-2-1: Kaplan-Meier Graph to 1800 Days – Freedom from Target Lesion Revascularization RAVEL and SIRIUS Pooled Data in Diabetes Patients

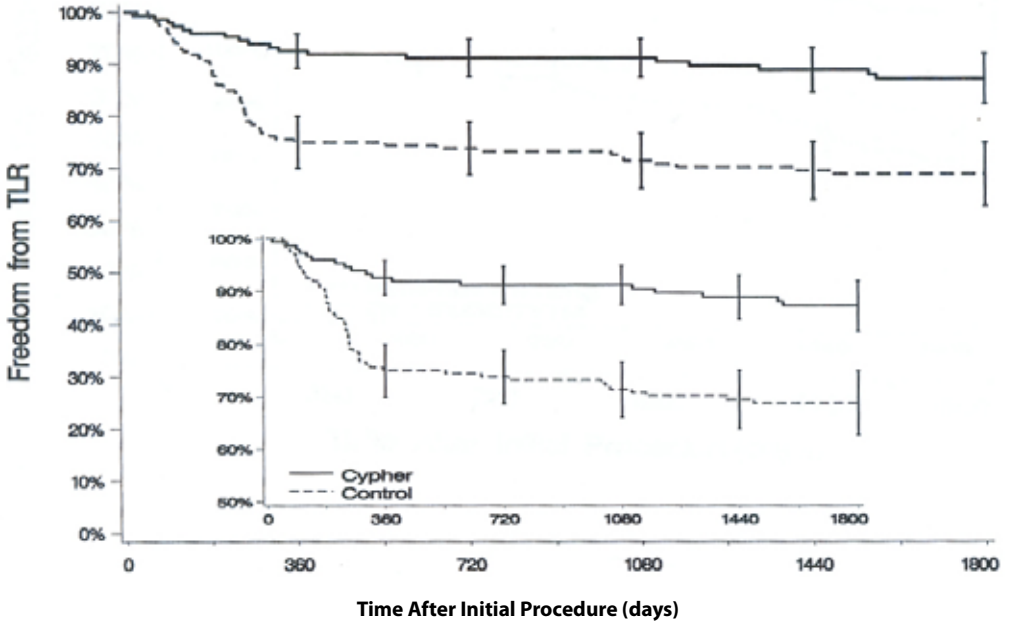


Figure 9-4-2-2: Kaplan-Meier Graph to 1800 Days – Freedom from Target Vessel Failure – RAVEL and SIRIUS Pooled Data in Diabetes Patients

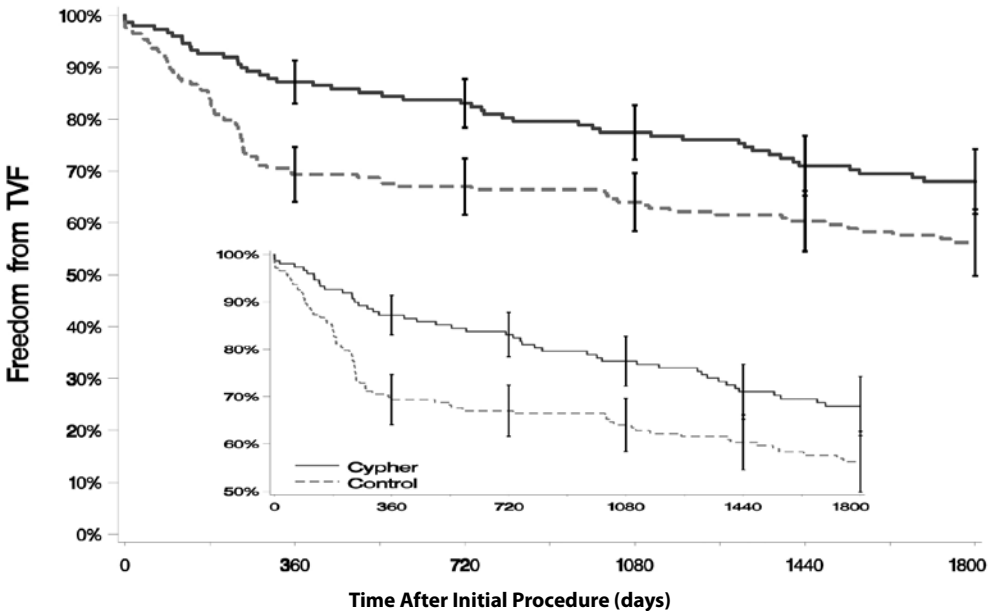


Figure 9-4-2-3: Kaplan-Meier Graph to 1800 Days -
Freedom from Any Death – RAVEL and SIRIUS Pooled Data in Diabetes Patients

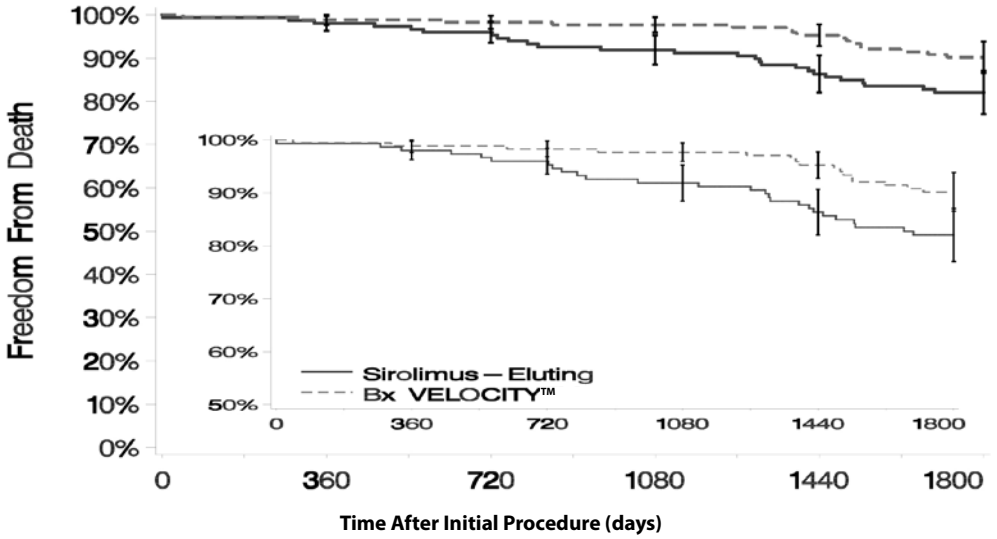


Figure 9-4-2-4: Kaplan-Meier Graph to 1800 Days -
Freedom from Any Myocardial Infarction – RAVEL and SIRIUS Pooled Data in Diabetes Patients

