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By Lynne Peterson

SUMMARY

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Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
561-334-7409 Fax 561-334-0856
www.trends-in-medicine.com

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Boston Scientific's Taxus drug-eluting stent stole the show at TCT this year. The data was so surprisingly good, that doctors talked about little else. However, questions were raised about how the results were computed (*See page 6*).

Johnson & Johnson's sirolimus-eluting Cypher stent was the first drug-eluting stent on the market, and it still has 100% of the U.S. market, which was estimated to be about 60% penetrated in August 2003. J&J announced that U.S. supply problems are over, but doctors at the meeting said they are continuing to see inventory shortages.

However, competitors are getting closer. Boston Scientific's paclitaxel-eluting Taxus stent is already on the European market, where it probably has captured about half the market. Boston Scientific claims Taxus has 67% of the European market, and J&J claims to have 65% market share in Europe (as well as 55% share in Canada/Asia-Pacific/Latin America, for an overall non-U.S. share of 60%). Thus, someone obviously is over-estimating, suggesting that the market may be more evenly split than either company wants to admit.

European adoption of drug-eluting stents has been slow. European penetration was estimated at 15%-20% in August, with a monthly growth rate of about 1%. One of the hold-ups in Europe has been lack of reimbursement in France, but on September 25, 2003, the French Ministry of Health granted private sector (which J&J estimates is 50% of the French market) reimbursement at a rate of 2000 euros, effective immediately. The French decision applies only to Cypher, not to Taxus, which reportedly filed about a year after J&J for its coverage approval. Public sector coverage in France is left up to hospitals because the cost of drug-eluting stents comes out of their budgets.

The Taxus stent is expected to be on the U.S. market in early 2004. If J&J's experience is any guide, Boston Scientific may have a tougher and longer regulatory path than it expects. One of the reasons for the long review of Cypher was CDER's insistence on the drug dose per stent staying in the 80%-110% range required for pills. A J&J official said his company had to destroy "lots and lots" of Cyphers with 79% sirolimus. Sources all agreed that stent use will increase in both Europe and the U.S. One expert predicted, "I think you'll see 80% use (in the U.S.) in the next six to nine months." Doctors questioned at TCT estimated that about 45% of their stents are Cyphers. Some said the percentage was low because of deliberate patient selection, but others blamed supply/availability

problems. A Michigan doctor said, "We're using 50% drug-eluting stents now, and that will go up to at least 70% in a year."

Over the next year, three-quarters of sources predicted that stent usage would increase substantially. Many sources said drug-eluting stents would account for 70% or more of their stents by the end of 2004.

Boston Scientific expects to be able to meet any and all demand for Taxus when it is approved. The company does not anticipate any supply problems. An official said, "We have stent capacity in an unconstrained way around the world, and we are gearing up to do the same in the U.S." Boston Scientific also is gearing up for a major sales campaign. It is hiring another 1,200 sales reps, and has been training existing staff for 19 months, so it really should be ready when Taxus is approved.

Medtronic's everolimus-eluting Endeavor stent may get FDA approval in late 2005, and Guidant likely to have its own everolimus-eluting stent on the U.S. in 2006. An FDA official said that the Cypher experience added to the agency's knowledge base, but he noted that it is not making the process quicker for Boston Scientific, particularly on the CDER side. That is, he indicated Boston's submission is not having an easier time of it than Johnson & Johnson's did.

Medtronic may be the come-from-behind horse in this race. Early results with Endeavor look good, and the pivotal U.S. trial is scheduled to get underway soon. Importantly, Endeavor utilizes Medtronic's new chromium cobalt Driver stent, which was recently launched in Europe as a bare stent and is selling well there. Guidant has four everolimus-eluting programs ongoing that could lead to a marketable drug-eluting stent by late 2005, but the oulook is more likely 2006.

Below is a chart with the key findings of the drug-eluting stent trials. Remember that these are very different trials, with different sizes, different angiographic follow-up, different patient populations, etc.

