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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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Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

1. Product Description

The **CYPHER™** Sirolimus-eluting Coronary Stent (**CYPHER** Stent) is a combination product comprised of two regulated components: a device (a stent system) and a drug product (a formulation of sirolimus in a polymer coating).

1.1. Device Component Description

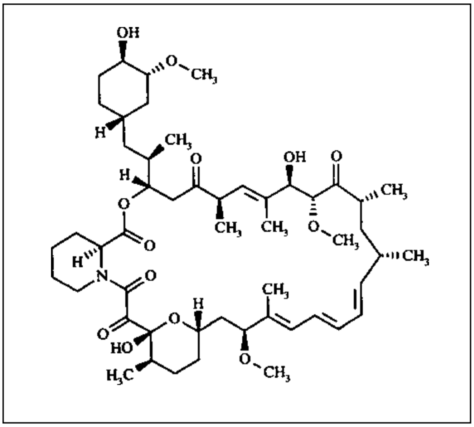
The device component consists of a stent mounted onto a stent delivery system (SDS). The physical characteristics of the device component are shown in Table 1-1.

Table 1-1: Device Component Description

	CYPHER™ Sirolimus-eluting Coronary Stent on RAPTOR™ Over-the-Wire (OTW) Stent Delivery System	**CYPHER™ Sirolimus-eluting Coronary 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:	Electropolished stainless steel (316L), laser-cut from seamless tubing in a sinusoidal pattern coated with a polymer and sirolimus mixture.	
Stent Geometry:	Six circumferential cells (2.50 – 3.00 mm stents) or Seven circumferential cells (3.50 mm stents)	
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. Mounted stent length and location is defined by 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).

1.2. Drug Component Description

The active ingredient in the **CYPHER** Sirolimus-eluting Coronary Stent is sirolimus (also known as rapamycin). Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. The chemical name of sirolimus (also known as rapamycin) is (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4] oxaazacyclohentriacontine-1,5,11,28,29 (4*H*,6*H*,31*H*)-pentone. Its molecular formula is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.2. The structural formula 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** Sirolimus-eluting Coronary Stents.

The inactive ingredients in the **CYPHER** Sirolimus-eluting Coronary 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 of PBMA polymer is applied to the stent surface to control the release kinetics of sirolimus. 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:

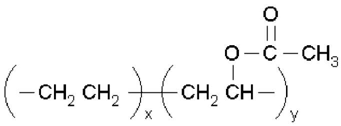
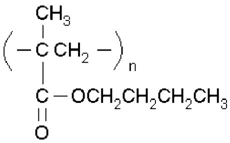
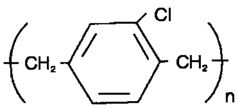
PEVA	PBMA	Parylene C
		

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** Sirolimus-eluting Coronary 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 ≥ 2.5 to ≤ 3.5 mm.

Long-term outcome (beyond 12 months) for this permanent implant is unknown at present.

3. Contraindications

Use of the **CYPHER** Sirolimus-eluting Coronary Stent is contraindicated in the following patient types:

- Patients with a hypersensitivity to sirolimus or its derivatives.
- Patients with a known hypersensitivity to polymethacrylates or polyolefin copolymers.

Coronary artery stenting is contraindicated for use in:

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

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 device carries the risks associated with coronary artery stenting, including subacute thrombosis, vascular complications, and/or bleeding events.
- Patients with a known hypersensitivity to 316L stainless steel may suffer an allergic reaction to this implant.

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.
- To avoid the possibility of dissimilar metal corrosion, do not implant stents of different materials in tandem where overlap or contact is possible.
- Do not use Ethiodol or Lipiodol contrast media.[1]
- Do not expose the delivery system to organic solvents, such as alcohol, or detergents.

5.2. 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 will result in the patient receiving larger amounts of drug and polymer than the experience reflected in the clinical studies.

5.3. 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 remodeling. The synergy between these two treatments has not been determined.

[1] Ethiodol and Lipiodol are trademarks of Guerbet, S.A.

5.4. 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.

5.5. Use in Special Populations

5.5.1. Pregnancy: Pregnancy Category C. See **Drug Information – 6.6 Pregnancy**.
There are no adequate and well controlled studies in pregnant women. 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.

5.5.2. 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.

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

5.5.4. 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. Lesion/Vessel Characteristics

The safety and effectiveness of the **CYPHER** Stent have not been established in the following patient populations:

- Patients with unresolved 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 the left main coronary artery, ostial lesions, or lesions located at a bifurcation.
- Patients with diffuse disease or poor overflow distal to the identified lesions.
- Patients with tortuous vessels in the region of the obstruction or proximal to the lesion.
- Patients with a recent acute myocardial infarction where there is evidence of thrombus or poor flow.

5.7. 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 IIIA4 (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.

5.8. 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.

5.9. 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 insufficiently 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.

5.10. 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.