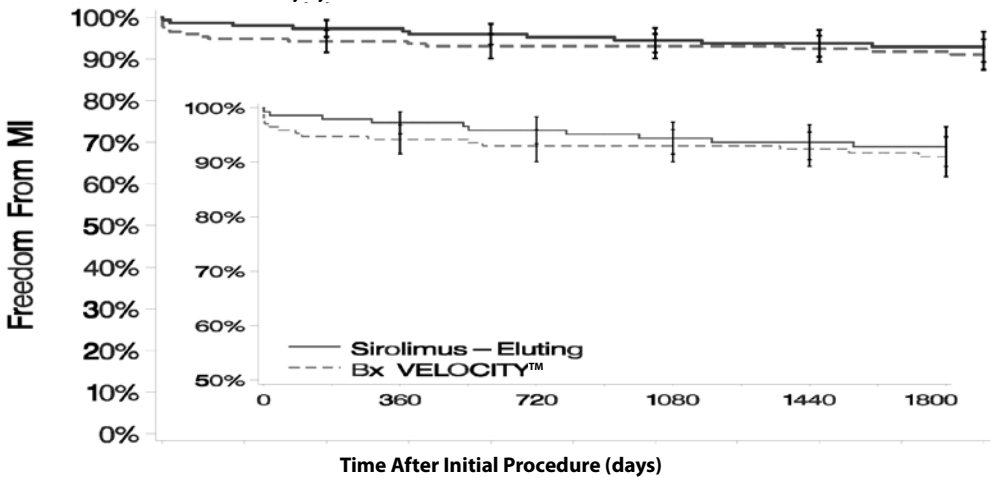


Figure 9-4-2-5: Kaplan-Meier Graph to 1800 Days – Cumulative Incidence of Protocol Thrombosis – RAVEL and SIRIUS Pooled Data in Diabetes Patients

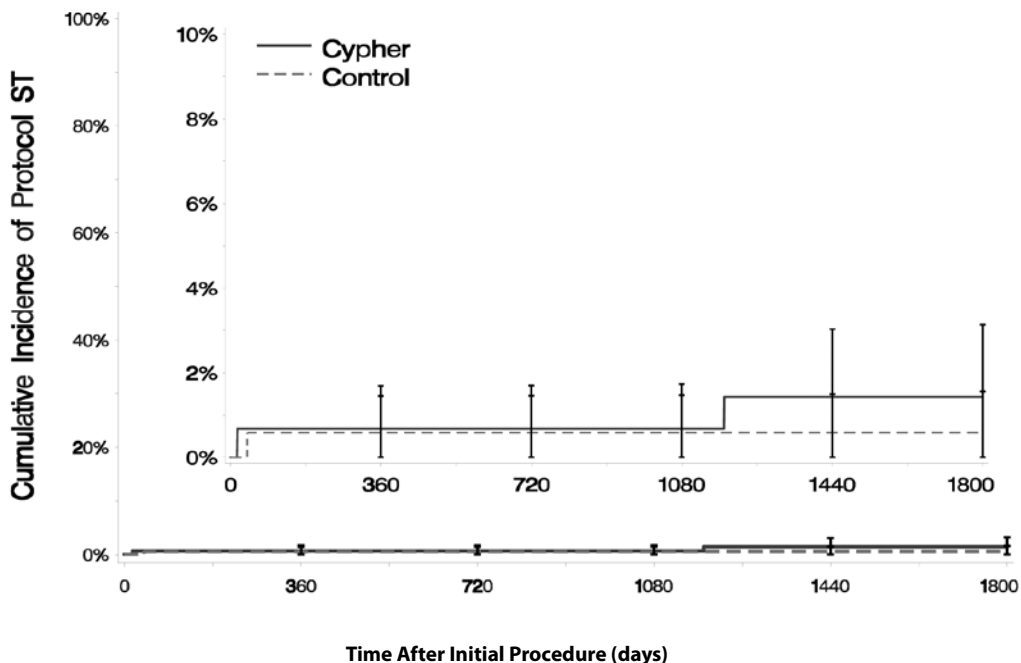


Figure 9-4-2-6: Kaplan-Meier Graph to 1800 Days – Cumulative Incidence of ARC Definite/Probable Thrombosis – RAVEL and SIRIUS Pooled Data in Diabetes Patients

