

Questions for Discussion

Circulatory System Devices Panel

CYPHER™ Sirolimus-Eluting Coronary Stent System P020026

October 22, 2002

Evaluation of Safety and Effectiveness

The sponsor has conducted a multi-center, double-blinded, randomized, clinical investigation, referred to as the SIRIUS Trial (N = 1101 at 53 sites; 43 subjects “deregistered”) with the CYPHER™ Sirolimus-Eluting Coronary Stent System (CSS) in the following patient population:

patients with *de novo* native coronary artery lesions \geq 15mm and \leq 30mm in length and \geq 2.5mm and \leq 3.5mm in diameter (by visual estimate).

The only stent sizes available for implantation in the SIRIUS study were the 2.5mm, 3.0mm and 3.5mm diameter stents in lengths of 8mm and 18mm, which meant that the nominal drug dosage per stent ranged from 71?g to 175?g. The average vessel diameter in the study was 2.8mm \pm 0.5mm and the average lesion length was 14mm \pm 6mm. The control (uncoated Bx Velocity stent) device is approved for use in *de novo* lesions with diameters \geq 3.0mm to \leq 5.0mm. Because the control stent is not approved for *de novo* stenosis in vessels of diameter less than 3.0 mm, the applicant provided additional analyses for small vessels, including a Bayesian comparison to historical angioplasty data.

For this PMA application, the sponsor is requesting approval for use in the following patient population with the stent sizes designated in Table 1:

patients with *de novo* native coronary artery lesions (length \leq 30mm) and reference vessel diameters ranging from 2.25mm to 5.0mm.

Table 1: Proposed CYPHER™ Sirolimus-Eluting CSS Product Matrix & Nominal Drug Dosages

Stent Diameter (mm)	Stent Length											
	8mm		13mm		18mm		23mm		28mm		33mm	
2.25	X	71?g	X	111?g	X	150?g	X	190?g	X*	229?g	X*	268?g
2.5	X	71?g	X	111?g	X	150?g	X	190?g	X	229?g	X	268?g
2.75	X	71?g	X	111?g	X	150?g	X	190?g	X	229?g	X	268?g
3.0	X	71?g	X	111?g	X	150?g	X	190?g	X	229?g	X	268?g
3.5	X	83?g	X	129?g	X	175?g	X	221?g	X	268?g	X	314?g
4.0	X	83?g	X	129?g	X	175?g	X	221?g	X	268?g	X	314?g
4.5	X	105?g	X	164?g	X	223?g	X	281?g	X	340?g	X	399?g
5.0			X	164?g	X	223?g	X	281?g	X	340?g	X	399?g

Note: The device sizes used in the SIRIUS Trial included only the 2.5, 3.0 and 3.5mm diameter stents in lengths of 8 and 18mm.

* Only OTW version available in these stent sizes

Safety

The safety endpoints evaluated in the SIRIUS study included:

Safety endpoint	Cypher™ Product	Bx VELOCITY™ Stent
MACE to 270 days	7.1% (38/533)	18.9% (99/525)
Stent thrombosis to 30 days	0.2% (1/533)	0.2% (1/525)
Late thrombosis to 270 days	0.2% (1/533)	0.6% (3/525)

1. Do the data submitted on the Cypher™ product provide adequate assurance of safety?

The sponsor has requested approval for a range of stent diameters and lengths that corresponds to a nominal drug dosage as high as 399µg. The animal studies conducted by the sponsor on dosages higher than 180µg were limited to 30-day follow-up. The SIRIUS study only evaluated 15 subjects who received stents with a total nominal drug dosage greater than 350µg.

2a. Given the limited preclinical and clinical information outlined above, please comment on whether there is adequate evidence to support the use of stent diameters and lengths (i.e., 4.5 mm and 5.0 mm diameter with a 33 mm length) with a nominal drug dosage greater than 350µg.

2b. If not, what additional studies or information would be necessary to support the safety of stents with a nominal drug dosage greater than 350µg?

Additionally, the nominal amount of total polymer ranges from 208?g to 1,184?g for the currently requested range of stent sizes. The animal studies conducted by the sponsor on polymer dosages higher than 500?g were limited to 28-day follow-up. The nominal total polymer amounts tested in the SIRIUS study ranged from 208?g to 520?g.

2c. Please comment on whether there is adequate evidence to support the use of stent diameters and lengths (i.e., 6-cell and 7-cell stents in lengths of 23, 28 and 33 mm and 9-cell stents in lengths of 18, 23, 28, and 33mm) with a nominal polymer dosage greater than 520µg.

2d. If not, what additional studies or information would be necessary to support the safety of stents with a nominal polymer dosage greater than 520µg?

In the SIRIUS study, the Cypher™ group had a 19% rate of incomplete apposition at follow-up versus 9% for the control. This included a 10% rate of late incomplete apposition for Cypher™ versus 0% for the control. In the RAVEL study, the rate of late incomplete apposition was 21% versus 4% for the control.

There was no obvious clinical correlation between late appositions and adverse events.

3a. Please comment on whether additional information is necessary to evaluate the significance of the late stent malapposition found in the clinical studies?

3b. Is there any specific targeted follow-up, additional clinical investigations, animal studies, or bench testing that should be requested to contribute important information regarding this clinical finding?

In the RAVEL study, subjects received ASA for 6 months and clopidogrel or ticlopidine for 2 months. In the SIRIUS study, subjects received ASA for 9 months and clopidogrel or ticlopidine for 3 months.