5.11. Magnetic Resonance Imaging (MRI) – Stent Migration

An MRI scan should not be performed on a patient after stent implantation until there is adequate neointimal investment of the stent because of a potential for stent migration. For a conventional uncoated 316L stainless steel stent this period is usually considered to be eight weeks. Because of the reduced neointimal formation associated with the **CYPHER** Stent, the period of vulnerability may be longer, but there is currently insufficient information to provide a specific recommendation.

5.12. Stent Handling Precautions

- **For single use only.** Do not resterilize or reuse this device. Note the “Use By” date on the product label.
- **Do not remove the stent from the delivery balloon – removal may damage the stent and/or lead to stent embolization.** 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 loosen the stent from the delivery system balloon and cause dislodgment.
- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.

5.13. Stent Placement Precautions

- **Do not prepare or pre-inflate the balloon prior to stent deployment other than as directed. Use the balloon purging technique described in Section 12 – Operator's Manual.**
- Guiding catheters used must have lumen sizes that are suitable to accommodate the stent delivery system (see **Product Description – 1.1 Device Component Description**).
- Do not induce a negative pressure on the delivery catheter prior to placement of the stent across the lesion. This may cause premature dislodgment of the stent from the balloon.
- 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 – 5.14 Stent/System Removal Precautions**.)
- Placement of the stent has the potential to compromise side branch patency.
- Balloon pressures should be monitored during inflation. **Do not exceed rated burst pressure as indicated on the product label.** (See **Inflation Pressure Recommendations** in Table 12-1.) 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 dislodgment of the stent from the balloon may occur. Remove as a single unit per instructions in Precautions – 5.14 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.

5.14. 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.

5.15. Post Implantation Precautions

- Great care must be exercised **when crossing a newly deployed stent** with an intravascular ultrasound (IVUS) catheter, a coronary guidewire or balloon catheter to avoid disrupting the stent geometry.
- Do not perform a **magnetic resonance imaging** (MRI) scan on a patient after stent implantation until there is adequate neointimal investment of the stent (see **Precautions – 5.11 Magnetic Resonance Imaging (MRI) – Stent Migration**). The stent may cause artifacts in MRI scans due to distortion of the magnetic field.

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. It is known that 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 G_1 to the S phase.

6.2. Pharmacokinetics of the CYPHER Sirolimus-eluting Coronary Stent

The pharmacokinetics of sirolimus as delivered by the **CYPHER** Sirolimus-eluting Coronary 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 1 and 2 **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 ± 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 ± 0.17	78.2 ± 18.3	970 ± 272
Renal Transplant (n=19)	2 mg/day multiple dose oral solution	3.01 ± 2.4	12.2 ± 6.2	158 ± 70
Renal Transplant (n=23)	5 mg/day multiple dose oral solution	1.84 ± 1.3	37.4 ± 21	396 ± 193
Renal Transplant (n=13)	2 mg/day multiple dose tablets	3.46 ± 2.4	15.0 ± 4.9	230 ± 67
Hepatic Impairment (n=18)	15 mg single dose oral solution	0.84 ± 0.17	77.9 ± 23.1	1567 ± 616

6.3.1. Distribution
The mean (±SD) blood to plasma ratio of sirolimus was 36 (±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 ± 12 hours in subjects with normal hepatic function to 113 ± 41 hours in patients with impaired hepatic function. However, hepatic diseases with varying etiologies may show different 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** Sirolimus-eluting Coronary Stent. Sirolimus is extensively metabolized by cyctochrome 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.

6.4.5. 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

6.4.6. Other drug interactions

Drugs that may increase sirolimus blood concentrations include:

- **Calcium channel blockers:** nicardipine, verapamil.
- **Antifungal agents:** clotrimazole, fluconazole, itraconazole.
- **Macrolide antibiotics:** clarithromycin, erythromycin, 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.

6.4.7. Grapefruit juice: Grapefruit juice reduces CYP3A4-mediated metabolism of sirolimus.

6.4.8. 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.

6.4.9. 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.

6.4.10. 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 $\geq$ 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 $\geq$ 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. Adverse Events

7.1. Observed Adverse Events

Observed adverse event experience comes from three clinical studies, the SIRIUS trial, the RAVEL trial, and the First-In-Man study. See Section 8 – **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**, 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 7-2.

Table 7-1: Clinical Studies - Major Characteristics

	SIRIUS Trial	**RAVEL Trial**	**First-in-Man Study**
Study Type	prospective, randomized	prospective, randomized	non-randomized
Number of Patients	1058 (533 **CYPHER** Stent, 525 Control)	238 (120 **CYPHER** Stent, 118 Control)	45 (30 **CYPHER** Stent, 15 other)
Lesion Criteria	*De novo* lesion in native coronary artery $\geq$ 2.5 to $\leq$ 3.5 mm in diameter, lesion 15 to 30 mm in length and coverable with 2 stents	*De novo* lesion in native coronary artery $\geq$ 2.5 to $\leq$ 3.5 mm in diameter, lesion coverable by one 18 mm stent	*De novo* lesion in native coronary artery $\geq$ 3.0 to $\leq$ 3.5 mm diameter, lesion coverable by one 18 mm stent
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