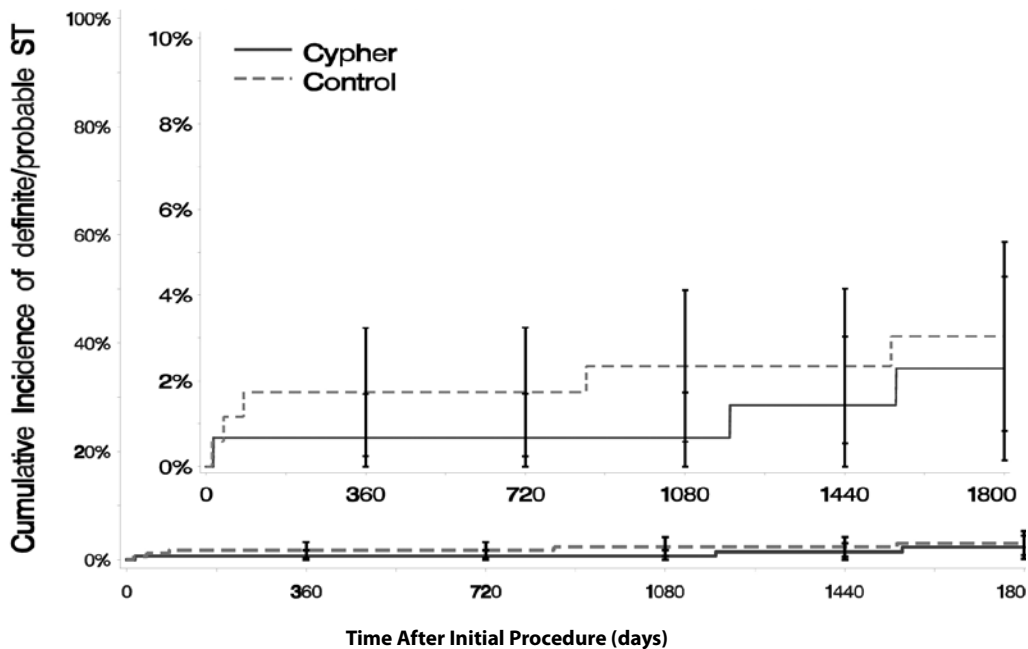
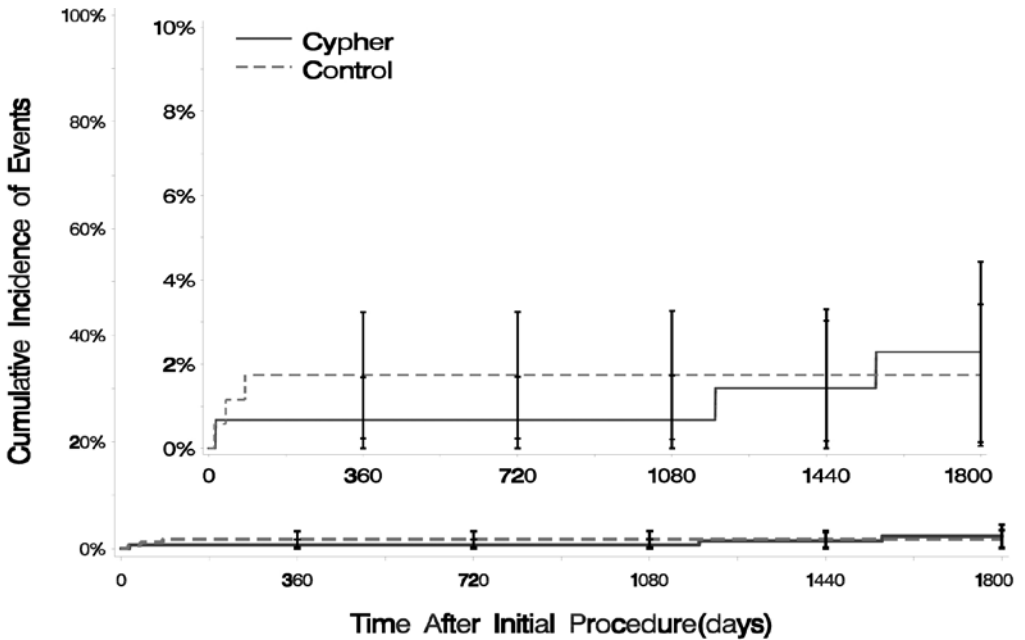


Figure 9-4-2-7: Kaplan-Meier Graph to 1800 Days – Cumulative Incidence of ARC Definite/Probable Thrombosis Censored for Prior TLR – RAVEL and SIRIUS Pooled Data in Diabetes Patients



9.5. U.S. e-CYPHER Stent Registry

Purpose: The purpose of the e-CYPHER Stent Registry was to collect post marketing surveillance data on the CYPHER® Sirolimus-eluting Coronary Stent following marketing approval when used in real world clinical practice. In unselected patients following market approval, use of the CYPHER Stent demonstrated safety and efficacy outcomes at one year that were qualitatively similar to those observed in the pivotal randomized SIRIUS trial; no previously unrecognized safety issues were identified. Elevated event rates for subgroups not formally studied or included in the pivotal study were observed; the cause of these elevated event rates cannot be determined from these data.

Design: This was a prospective, multi-center, non-randomized registry performed in the United States in which patients treated with at least one CYPHER stent were consecutively enrolled; there are no specific entry criteria. All patients were followed for 12 months post-procedure. There was no pre-specified primary endpoint; clinical outcome and safety data, including MACE, TVR, angina, stent thrombosis, and adverse events related to the device or the procedure, were collected. An Advisory Board obtained a safety overview and reviewed data from procedural perspectives, treatment techniques, epidemiological findings, and patient demographics. Analysis of the following subgroups was undertaken and outcomes of interests have been provided in Table 9-5-1: on-label patients in addition to higher risk patient/lesion subsets including diabetes; long lesions; small vs. large vessels; acute MI patients; in-stent restenosis lesions; left main lesions; bifurcation lesions; SVG lesions; overlapping stents; multiple stents; and multiple plus overlapping stents.

Demography: Baseline patient characteristics evaluated included age (mean 63.7 years), gender (31.6% female), race (90.2% Caucasian, 6.3% African American, and 3.5% other), diabetes (31.9%), prior MI (50.6%), hypertension (76%), hyperlipidemia (77.1%), smoking (18.3%), CSS Angina Class (10.7% III or IV). Procedural and lesion characteristics included use of GP IIb/IIIa inhibitors (41.9%), LAD (36.6%), LCX (28.8%), RCA (33.1%), LM (1.6%), SVG (5.7%), reference vessel diameter (mean 2.94 mm), lesion diameter < 2.5 mm (6.3%), minimum lumen diameter (mean 0.83 mm), percent diameter stenosis (mean 85.6%), lesion length (mean 15.6 mm), lesion length >30 mm (5.2%), *de novo* lesions (91.2%), restenotic lesions (8.8%), total occlusion lesions (6.7%), bifurcation lesions (12.7%), thrombus present (8.8%), pre-dilatation used (58.7%), direct stenting used (41.3%), lesions treated by patient (1 lesion – 60.0%, 2 lesions – 26.9%, 3 lesions - 8.3%, 4 lesions - 3.0%, and > 4 lesions - 1.8%). The overall patient information including sub-group information is presented in Table 9-5-1.

Methods: Baseline clinical and angiographic data were collected by clinical coordinators at the clinical sites and entered into an internet accessible and secure 21 CFR Part 11 compliant database. An independent Clinical Events Committee adjudicated clinical events. An independent Data and Safety Monitoring Committee monitored the trial.

Results: 2067 patients were enrolled at 38 sites. CYPHER Stent placement resulted in a rate of MACE at 12 months of 7.3% and a rate of TVF of 8% at 12 months; these rates are qualitatively similar to the rates of MACE and TVF reported for the CYPHER stent arm of the SIRIUS trial at 12 months (8.3% and 9.8%, respectively). Rates of protocol-defined stent thrombosis were 0.1% acute, 0.4% sub-acute, and 0.2% late for a total 1-year stent thrombosis rate of 0.8%.