4. Please discuss your recommendations for the antiplatelet therapy for patients receiving the Cypher™ product.

The potential for interactions with several drugs has been evaluated as described in the Rapamune labeling. Interactions with other drugs might be expected based on known metabolism by CYP3A4.

5a. Please comment on whether the application adequately addresses drug interactions that are likely to be important or of interest. If not, what other information or studies should be requested?

5b. Has follow-up been adequate to address concerns about possible systemic adverse drug effects?

Effectiveness

The primary effectiveness endpoint for the SIRIUS study was target vessel failure (TVF) at 9 months (270 days). Rates of TVF at 270 days were 8.6% (436/533) for the Cypher™ group and 21.0% (110/525) for the Bx VELOCITY group.

6. Does the evidence presented on the Cypher™ product provide reasonable assurance of effectiveness at 270 days?

Prolonged inflammation and notably increased restenosis were observed when polymer-coated, but drug-free, stents were implanted in swine. In swine implanted with Cypher product™ (i.e., coated with both drug and polymer), this effect was not observed at one month post-implant, but was observed at both three and six months post-implant.

7. Given the unparallel timelines of healing between juvenile normal pigs and atherosclerotic older patients, do these findings raise significant concerns about the ability of the clinical follow-up to address the possibility of a similar delayed occurrence of neointimal hyperplasia? If so, please comment on whether additional testing or follow-up (pre- or post-approval) is necessary to support the effectiveness of the Cypher™ product.

The temporal relationship between scheduled angiography and revascularization, and analysis of the subgroup that did not have angiography, suggest that angiographic outcomes may have influenced the clinical outcomes in a way that differentially affected the control group.

8. Please comment on the adequacy of the primary endpoint (9-month TVF) for capturing the expected clinical benefit of the Cypher™ product, in light of the possible influence of 8-month angiography results. Are there other ways the clinical impact should be assessed, either for a) evaluation of efficacy in determining the appropriate indication, or b) for information to be conveyed in labeling?

Because the control stent is not approved for *de novo* stenosis in vessels of diameter less than 3.0 mm, the applicant provided additional analyses, including a Bayesian comparison to historical angioplasty data.

9. Please comment on adequate evidence has been presented to demonstrate effectiveness for stents with diameters less than 3.0 mm?

Univariate regression analyses of data collected in the SIRIUS study suggest that the treatment effect may be reduced in longer length lesions. This could be due to either a true diminished treatment effect or a lack of power (too few subjects) to detect a treatment difference in subjects with longer lesions. The sponsor has performed logistic regression analyses, but these analyses only included main effects and did not specifically evaluate the possible interaction between each variable (in this case, lesion length) and the treatment effect (i.e., an analysis of treatment effect by covariate interaction).

10a. Do the data presented provide reasonable assurance of effectiveness for treatment of the full requested range of vessel lengths (= 30 mm)?

- 10b. The protocol for the SIRIUS study specifies the inclusion of subjects with reference vessel diameters of 2.5 mm to 3.5 mm. The proposed indications for use include reference vessel diameters of 2.25 mm as well. Do the data presented provide reasonable assurance of effectiveness for vessel diameters of 2.25 mm?**

Product Labeling

One aspect of the pre-market evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize benefits and minimize adverse effects. Please address the following questions regarding the product labeling (Section 4).

- 11a. Please comment on the INDICATIONS FOR USE section as to whether it identifies the appropriate patient populations for treatment with this device.**
- i. Has the application provided reasonable assurance of efficacy for treating the full requested range of vessel diameters (2.5 mm to 5.0 mm)? If not the full requested range, what range of vessel diameters should be included?**
 - ii. What length of lesions should be included in the indications for use?**
- 11b. Please comment on the CONTRAINDICATIONS section as to whether there are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit.**
- 11c. Please comment on the WARNING/PRECAUTIONS section as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events. Specifically, please comment on whether a warning or precaution related to subsequent brachytherapy should be included in this section.**
- 11d. Please comment on the OPERATOR'S INSTRUCTIONS as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.**
- 11e. Please comment on what aspects of drug pharmacology, mechanism of action, pharmacokinetics, drug interactions, or systemic effects should be added to the labeling to maximize benefits and minimize adverse events.**
- 11f. Please comment on the remainder of the device labeling as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.**

Post-Market Evaluation

The Panel Package includes the available 9-month data for the Cypher™ product in the SIRIUS Study (Section 5.3.1) and (Section 5.3.2). In addition, the available 12-month data were provided from the RAVEL Study (Section 5.3.3) and the available 18- to 24-month data from the First-in-Man Feasibility Study (Section 5.3.4) were provided. The sponsor has proposed continued follow-up (to 5 years) on subjects from the SIRIUS study, the RAVEL study and the FIM study. The sponsor has also proposed to collect data through one year on approximately 1000-2000 patients implanted with the marketed product, using an electronic database.

- 12a. Please discuss long term adverse effects that may be associated with implantation of the Cypher™ product including late thrombosis formation, aneurysm formation, MI, and late stent malapposition.**

12b. Based on the clinical data provided in the Panel Package, do you believe that additional follow-up as proposed by the sponsor is appropriate to evaluate the chronic effects of the implantation of the Cypher™ product. If not, what additional follow-up information should be collected? Specifically, how long should patients be followed and what endpoints and adverse events should be measured?