Table 7-2: Principal Adverse Events Observed in Clinical Studies In-Hospital and Out-of-Hospital					
	SIRIUS Trial to 360 Days		RAVEL Trial to 720 Days		First-in-Man to 720 Days
	CYPHER Stent (N=533)	Control Stent (N=525)	CYPHER Stent (N=120)	Control Stent (N=118)	CYPHER Stent Stent (N=30)
MACE[1]					
In-Hospital	2.4% (13)	1.5% (8)	2.5% (3)	2.5% (3)	6.7% (2)
Out-of-Hospital	6.0% (32)	21.3% (112)	7.5% (9)	17.8% (21)	3.3% (1)
Death					
In-Hospital	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3.3% (1)
Out-of-Hospital	1.1% (6)	0.8% (4)	5.0% (6)	2.5% (3)	0.0% (0)
Myocardial Infarction					
In-Hospital	2.3% (12)	1.5% (8)	2.5% (3)	2.5% (3)	3.3% (1)
Out-of-Hospital	0.8% (4)	1.9% (10)	1.7% (2)	2.5% (3)	0.0% (0)
Q-wave					
In-Hospital	0.4% (2)	0.0% (0)	1.7% (2)	0.8% (1)	0.0% (0)
Out-of-Hospital	0.4% (2)	0.4% (2)	0.0% (0)	0.0% (0)	0.0% (0)
Non Q-wave					
In-Hospital	1.9% (10)	1.5% (8)	0.8% (1)	1.7% (2)	3.3% (1)
Out-of-Hospital	0.4% (2)	1.5% (8)	1.7% (2)	2.5% (3)	0.0% (0)
Emergent CABG					
In-Hospital	0.0% (0)	0.0% (0)	--	--	0.0% (0)
Out-of-Hospital	0.0% (0)	0.0% (0)	--	--	0.0% (0)
Target Lesion Revascularization (TLR)					
In-Hospital	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Out-of-Hospital	4.7% (25)	20.0% (105)	2.5% (3)	13.6% (16)	3.3% (1)
TVR not Target Lesion					
In-Hospital	0.0% (0)	0.0% (0)	0.8% (1)	0.8% (1)	3.3% (1)
Out-of-Hospital	3.6% (19)	6.7% (35)	0.0% (0)	1.7% (2)	3.3% (1)
Target Vessel Failure[2]					
In-Hospital	2.4% (13)	1.5% (8)	2.5% (3)	2.5% (3)	6.7% (2)
Out-of-Hospital to 270 days[3]	6.6% (35)	19.6% (103)	--	--	--
Out-of-Hospital to 360/720 days	7.5% (40)	23.6% (124)	3.3% (4)	19.5% (27)	3.3% (1)
Stent Thrombosis					
In-Hospital	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Out-of-Hospital	0.2% (1)	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Sub-acute Closure					
In-Hospital	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Out-of-Hospital	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Late Thrombosis					
Out-of-Hospital	0.2% (1)	0.6% (3)	0.0% (0)	0.0% (0)	0.0% (0)
CVA					
In-Hospital	0.2% (1)	0.8% (4)	0.0% (0)	0.0% (0)	3.3% (1)
Out-of-Hospital	0.9% (5)	1.3% (7)	0.8% (1)	0.0% (0)	3.3% (1)

[1] MACE is defined as Death, Q-wave or non Q-wave MI, Emergency 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.
Tabulated entries are represented as: percentage (number of patients with event).

In the SIRIUS trial, a subset of patients underwent intravenous 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 7-3.

Table 7-3: Frequency of Incomplete Stent Apposition				
	SIRIUS Trial		RAVEL Trial	
	CYPHER Stent	Control Stent	CYPHER Stent	Control Stent
Incomplete Stent Apposition Rate at Follow-up	18% (18/101)	9% (7/78)	21% (10/41)	4% (2/27)
Changes from Baseline				
Healed	10% (8/80)	5% (3/61)	--	--
Preserved	8% (6/80)	10% (6/61)	--	--
Late Incomplete Stent Apposition	9% (7/80)	0% (0/61)	--	--

7.2. 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 7-2 and Table 7-3):

7.2.1. 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 compression
- Stent migration
- Stroke
- Thrombosis (acute, subacute, or late)
- Ventricular fibrillation
- Vessel spasm
- Vessel perforation

7.2.2. 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 5.10)
- Hypokalemia
- Infections
- Interstitial lung disease
- Leukopenia
- Lymphoma and other malignancies
- Thrombocytopenia

8. Clinical Studies

8.1. Overview of Clinical Studies

The principal safety and efficacy evidence for the **CYPHER** Stent came from three clinical studies, the SIRIUS trial, the RAVEL trial, and the First-In-Man study. All three of these studies evaluated the performance of the **CYPHER** Stent in patients with symptomatic ischemic disease due to *de novo* lesions in native coronary arteries. Major study characteristics are summarized below and in Table 8-1.