Table 9-5-1: Baseline Demographics, Lesion, and Procedural Characteristics in e-CYPHER® US Patients

| Study Variable | All Pat (N=2067 Pat N=3367 Les) | Diabetes (N=640 Pat N=1070 Les) | IDDM ¹ (N=200 Pat N=336 Les) | Non-IDDM (N=440 Pat N=734 Les) | AMI ² (N=155 Pat N=212 Les) | Bifurcation (N=260 Pat N=599 Les) | SVG ³ (N=129 Pat N=261 Les) | Multi-Stent (N=148 Pat N=306 Les) | MultiVessel (N=318 Pat N=863 Les) | RVD ⁴ <2.5 mm (N= 124 Pat N=267 Les) | On-Label (N=1313 Pat N=1863 Les) | Long Lesion > 30 mm (N=96 Pat N=96 Les) | ISR ⁵ (N=65 Pat N=75 Les) |
|------------------------------------------------|---------------------------------|---------------------------------|-----------------------------------------|--------------------------------|----------------------------------------|-----------------------------------|----------------------------------------|-----------------------------------|-----------------------------------|-------------------------------------------------|----------------------------------|-----------------------------------------|--------------------------------------|
| Patient Age (years) * | 63.75 ±11.27 | 63.95 ±10.17 | 61.7 ±10.7 | 65.0 ±9.8 | 60.56 ±11.63 | 63.10 ±11.04 | 67.78 ±10.31 | 62.22 ±12.29 | 63.7 ±11.6 | 63.6 ±10.8 | 63.8 ±11.3 | 63.1 ±10.7 | 66.1 ±8.5 |
| Number of Male | 68.40% | 64.10% | 54.00% | 68.60% | 74.20% | 67.70% | 80.60% | 71.60% | 71.10% | 62.10% | 66.60% | 75.00% | 67.70% |
| Prior MI | 50.60% | 47.10% | 46.60% | 47.30% | 78.30% | 52.40% | 43.00% | 52.10% | 51.10% | 38.80% | 50.40% | 48.20% | 41.30% |
| Prior PTCA | 69.30% | 67.80% | 65.40% | 69.00% | 49.20% | 74.30% | 60.50% | 57.30% | 68.60% | 58.80% | 68.10% | 69.60% | 98.40% |
| Prior CABG | 32.80% | 40.30% | 40.60% | 40.20% | 20.30% | 25.50% | 97.70% | 17.70% | 33.90% | 47.50% | 25.30% | 33.90% | 31.10% |
| CVA/TIA | 13.30% | 15.20% | 18.80% | 13.40% | 11.90% | 11.10% | 7.80% | 18.80% | 15.80% | 18.80% | 15.20% | 12.50% | 11.70% |
| Family History of Heart Disease | 59.00% | 59.90% | 58.50% | 60.50% | 59.40% | 60.30% | 62.50% | 58.00% | 65.80% | 56.90% | 58.00% | 54.70% | 65.60% |
| PVD | 13.80% | 17.20% | 20.50% | 15.60% | 7.60% | 8.70% | 18.90% | 14.70% | 12.00% | 14.60% | 14.70% | 13.70% | 18.80% |
| Hypertension | 76.00% | 86.10% | 89.00% | 84.80% | 60.00% | 74.10% | 86.70% | 77.80% | 78.80% | 81.30% | 76.50% | 77.90% | 86.20% |
| Hyperlipidemia | 77.10% | 80.50% | 79.50% | 80.90% | 63.40% | 78.00% | 89.10% | 72.20% | 76.00% | 84.60% | 76.70% | 83.60% | 80.00% |
| Current Smoker | 18.30% | 14.10% | 16.00% | 13.20% | 33.80% | 16.50% | 7.80% | 21.60% | 20.40% | 15.30% | 18.20% | 18.80% | 9.20% |
| Diabetes | 31.90% | 100.00% | 100.00% | 100.00% | 22.10% | 31.90% | 49.20% | 32.60% | 30.80% | 41.50% | 31.60% | 32.60% | 38.50% |
| Insulin dependent | 10.00% | 31.30% | 100.00% | 0.00% | 6.20% | 9.10% | 14.80% | 11.50% | 9.60% | 17.10% | 10.30% | 13.70% | 6.20% |
| Stable Angina | 27.10% | 26.20% | 25.10% | 26.70% | 0.00% | 28.00% | 31.30% | 24.50% | 33.50% | 36.60% | 28.90% | 26.30% | 33.80% |
| Unstable Angina | 31.30% | 32.50% | 31.00% | 33.20% | 0.00% | 30.40% | 36.40% | 32.40% | 28.90% | 27.40% | 33.50% | 32.90% | 30.80% |
| Silent Ischemia | 6.90% | 8.60% | 9.00% | 8.40% | 0.00% | 6.60% | 6.20% | 4.10% | 7.30% | 7.30% | 7.60% | 8.40% | 13.80% |
| Recent MI | | | | | | | | | | | | | |
| <= 24 hour | 7.50% | 5.00% | 4.50% | 5.30% | 100.00% | 10.50% | 3.90% | 12.20% | 4.70% | 4.90% | 0.00% | 9.50% | 1.50% |
| 24 to 72 hours | 7.30% | 4.90% | 5.00% | 4.80% | 0.00% | 3.10% | 3.90% | 12.20% | 7.00% | 5.70% | 9.00% | 7.40% | 3.10% |
| > 72 hours | 5.70% | 6.60% | 10.60% | 4.80% | 0.00% | 6.60% | 6.30% | 6.10% | 4.70% | 5.70% | 5.90% | 6.30% | 1.50% |
| Number diseased arteries | | | | | | | | | | | | | |
| Single | 41.10% | 33.80% | 30.00% | 35.50% | 45.20% | 38.80% | 18.10% | 31.80% | 5.00% | 29.80% | 43.80% | 44.20% | 49.20% |
| Double | 31.30% | 32.20% | 33.00% | 31.90% | 34.80% | 33.70% | 20.50% | 41.90% | 50.80% | 33.10% | 31.60% | 29.50% | 24.60% |
| Triple | 27.60% | 34.00% | 37.00% | 32.60% | 20.00% | 27.50% | 61.40% | 26.40% | 44.20% | 37.10% | 24.60% | 26.30% | 26.20% |
| Reference Vessel Diameter (mm) | 2.94 ±0.45 | 2.91 ±0.44 | 2.87 ±0.45 | 2.92 ±0.44 | 2.99 ±0.41 | 2.90 ±0.42 | 3.13 ±0.57 | 2.86 ±0.38 | 2.92 ±0.47 | 2.45 ±0.44 | 2.94 ±0.44 | 3.01 ±0.41 | 3.14 ±0.59 |
| Lesion length (mm) | 15.64 ±8.93 | 15.69 ±9.71 | 17.22 ±11.66 | 14.91 ±8.46 | 16.76 ±8.00 | 14.88 ±8.26 | 16.04 ±9.53 | 21.16 ±14.00 | 15.62 ±8.92 | 14.72 ±8.42 | 15.52 ±8.92 | 42.14 ±9.76 | 17.27 ±10.30 |
| De novo Lesion | 91.20% | 90.50% | 89.60% | 90.90% | 95.00% | 86.00% | 78.20% | 90.80% | 88.60% | 94.80% | 99.70% | 90.60% | 0.00% |
| Restenotic following failed history of PCI | 8.80% | 9.50% | 10.40% | 9.10% | 5.00% | 14.00% | 21.80% | 9.20% | 11.40% | 5.20% | 0.30% | 9.40% | 100.00% |
| Total occlusion | 6.70% | 3.90% | 4.30% | 3.60% | 18.30% | 7.90% | 5.20% | 7.90% | 6.20% | 6.10% | 0.00% | 8.70% | 11.40% |
| Bifurcated lesion (Requiring double guidewire) | 12.70% | 13.70% | 10.90% | 15.00% | 15.90% | 68.40% | 6.80% | 1.60% | 10.80% | 15.60% | 0.00% | 10.40% | 10.60% |
| Lesion contour | | | | | | | | | | | | | |
| Smooth | 47.50% | 49.40% | 49.10% | 49.60% | 39.80% | 47.00% | 47.30% | 40.00% | 52.10% | 44.80% | 48.10% | 25.00% | 47.20% |
| Irregular | 52.50% | 50.60% | 50.90% | 50.40% | 60.20% | 53.00% | 52.70% | 60.00% | 47.90% | 55.20% | 51.90% | 75.00% | 52.80% |
| Lesion class | | | | | | | | | | | | | |
| A | 5.60% | 5.70% | 6.70% | 5.20% | 2.10% | 3.40% | 3.50% | 4.80% | 7.10% | 5.90% | 5.60% | 0.00% | 7.40% |
| B1 | 20.50% | 22.10% | 21.10% | 22.60% | 11.00% | 16.70% | 15.50% | 17.70% | 22.60% | 18.60% | 21.80% | 0.00% | 22.10% |
| B2 | 51.70% | 50.50% | 46.00% | 52.70% | 60.30% | 51.70% | 44.40% | 38.00% | 47.50% | 48.60% | 54.80% | 1.10% | 36.80% |
| C | 22.20% | 21.70% | 26.20% | 19.60% | 26.70% | 28.30% | 36.60% | 39.50% | 22.80% | 26.90% | 17.90% | 98.90% | 33.80% |
| Lesion Thrombus | 91.20% | 94.10% | 92.60% | 94.70% | 63.70% | 89.80% | 92.20% | 91.80% | 94.50% | 95.90% | 94.30% | 8.40% | 89.80% |
| Pre-dilated | 58.70% | 58.90% | 58.70% | 59.00% | 63.80% | 61.90% | 47.90% | 66.00% | 56.40% | 59.60% | 57.30% | 80.20% | 67.60% |
| Direct stenting | 41.30% | 41.10% | 41.30% | 41.00% | 36.20% | 38.10% | 52.10% | 34.00% | 43.60% | 40.40% | 42.70% | 19.80% | 32.40% |
| Post-Dilation | 38.00% | 36.40% | 35.80% | 36.70% | 40.10% | 45.00% | 29.90% | 42.90% | 36.00% | 22.90% | 37.10% | 59.40% | 36.50% |