The SIRIUS and RAVEL trials were multi-center, double-blind, randomized clinical trials that compared the **CYPHER** Stent to a Control consisting of an uncoated 316L stainless steel stent (the **BX VELOCITY** Stent). Eligibility was based on visual estimates of vessel diameter and lesion length. Following treatment, patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 2 or 3 months, depending on the study. The SIRIUS trial was a large study with a primary clinical endpoint of target vessel failure at 9 months. Angiographic follow-up was scheduled for a majority of patients at 8 months. The RAVEL trial was a smaller study with a primary angiographic endpoint of late loss at 6 months. Clinical follow-up through one year is available for both trials, and follow-up through five years is planned.

The First-in-Man study was a small, non-randomized, initial feasibility study that involved angiographic and clinical follow-up. Its primary value is that it provides the longest available follow-up information, through 2 years.

Table 8-1: Clinical Study Comparison

	SIRIUS Trial	**RAVEL Trial**	**First-in-Man Study**
Study Type	Pivotal Study	Supportive Study	Feasibility Study
	Multi-center (N=53), prospective, randomized	Multi-center (N=19), prospective, randomized	Multi-center (N=2) Non-randomized
Number of Patients	1058 (533 **CYPHER** Stent, 525 Control)	238 (120 **CYPHER** Stent, 118 Control)	45 (30 **CYPHER** Stent, 15 other)
Lesion Criteria	*De novo* lesion in native coronary artery $\geq$ 2.5 to $\leq$ 3.5 mm in diameter, lesion 15 to 30 mm in length and coverable with 2 stents	*De novo* lesion in native coronary artery $\geq$ 2.5 to $\leq$ 3.5 mm in diameter, lesion coverable by one 18 mm stent	*De novo* lesion in native coronary artery $\geq$ 3.0 to $\leq$ 3.5 mm diameter, lesion coverable by one 18 mm stent
Device 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
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
Follow-up	8 months angiographic 9 months clinic 1, 3, 6, 12 months and 2, 3, 4 and 5 years telephone F/U	6 months angiographic 1 and 6 month clinic 12 months and 2, 3, 4, and 5 years telephone F/U	Brazil: 4, 12, 24 months angio & IVUS The Netherlands: 6 & 18 months angio & IVUS and 24 months clinical F/U

8.2. 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. 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.

Patients were randomized with equal probability to receive either the **CYPHER** Stent or the Control. 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 12-month (± 2 weeks) endpoint was available on 1027 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 one year.

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 (8.8% 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 mm^3 vs. 57.6 mm^3, $p < 0.001$), but there was a higher rate of incomplete stent apposition (18% vs. 9%, $p = 0.13$). There were no clinical events related to the occurrence of incomplete stent apposition. Clinical outcomes through 12 months were consistent with the 9 month outcomes. Twenty-eight percent (28%) of the patients in the **CYPHER** Stent arm of the SIRIUS trial received 2 or more (overlapping) stents. The incidence of major adverse cardiac events in these patients was statistically lower than the patients who received an uncoated stent.

Table 8-2 summarizes the principal effectiveness and safety results of the SIRIUS Trial through 360 days. Figure 8-1 provides the cumulative TVF rates through 360 days.

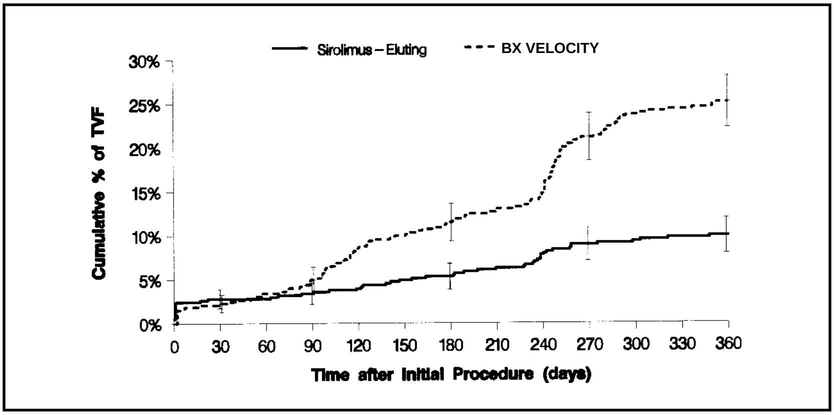
Table 8-2 SIRIUS Principal Effectiveness and Safety Results (to 360 Days)
All Patients Treated (N=1058)

Effectiveness Measures	**CYPHER Stent (N=533 Patients N=533 Lesions)**	**Control (N=525 Patients N=531 Lesions)**	**Difference [95% CI]**	**P-Value**
Device 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
Post-Procedure MLD (mm)				
In-Stent	2.67 ± 0.40 (528)	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
Eight-Month Minimum Lumen Area (mm^3)	5.4 ± 2.1 (101)	3.9 ± 1.9 (75)	1.5 [0.9, 2.1]	<0.001
Eight-Month NIH Volume (mm^3)	4.4 ± 6.5 (51)	57.6 ± 32.7 (45)	-53.2 [-62.5, -43.9]	<0.001
TVF to 9 Months (Primary Endpoint)*	8.8% (47/533)	21.0% (110/525)	-12.1% [-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 360 Days				
TLR-Free†	95.0%	79.5%	15.5% [11.4%, 19.7%]	<0.001
TVR-Free†	92.7%	76.9%	15.8% [11.4%, 20.1%]	<0.001
TVF-Free †	90.1%	74.9%	15.2% [10.6%, 19.9%]	<0.001
MACE-Free†	91.7%	77.4%	14.2% [9.8%, 18.7%]	<0.001
Safety Measures				
In-Hospital MACE*	2.4% (13/533)	1.5% (8/525)	0.9% [-0.8%, 2.6%]	0.379
Out-of-Hospital MACE to 270 days*	4.9% (26/533)	17.7% (93/525)	-12.8% [-16.6%, -9.1%]	<0.001
Out-of-Hospital MACE to 360 days*	6.0% (32/533)	21.3% (112/525)	-15.3% [-19.4%, -11.3%]	<0.001
MACE to 270 days*	7.1% (38/533)	18.9% (99/525)	-11.7% [-15.7%, -7.7%]	<0.001
MACE to 360 days*	8.3% (44/533)	22.3% (117/525)	-14.0% [-18.3%, -9.8%]	<0.001
TVF to 270 days (Primary endpoint)*	8.8% (47/533)	21.0% (110/525)	-12.2% [-16.4%, -7.9%]	<0.001
TVF to 360 days*	9.8% (52/533)	24.8% (130/525)	-15.0% [-19.5%, -10.5%]	<0.001
Stent Thrombosis to 30 days	0.2% (1/533)	0.2% (1/525)	0.0% [-0.5%, 0.5%]	1.000
Late Thrombosis to 360 days	0.2% (1/533)	0.6% (3/525)	-0.4% [-1.1%, 0.4%]	0.371
Subacute Closure	0.2% (1/533)	0.0% (0/525)	0.2% [-0.2%, 0.6%]	1.000
Cerebrovascular Accident (CVA) to 360 days	1.1% (6/533)	2.1% (11/525)	-1.0% [-2.5%, 0.5%]	0.231
Major Bleeding Complications	3.6% (19/533)	3.4% (18/525)	0.1% [-2.1%, 2.3%]	1.000
Major (Hemorrhagic) Vascular Complications	1.5% (8/533)	2.3% (12/525)	-0.8% [-2.4%, 0.9%]	0.376
Hematological Dyscrasia to 360 days	0.6% (3/533)	0.8% (4/525)	-0.2% [-1.2%, 0.8%]	0.724

Numbers are % (counts/sample size) or Mean ± SD.
Relative Risk = Sirolimus/**BX VELOCITY** Stent
CI = RR•exp(±1.96•SE)
CI = Confidence Interval
SE = Calculated in SAS[2] software using Mantel-Haenszel Method
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.
Device Success (Lesion Based) – Achievement of a final residual diameter stenosis of <50% (by QCA) using the assigned device only (if QCA was not available, the visual estimate of diameter stenosis was used).
Procedure Success (Lesion Based) – Achievement of a final diameter stenosis of <50% (by QCA) using any percutaneous method, without the occurrence of death, Q-wave or WHO-defined non Q-wave MI, or repeat revascularization of the target lesion during the hospital stay (if QCA was not available, the visual estimate of diameter stenosis was used).
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
* Events 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.
† The following survival estimates are by Kaplan-Meier Methods with standard error estimates by Peto formula:
TLR-Free– No target lesion revascularization.
TVR-Free – No target vessel revascularization.
TVF-Free – No cardiac death, Q-wave or WHO-defined non Q-wave MI, or target vessel revascularization.
MACE-Free – No death, Q-wave or WHO-defined non Q-wave MI, or target vessel revascularization.
Major Adverse Cardiac Events (MACE) – A composite endpoint comprised of death, Q-wave or WHO-defined non Q-wave MI, or target vessel revascularization.
Target Vessel Failure (TVF) – A composite endpoint comprised of cardiac death, Q-wave or WHO-defined non Q-wave MI, or target vessel revascularization
Stent Thrombosis – A 30-day endpoint including subacute closure or unexplained death or Q-wave MI.
Late Thrombosis – Myocardial infarction occurring >30 days after the index procedure and attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and freedom from an interim revascularization of the target vessel.
Subacute (Subabrupt) Closure – Abrupt closure that occurred after the index procedure was completed (and the patient left the catheterization laboratory) and before the 30-day follow-up endpoint.
Cerebrovascular Accident (CVA) – Sudden onset of vertigo, numbness, aphasia, or dysarthria due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persisted >24 hours.
Major Bleeding Complications – Bleeding requiring transfusions or associated with hemoglobin drop > 5.0 g/dL.
Major (hemorrhagic) Vascular Complication – Hematoma at access site >5 cm; false aneurysm; AV fistula; retroperitoneal bleed; peripheral ischemia/nerve injury; any transfusion required was reported as a vascular complication unless clinical indication clearly other than catheterization complication; and vascular surgical repair.