continued on next page

| | | | | | | | | | | | | | |
|------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|----------------|----------------|----------------|-----------------|
| Lesion Length > 30mm | 5.20% | 5.30% | 7.60% | 4.10% | 5.50% | 4.70% | 7.50% | 15.50% | 6.10% | 4.10% | 5.00% | 100.00% | 13.30% |
| Lesion Diameter < 2.5mm | 6.30% | 8.00% | 10.80% | 6.50% | 33.30% | 7.00% | 39.50% | 5.40% | 7.30% | 57.70% | 6.30% | 2.10% | 2.20% |
| Pre-procedure MLD (mm)* | 0.83 ±0.82 | 0.82 ±0.74 | 0.92 ±0.89 | 0.76 ±0.62 | 0.61 ±0.69 | 0.67 ±0.65 | 0.96 ±0.95 | 0.71 ±0.69 | 0.90 ±0.93 | 0.49 ±0.39 | 0.90 ±0.83 | 0.43 ±0.42 | 0.89 ±0.88 |
| Post-procedure MLD (mm)* | 2.98 ±0.50 | 2.92 ±0.47 | 2.88 ±0.52 | 2.95 ±0.43 | 3.11 ±0.44 | 2.85 ±0.54 | 3.20 ±0.55 | 2.89 ±0.39 | 2.92 ±0.54 | 2.54 ±0.62 | 2.99 ±0.47 | 3.11 ±0.39 | 3.10 ±0.50 |
| Pre-Procedure Stenosis (%)* | 85.57 ±10.54 | 84.66 ±10.55 | 84.67 ±10.82 | 84.66 ±10.42 | 88.77 ±10.88 | 85.03 ±11.64 | 85.55 ±11.37 | 85.02 ±11.39 | 85.08 ±10.34 | 83.69 ±9.71 | 84.63 ±9.86 | 89.57 ±8.67 | 86.72 ±10.44 |
| Post-Procedure Stenosis (%)* | 2.59 ±8.73 | 2.91 ±9.65 | 2.57 ±10.08 | 3.07 ±9.44 | 3.14 ±8.30 | 4.75 ±11.00 | 2.79 ±7.81 | 2.46 ±6.69 | 3.38 ±10.88 | 4.98 ±15.66 | 1.82 ±7.23 | 0.77 ±2.44 | 1.38 ±3.83 |

- * Mean ± Standard Deviation
1. IDDM – Insulin dependent diabetic mellitus
2. AMI – Acute myocardial infarction
3. SVG – Saphenous vein graft
4. RVD – Reference Vessel diameter
5. ISR – In-Stent restenosis