[2] SAS is a trademark of SAS Institute, Inc.

Figure 8-1
Kaplan-Meier Graph and Life Table to 360 Days
SIRIUS Cumulative Percentage of Target Vessel Failure



Error Bars indicate 1.5 Standard Error

	Time after initial procedure (days) 0	7	14	30	60	90	120	150	180	210	240	270	360
Sirolimus-Eluting Bx VELOCITY™													
# Entered	533	530	519	519	517	514	509	505	499	496	490	481	474
# Censored	0	1	0	0	3	2	1	1	1	1	1	1	20
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# at risk	533.0	529.5	519.0	519.0	515.5	513.0	508.5	504.5	498.5	495.5	489.5	480.5	464.0
# Events	3	10	0	2	0	3	3	5	2	5	8	6	5
# Events/Month		42.9	0.0	3.8	0.0	3.0	3.0	5.0	2.0	5.0	8.0	6.0	1.7
% with Events	0.6%	2.4%	2.4%	2.8%	2.8%	3.4%	4.0%	4.9%	5.3%	6.2%	7.8%	8.9%	9.9%
SE	0.3%	0.7%	0.7%	0.7%	0.7%	0.8%	0.9%	0.9%	1.0%	1.1%	1.2%	1.2%	1.3%
Bx VELOCITY™													
# Entered	525	525	515	515	513	507	499	475	468	460	450	439	406
# Censored	0	0	0	0	0	0	4	0	1	2	0	2	19
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# at risk	525.0	525.0	515.0	515.0	513.0	507.0	497.0	475.0	467.5	459.0	450.0	438.0	396.5
# Events	0	10	0	2	6	8	20	7	7	8	11	31	20
# Events/Month		42.9	0.0	3.8	6.0	8.0	20.0	7.0	7.0	8.0	11.0	31.0	6.7
% with Events	0.0%	1.9%	1.9%	2.3%	3.4%	5.0%	8.8%	10.1%	11.5%	13.0%	15.1%	21.1%	25.1%
SE	0.0%	0.6%	0.6%	0.7%	0.8%	1.0%	1.3%	1.4%	1.4%	1.5%	1.6%	1.8%	2.0%

Tests Between Groups

Test	Chi-Square	Deg Frdm	P-value
Log-Rank	40.01	1	<0.001
Wilcoxon	38.29	1	<0.001

Standard error estimates by Peto formula.

8.3. 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 the rate of in-stent late loss at 6 months compared to the Control (**BX VELOCITY**, an uncoated 316L stainless steel stent). Clinical outcomes at 24 months 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 217 patients. IVUS follow-up (but without baseline studies) was obtained on 110 patients. Clinical follow-up is currently available through 2 years (± 1 month) in 90% 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 mm^3 vs. 34.3 mm^3, 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 < .001).

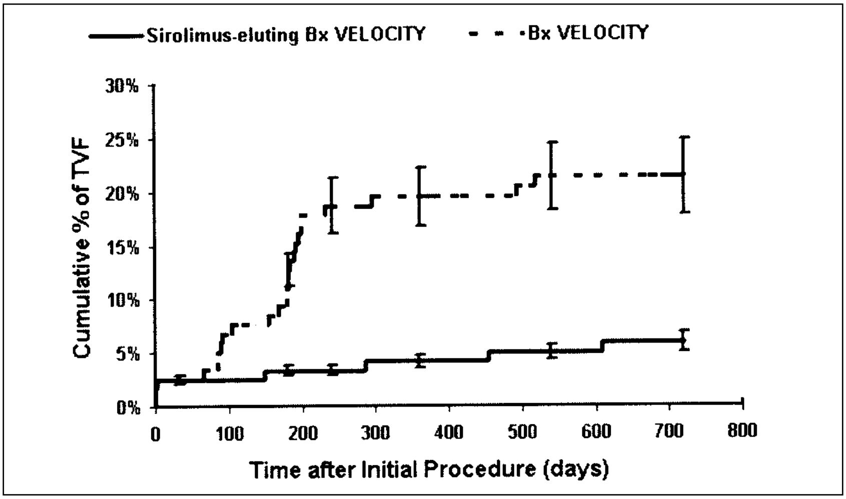
Table 8-3 summarizes the principal effectiveness and safety results of the RAVEL Trial to 720 days. Figure 8-2 provides the cumulative TVF rates to 720 days.

Table 8-3: RAVEL Principal Effectiveness and Safety Results (to 720 days)
All Patients Treated (N=238)

Effectiveness Measures	CYPHER Stent (N=120)	Control (N=118)	Difference [95% CI]	P-value
Procedure Success	96.7% (116/120)	93.1% (108/116)	3.6% [-2.1%, 9.2%]	0.248
Binary Restenosis Rate	0.0% (0/109)	26.6% (29/109)	-26.6% [-34.9%, -18.3%]	<0.001
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
6 month f/u 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
6 month f/u % 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
6 month f/u				
Late loss (mm)	-0.01 ± 0.33 (N=109)	0.80 ± 0.53 (N=108)	-0.81 [-0.93, -0.70]	<0.001
Volume obstruction in-stent (mm)	1.1 ± 2.5 (N=56)	26.1 ± 20.2 (N=54)	-25.0 [-30.3, -19.7]	<0.001
TLR-Free to 720 days*	97.4%	86.2%	11.2% [3.7%, 18.7%]	0.001
TVR-Free to 720 days*	96.6%	83.6%	13.0% [4.9%, 21.1%]	<0.001
TVF-Free to 720 days*	94.1%	78.7%	15.4% [6.2%, 24.6%]	<0.001
MACE-Free to 720 days*	89.9%	80.4%	9.5% [0.0%, 19.2%]	0.022
Safety Measures				
MACE in-Hospital	2.5% (3/120)	2.5% (3/118)	0.0% [-4.0%, 3.9%]	1.000
MACE out-of-Hospital to 720 days	7.5% (9/120)	17.8% (21/118)	-10.3% [-18.7%, -1.9%]	0.019
MACE to 720 days	10.0% (12/120)	19.5% (23/118)	-9.5% [-18.4%, -0.6%]	0.045
Sub-acute Occlusion	0.0% (0/120)	0.0% (0/118)	0.0% [—,—]	--
Stent Thrombosis	0.0% (0/120)	0.0% (0/118)	0.0% [—,—]	--
Late Thrombosis	0.0% (0/120)	0.0% (0/118)	0.0% [—,—]	--
CVA to 720 days	0.8% (1/120)	0.0% (0/118)	0.8% [-0.8%, 2.5%]	1.000
Major Bleeding Complications to 720 days	0.8% (1/120)	3.4% (4/118)	-2.6% [-6.2%, 1.1%]	0.211

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 device, attainment of < 30% diameter stenosis by angiographic corelab. Quantitative Coronary Angiography (QCA) determination, and freedom from in-hospital MACE.
% 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%.
* 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 720 days contact as determined by the independent Clinical Events Committee.
Late loss— Difference MLD after device— MLD at follow-up.
MACE – Major Adverse Cardiac Events: death, myocardial infarction (Q-wave and non Q-wave), target lesion CABG or target lesion revascularization.
Major Bleeding Events – Any intracranial bleeding, cardiac tamponade, bleeding events associated with a decrease in hemoglobin > 5.0 g/dL, transfusion or surgical repair.
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-acute occlusion – 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 subabrupt 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
CVA = Cerebrovascular Accident: Cerebral hemorrhage, thrombosis, or embolism leading to neurological deficit.

Figure 8-2
Kaplan-Meier Graph and Life Table to 720 Days
RAVEL Cumulative Percentage of Target Vessel Failure



Error Bars indicate ± 1.5 Standard Error
Standard Error based on the Peto formula

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

Interval ending day	0	2	7	30	60	120	180	240	300	360	420	480	540	600	660	720
Sirolimus-eluting Bx VELOCITY™ (N=120)																
# Entered	120	120	117	117	117	117	117	116	116	115	113	111	110	108	106	101
# Censored	0	0	0	0	0	0	0	0	0	2	2	0	2	2	4	21
# At risk	120	120	117	117	117	117	117	116	116	114	112	111	109	107	104	91
# Events	0	3	0	0	0	0	1	0	1	0	0	1	0	0	1	0
# Events / Month	0	45.0	0.0	0.0	0.0	0.0	0.5	0.0	0.5	0.0	0.0	0.5	0.0	0.0	0.5	0.0
% with Events	0.0	2.5	2.5	2.5	2.5	2.5	3.3	3.3	4.2	4.2	4.2	5.0	5.0	5.0	5.9	5.9
Std. Err. (%)	0.0	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.6
Bx VELOCITY™ (N=118)																
# Entered	118	118	115	115	115	115	109	105	96	93	92	88	88	85	85	85
# Censored	0	0	0	0	0	0	0	0	2	1	4	0	1	0	0	17
# At risk	118	118	115	115	115	115	109	105	95	93	90	88	88	85	85	77
# Events	0	3	0	0	0	6	4	9	1	0	0	0	2	0	0	0
# Events / Month	0	45.0	0.0	0.0	0.0	3.0	2.0	4.5	0.5	0.0	0.0	0.0	1.0	0.0	0.0	0.0
% with Events	0.0	2.5	2.5	2.5	2.5	7.6	11.0	18.6	19.5	19.5	19.5	19.5	21.3	21.3	21.3	21.3
Std. Err. (%)	0.0	0.2	0.2	0.2	0.2	0.7	1.0	1.7	1.8	1.8	1.9	1.9	2.1	2.1	2.1	2.3