Table 9-5-2: Results from US e-CYPHER® Stent Registry at 1-Year

| Patient Group | Clinical Event or Composite % (n) | | | | | | | | | | |
|--------------------------|-----------------------------------|------------|-----------|---------------|-------------------|-----------|-----------|-----------|------------|-----------|-------------|
| | N | MACE | Death | Cardiac Death | Non-Cardiac Death | MI | Q MI | Non Q MI | TLR | ST (0-30) | LT (31-360) |
| All Patients | 2067 | 7.3% (150) | 2.3% (47) | 1.4% (29) | 0.9% (18) | 1.4% (29) | 0.5% (11) | 0.9% (18) | 4.6% (95) | 0.6% (12) | 0.2% (5) |
| On-label | 1313 | 4.8% (63) | 2.0% (26) | 1.0% (13) | 1.0% (13) | 0.8% (10) | 0.2% (3) | 0.5% (7) | 2.6% (34) | 0.4% (5) | 0.0% (0) |
| Diabetes | 640 | 9.4% (60) | 3.0% (19) | 2.0% (13) | 0.9% (6) | 1.9% (12) | 0.6% (4) | 1.3% (8) | 5.8% (37) | 1.1% (7) | 0.0% (0) |
| IDDM | 200 | 16.0% (32) | 4.0% (8) | 4.0% (8) | 0.0% (0) | 5.0% (10) | 2.0% (4) | 3.0% (6) | 10.5% (21) | 3.0% (6) | 0.0% (0) |
| Non-IDDM | 440 | 6.4% (28) | 2.5% (11) | 1.1% (5) | 1.4% (6) | 0.5% (2) | 0.0% (0) | 0.5% (2) | 3.6% (16) | 0.2% (1) | 0.0% (0) |
| Long lesion > 30mm | 96 | 14.6% (14) | 2.1% (2) | 2.1% (2) | 0.0% (0) | 3.1% (3) | 0.0% (0) | 3.3% (3) | 9.4% (9) | 1.0% (1) | 1.0% (1) |
| Small vessel < 2.5mm | 124 | 11.3% (14) | 4.8% (6) | 1.6% (2) | 3.2% (4) | 1.6% (2) | 0.0% (0) | 1.6% (2) | 5.6% (7) | 0.0% (0) | 0.0% (0) |
| Acute MI < 24 hr | 155 | 6.5% (10) | 2.6% (4) | 2.6% (4) | 0.0% (0) | 0% (0) | 0% (0) | 0% (0) | 4.5% (7) | 0.6% (1) | 0.0% (0) |
| In-stent restenosis | 65 | 7.7% (5) | 4.6% (3) | 1.5% (1) | 3.1% (2) | 0.0% (0) | 0.0% (0) | 0.0% (0) | 3.1% (2) | 0.0% (0) | 0.0% (0) |
| Bifurcation | 260 | 10.4% (27) | 3.1% (8) | 2.7% (7) | 0.4% (1) | 4.2% (11) | 1.5% (4) | 2.7% (7) | 5.8% (15) | 0.8% (2) | 0.8% (2) |
| SVG | 129 | 10.1% (13) | 2.3% (3) | 2.3% (3) | 0.0% (0) | 1.6% (2) | 0.0% (0) | 1.6% (2) | 7.0% (9) | 0.0% (0) | 0.0% (0) |
| Multiple stent | 148 | 12.8% (19) | 1.4% (2) | 1.4% (2) | 0.0% (0) | 4.7% (7) | 2.0% (3) | 2.7% (4) | 7.4% (11) | 2.0% (3) | 0.7% (1) |
| Multiple Vessel Stenting | 318 | 10.1% (32) | 2.8% (9) | 2.2% (7) | 0.6% (2) | 2.5% (8) | 0.9% (3) | 1.6% (5) | 7.2% (23) | 0.9 (3)% | 0.9% (3) |

MACE - A composite endpoint comprised of death, Q wave or WHO-defined non-Q wave MI, or target lesion revascularization
MI - Q wave or WHO-defined non-Q wave MI
TLR - target lesion revascularization
ST - stent thrombosis in first 30 days
LT - late thrombosis is stent thrombosis >30 days and <361 days

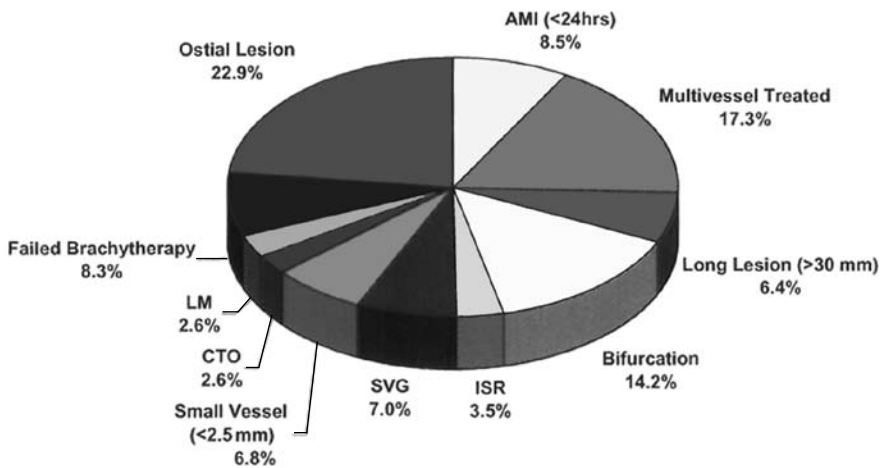
Table 9-5-3 summarizes stent thrombosis (ST) based on protocol definition.

Table 9-5-3: e-CYPHER® Registry - Summary of Stent Thrombosis

| | CYPHER |
|--------------------------------------|----------------|
| Cumulative ST through 5 years | 1.6% (17) |
| Acute ST (≤24 hrs) | 0.1% (3) |
| Subacute ST (>24 hrs and ≤ 30days) | 0.6% (9) |
| Late ST (>30 days and ≤12 months) | 0.8% (5) |
| Very Late ST (>12 months to 5 years) | Not Applicable |

For all calculations, event rates are cumulative incidences using Kaplan-Meier method
 Protocol Thrombosis is defined as the composite of Stent Thrombosis and Late Thrombosis, where, Stent Thrombosis is defined as a 30-day endpoint including sub-abrupt closure or unexplained death or Q-wave MI; Late Thrombosis is defined as 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.