Survival Curves Comparison

	Log-Rank P-value	Wilcoxon P-Value
Life-Table Analysis	<0. 001	<0. 001
Kaplan-Meier Analysis	<0. 001	<0. 001

Standard error estimates from Peto formula

8.4. 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, angiographic and clinical results through 24 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 and 24 months, or at 6 and 18 months, depending on the site. Angiographic follow-up is available for 24 patients, and IVUS follow-up is available for 15 patients. Clinical follow-up is available through 2 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 18 to 24 months following elective **CYPHER** Stent placement in native coronary *de novo* lesions, in-stent mean % diameter stenosis ranged from 1.4% to 3.2%, and mean in-stent late loss ranged from -0.09 mm to 0.20 mm. Mean obstructive volume by IVUS ranged from 2.3% to 7.5%. The overall MACE rate at 24 months was 10%.

Table 8-4: First-in-Man: Effectiveness and Safety Results
All Patients Treated with CYPHER Stent

Effectiveness Measures	CYPHER Stent (N=30 Patients, N=30 Lesions)
Procedure Success (QCA)	100.0% (30/30)
% Diameter Stenosis	
18 Months (The Netherlands)	3.2% ± 13.1% (10)
24 Months (Brazil)	1.4% ± 5.9% (14)
In-Stent Late Loss (mm)	
18 Months (The Netherlands)	0.20 ± 0.24 (10)
24 Months (Brazil)	-0.09 ± 0.24 (14)
Obstruction Volume (%)	
18 Months (The Netherlands)	2.3% ± 2.1% (7)
24 Months (Brazil)	7.5% ± 7.3% (8)
24-month Target Lesion Revascularization (TLR)	3.3% (1/30)
Safety Measures	
In-Hospital MACE Events	6.7% (2/30)
Out-of-Hospital MACE Events to 24 months	3.3% (1/30)
Combined (In and Out-of-Hospital) MACE to 24 months	10.0% (3/30)

Numbers are % (counts available 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 Corelab
MACE is a composite endpoint comprised of deaths, WHO-defined non Q-wave myocardial infarction, Q-wave myocardial infarction, or target lesion revascularization.

9. Individualization of Treatment

See also **Precautions– 5.5 Use in Special Populations** and **Precautions– 5.6 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.

10. Patient Counseling Information

Physicians should consider the following in counseling 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.

11. How Supplied

STERILE: This device 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).

12. Operator's Manual (Combined OTW and RX)

12.1. 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.

12.2. 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 device, carefully remove the system from the package and inspect it for bends, kinks, and other damage. Do not use the device if any damage to the packaging is noted.

12.3. 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 anti-platelet drugs

12.4. 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.

12.4.1. Rinse the catheter with sterile heparinized normal saline solution.

12.4.2. 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.

12.4.3. 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.

12.5. 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** – **5.14 Stent/System Removal Precautions** for specific stent delivery system removal instructions.

12.6. 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)**. 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** – **5.14 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.

12.7. 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 recrossed 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.

12.8. 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 – 5.14 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.

12.9. *In-vitro* Information

Table 12-1 Inflation Pressure Recommendations

Inflation Pressure atm (kPa)	2.50	2.75	3.00	3.50	
6 (608)	2.20	2.44	2.71	3.20	
7 (709)	2.27	2.51	2.78	3.27	
8 (811)	2.33	2.58	2.84	3.33	
9 (912)	2.39	2.64	2.90	3.39	
10 (1013)	2.45	2.70	2.95	3.45	
11 (1115)	2.50	2.75	3.00	3.50	**Nominal**
12 (1216)	2.55	2.80	3.05	3.55	
13 (1317)	2.59	2.84	3.09	3.60	
14 (1419)	2.62	2.88	3.13	3.64	
15 (1520)	2.66	2.92	3.16	3.69	
16 (1621)	2.69	2.95	3.19	3.73	**RBP**
17 (1723)	**2.71**	**2.98**	**3.22**	**3.76**	
18 (1824)	**2.73**	**3.00**	**3.24**	**3.79**	
19 (1925)	**2.74**	**3.02**	**3.25**	**3.82**	
20 (2026)	**2.75**	**3.03**	**3.27**	**3.85**	

Note: These nominal, *in vitro*, device specifications do not take into account lesion resistance. The stent sizing should be confirmed angiographically. Do not exceed the rated burst pressure (RBP). These data are based on *in vitro* testing at 37°C. Bolded text represents diameters at pressures above the rated burst pressure. These values are within ± 10% of the labeled diameter between the nominal pressure and the rated burst pressure.

13. Patient Information

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

- A Patient Implant Card that includes both patient and **CYPHER** Sirolimus-eluting Coronary 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** Sirolimus-eluting Coronary Stent System.

14. 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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