Figure 9-5-1. Important Subgroups - By Complex Lesions and patients in e-CYPHER US Post Marketing Study (PMS) Registry



LM – Left Main
 CTO – Chronic Total Occlusion
 SVG – Saphenous Vein Graft
 ISR – In-Stent restenosis
 AMI – Acute Myocardial Infarction

A patient could be in multiple subgroups in the above pie chart.
 The subgroup of Congestive Heart Failure (CHF) and Renal Dysfunction are not included, since the related information was not collected for e-CYPHER PMS registry.

- 10. Individualization of Treatment** See also **Precautions– 5.6 Use in Special Populations** and **Precautions– 5.7 Lesion/Vessel Characteristics**. The risks and benefits described above should be considered carefully for each patient before use of the **CYPHER®** Stent. Patient selection factors to be assessed should include a judgment regarding the risk of prolonged anticoagulation. Stenting is generally avoided in those patients at heightened risk of bleeding (e.g., those patients with recently active gastritis or peptic ulcer disease, see Section 3 –**Contraindications**).

Premorbid conditions that increase the risk of a poor initial result and the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed. The relation of baseline and procedural variables to Major Adverse Cardiac Events (MACE) was examined. Multivariable modeling suggested that treatment assignment remained an independent predictor of clinical and angiographic outcomes even after adjusting for other baseline and procedural confounding variables.

11. Patient Counseling Information

Physicians should consider the following in counseling the patient about this product:

- Discuss the risks associated with stent placement
- Discuss the risks associated with a sirolimus-eluting implant
- Discuss the risks/benefits issues for this particular patient
- Discuss alteration to current lifestyle immediately following the procedure and over the long term
- Discuss the risks of early discontinuation of the antiplatelet therapy

The following patient specific information regarding the **CYPHER** Stent is available in hard copy or on-line:

- A Patient Implant Card that includes both patient and **CYPHER** Stent specific information. All patients will be expected to keep this card in their possession at all times for procedure / stent identification.
- A Patient Information Guide, which includes information on the implant procedure, and the **CYPHER** Stent System.

12. How Supplied

STERILE: This product is sterilized with ethylene oxide gas and is nonpyrogenic. Do not use if the package is opened or damaged. For one use only. Do not resterilize.

CONTENTS: One (1) **CYPHER** Sirolimus-eluting Coronary Stent on **RAPTOR™** Over-the-Wire Delivery System or **RAPTORRAIL®** Rapid Exchange Delivery System.

STORAGE: Store in a cool, dark, dry place. Store at 25°C (77°F); excursions permitted to 15-30°C (59 – 86°F).

13. Operator’s Manual (Combined OTW and RX)

13.1. Access to Package Holding Sterile Stent Delivery System

Tear open the foil pouch to remove the product that is packaged in a coiled hoop and tray. Pass or drop the product into the sterile field using an aseptic technique.

13.2. Inspection Prior to Use

Before opening, carefully inspect the stent delivery system package, and check for damage to the sterile barrier. Prior to using the product, carefully remove the system from the package and inspect it for bends, kinks, and other damage. Do not use the product if any damage to the packaging is noted.

13.3. Materials Required

| Quantity | Material |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|
| N/A | Appropriate guiding catheter(s) |
| 2-3 | 10-20 cc syringes |
| 1,000 u /500 cc | Sterile Heparinized Normal Saline (HepNS) |
| 1 | 0.014" (0.36 mm) diameter guidewire (OTW: 300 cm long) |
| 1 | Rotating hemostatic valve with an appropriate internal diameter (OTW: min. I.D. of 0.074" [1.9 mm]) (RX: min. I.D. of 0.096" [2.4 mm]) |
| N/A | Contrast diluted 1:1 with normal saline |
| 1 | Inflation device |
| 1 | Stopcock (3-way minimum) |
| 1 | Torque device |
| 1 | Guidewire Introducer |
| N/A | Appropriate anticoagulation and antiplatelet drugs |

13.4. Preparation Precaution

- AVOID manipulation of the stent during flushing of the guidewire lumen, as this may disrupt the placement of the stent on the balloon.
- DO NOT apply negative or positive pressure to the balloon during the delivery system preparation.

13.4.1 Rinse the catheter with sterile heparinized normal saline solution.

13.4.2. Guidewire Lumen Flush

| | |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| OTW | 1. Locate the guidewire lumen hub and flush the guidewire lumen with HepNS. |
| RX | 1. Attach the syringe with HepNS to the flushing needle packaged with the catheter. 2. Insert the needle into the tip of the catheter and flush the guidewire lumen with HepNS. |

13.4.3 Delivery System Preparation

| Step | Action |
|-------------|---------------------------------------------------------------------------------------------------|
| 1. | Prepare the inflation device or syringe with diluted contrast medium. |
| 2. | Attach the inflation device or syringe to the stopcock; attach to the balloon inflation port hub. |
| 3. | Open the stopcock to stent delivery system . |
| 4. | Leave the inflation device or syringe on neutral. |

13.5. Delivery Procedure

| Step | Action |
|------|--------|
|------|--------|

- | | |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. | Prepare the vascular access site according to standard practice. |
| 2. | Predilate the lesion with a PTCA catheter. Limit the longitudinal length of pre-dilatation by the PTCA balloon to avoid creating a region of vessel injury that is outside the boundaries of the CYPHER® Stent. |
| 3. | Maintain neutral pressure on the inflation device. Open the rotating hemostatic valve as widely as possible. |
| 4. | Backload the delivery system onto the proximal portion of the guidewire while maintaining the guidewire position across the target lesion. |
| 5. | Advance the stent delivery system over the guidewire to the target lesion. Use the radiopaque balloon markers to position the stent across the lesion; perform angiography to confirm the position of the stent. |

Note: 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**. See **Precautions – 5.15 Stent/System Removal Precautions** for specific stent delivery system removal instructions.

13.6. Deployment Procedure

| Step | Action |
|------|--------|
|------|--------|

- | | |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. | Before deployment, reconfirm the correct position of the stent relative to the target lesion via the radiopaque balloon markers. |
| 2. | Attach the inflation device (only partially filled with contrast media) to a three-way stopcock and apply negative pressure to purge the balloon of air. |
| 3. | Turn the stopcock on the catheter to the off position and purge the inflation device of air. Close the side port of the stopcock. |
| 4. | Under fluoroscopic visualization, inflate the balloon to at least the nominal pressure to deploy the stent, but do not exceed the labeled rated burst pressure of 16 atm (1621 kPa) . Maintain inflation pressure for 15-30 seconds for full expansion of the stent. Optimal expansion requires the stent to be in full contact with the artery wall, with the stent internal diameter matching the size of the reference vessel diameter. Stent wall contact should be verified through routine angiography or intravascular ultrasound. |
| 5. | Fully cover the entire lesion and balloon treated area (including dissections) with the CYPHER Stent, allowing for adequate stent coverage into healthy tissue proximal and distal to the lesion. |
| 6. | If more than one CYPHER Stent is needed to cover the lesion and balloon treated area, adequately overlap stents, taking into account stent foreshortening. Ensure no gaps between stents by positioning the balloon marker bands of the second CYPHER Stent inside the deployed stent prior to expansion. See Precautions – 5.15 Stent/System Removal Precautions . |
| 7. | Deflate the balloon by pulling a vacuum with the inflation device. Make certain that the balloon is fully deflated before attempting to move the catheter. |
| 8. | Confirm that the stent is adequately expanded by angiographic injection through the guiding catheter. |

13.7. Further Dilatation of Stented Segments

Precaution: Do not dilate the stent beyond the following limits:

| Nominal Stent Diameter | Dilatation Limits |
|------------------------|-------------------|
| 2.50 mm – 3.00 mm | 3.75 mm |
| 3.50 mm | 4.75 mm |

All efforts should be taken to assure that the stent is not underdilated. If the deployed stent size is still inadequate with respect to vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. The stent may be further expanded using a low profile, high pressure, and non-compliant balloon catheter. If this is required, the stented segment should be recessed carefully with a prolapsed guidewire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

13.8. Removal Procedure

| Step | Action |
|------|--------|
|------|--------|

- | | |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. | Ensure that the balloon is fully deflated. |
| 2. | While maintaining the guidewire position and negative pressure on the inflation device, withdraw the stent delivery system. Note: Should unusual resistance be felt at any time during either lesion access or removal of stent delivery system before stent implantation, the entire system should be removed as a single unit . See Precautions – 5.15 Stent/ System Removal Precautions for specific stent delivery system removal instructions. |
| 3. | Repeat angiography to assess the stented area. If an adequate expansion has not been obtained, exchange back to the original stent delivery catheter or exchange to another balloon catheter of appropriate balloon diameter to achieve proper stent apposition to the vessel wall. |
| 4. | The final stent diameter should match the reference vessel. ASSURE THAT THE STENT IS NOT UNDERDILATED. |

13.9. In-vitro Information

Table 13-1: Inflation Pressure Recommendations

| Inflation Pressure atm (kPa) | 2.50 mm | 2.75 mm | 3.00 mm | 3.50 mm | |
|------------------------------|-------------|-------------|-------------|-------------|----------------|
| 6 608 | 2.17 | 2.43 | 2.64 | 3.13 | |
| 7 709 | 2.25 | 2.51 | 2.72 | 3.23 | |
| 8 811 | 2.32 | 2.58 | 2.80 | 3.32 | |
| 9 912 | 2.38 | 2.67 | 2.87 | 3.40 | |
| 10 1013 | 2.44 | 2.71 | 2.94 | 3.47 | |
| 11 1115 | 2.49 | 2.76 | 2.99 | 3.52 | Nominal |
| 12 1216 | 2.53 | 2.82 | 3.03 | 3.57 | |
| 13 1317 | 2.56 | 2.84 | 3.07 | 3.61 | |
| 14 1419 | 2.59 | 2.87 | 3.11 | 3.64 | |
| 15 1520 | 2.62 | 2.89 | 3.14 | 3.67 | |
| 16 1621 | 2.64 | 2.92 | 3.16 | 3.70 | RBP |
| 17 1723 | 2.67 | 2.95 | 3.19 | 3.73 | |
| 18 1824 | 2.69 | 2.97 | 3.22 | 3.76 | |
| 19 1925 | 2.73 | 2.99 | 3.24 | 3.79 | |
| 20 2026 | 2.74 | 3.02 | 3.27 | 3.82 | |

Note: The values are representative of average stent/balloon diameters at specific balloon inflation pressures obtained during *in-vitro* testing at 37°C. These values do not take into account lesion resistance. The stent sizing should be confirmed angiographically. Do not exceed the rated burst pressure (RBP). Bolded text represents diameters at pressures above the rated burst pressure. The values between the nominal pressure and the rated burst pressure are within $\pm 10\%$ of the labeled stent diameter.

14. Patient Information

In addition to this Instructions for Use booklet, the following patient specific information regarding the **CYPHER®** Stent is available:

- A Patient Implant Card that includes both patient and **CYPHER** Stent specific information. All patients will be expected to keep this card in their possession at all times for procedure / stent identification.
- A Patient Information Guide, which includes information on the implant procedure, and the **CYPHER** Stent System.

15. Patents

Protected under one or more of the following U.S. patent Nos.: 4,597,755; 4,733,665; 4,739,762; 4,748,982; 4,775,371; B1 4,776,337; 4,782,834; 4,906,244; 4,927,418; 4,938,220; 4,981,478; 5,017,325; 5,040,548; 5,061,273; 5,102,417; 5,108,415; 5,135,535; 5,154,725; 5,156,612; 5,176,661; 5,223,205; 5,234,416; 5,236,659; 5,242,396; 5,288,711; 5,290,230; 5,300,025; 5,300,085; 5,304,197; 5,316,706; 5,346,505; 5,350,395; 5,356,591; 5,387,193; 5,413,559; 5,433,713; 5,439,447; 5,449,371; 5,451,209; 5,451,233; 5,458,613; 5,480,383; 5,496,275; 5,496,346; 5,498,240; 5,501,227; 5,516,781; 5,538,510; 5,554,121; 5,563,146; 5,585,057; 5,626,600; 5,643,279; 5,643,312; 5,646,160; 5,665,728; 5,685,312; 5,697,971; 5,709,658; 5,738,653; 5,743,875; 5,749,888; 5,769,868; 5,807,355; 5,868,706; 5,879,370; 5,902,332; 6,010,521; 6,013,069; 6,027,475; 6,036,715; 6,086,604; 6,110,142 and other patents pending in the U.S. and other countries.

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