While technical questions were raised about the data in all of these trials – and the TAXUS-IV trial in particular -- doctors generally found the data persuasive that paclitaxel is safe and effective. They also indicated the data was strongly suggestive of the efficacy/safety of the "limus" analogs, everolimus and ABT-578. The question of the future for physicians will be how to choose among the drug-eluting stents. A Taxus investigator said, "Physician will weigh the data and make up their own minds…Most physicians find Taxus somewhat more flexible and easier to deliver than the BX Velocity; there is not much doubt about that." Another interventional cardiologist said, "Price will drive the choice for many doctors and hospitals." Another doctor said he planned to "match stents to individual patients…I believe competition is healthy…and it makes for a better product. I think at this meeting you will find that there are whole new dimensions to improving these products…We will be strong advocates for promoting that competition."

Doctors questioned at TCT predicted the switchover from Cypher to Taxus would be quick and dramatic. If Taxus is priced comparable to Taxus 48% market share within a couple of months. Almost half the sources said they would switch to 100% Taxus stents, but a few said they would stay 100% with Cypher until there is more real-world experience with Taxus. The others generally plan to use Taxus for the majority of cases, but will continue to use some Cyphers as well. The reasons doctors cited for their plans to shift from Cypher to Taxus: better ease of use and deliverability of Taxus, continuing availability issues with Cypher, and animosity toward Johnson & Johnson. A Michigan doctor said, "A lot of us will switch to Taxus because of its ease of use." An Ohio doctor said, "Boston Scientific's strength is balloons and catheters, and I expect them to bundle those with the Taxus stents. We expect to go to 65% Taxus stents." A Florida doctor said, "I expect we'll use 65% Taxus. It has better deliverability – and there is huge animosity toward J&J."

However, if Boston Scientific makes special deals that effectively make the Taxus price substantially less than Cypher – as doctors expect the company to do – then they predicted Taxus would take 68% market share within a couple of

Measurement	Johnson & Johnson's SIRIUS	Boston Scientific's TAXUS-IV	Medtronic's ENDEAVOR-I	Guidant's FUTURE II
Stent	Cypher	Taxus	Endeavor	Challenger
Drug-eluting stent patients	533	662	100	21
Late loss (in-stent)	0.17 mm	0.39 mm	0.33 mm	0.12 mm
Restenosis in-segment (drug vs. control)	8.9% vs. 36.3%	7.9% vs. 26.6%	2.1%	0% vs. 19.4%
Restenosis in-stent (drug vs. control)	3.2% vs. 42.3%	5.5% vs. 24.4%		0
TLR (drug vs. control)	4.1%	3.0% vs. 11.3%	1.0%	4.8%
TVR (drug vs. control)	6.4% vs. 19.2%	4.7% vs. 12.0%	N/A	----
MACE	7.1%	8.5%	2.0%	4.8%

months. But J&J isn't likely to let Taxus take market share on price alone. A J&J official indicated J&J plans to fight to hold its customers. A New York doctor said, "We'll probably switch 100% to Taxus, unless we get a better deal form J&J." A Connecticut doctor said, "We'll probably stay 100% with Cypher because we have experience with that, but we will go for whoever gives us (the best) volume discount."

However, doctors pointed out all of their usage plans are likely to be affected by pricing. Given the high cost of drug-eluting stents, price will have a huge impact on purchase decisions. Even if the base prices of Cypher and Taxus are similar, doctors pointed out that contracts, volume discounts, bundling and special deals may make one or the other less expensive for a particular hospital, and thus may determine the choice between Cypher and Taxus.

Sources do not expect Boston Scientific to price Taxus much, if anything, lower than Cypher, but they do expect both companies to be offering "deals" and "bundling" drug-eluting stents with other products. There was even a rumor that J&J would bundle Procrit (epoetin alpha) with stents, but that could not be confirmed.

A survey by **TheHeart.org** after the meeting asked: When it becomes available would you prefer to use the paclitaxel-eluting Express^2 stent over the sirolimus-eluting Cypher stent? A majority — 74% — of poll respondents said, "Yes."

According to one analysis, the cost of drug-eluting stents to a hospital doing an average of 1,500 CABGs and 2,000 PCIs annually: a loss of $22.49 million from 2003 through 2007. The analysis was based on the Cypher price before the recent price rollback.

On average, 1.5 stents per patient are being used, according to a study by Ernst & Young (commissioned by J&J) of 119 hospitals. A J&J official said, "This has not changed appreciably…There has been no dramatic change even though everyone expects it may change." A doctor at a high volume lab said the average at his hospital is 1.8-1.9 drug-eluting stents per patient, and slightly higher than that – about 1.95 stents per patient – overall. He said, "Overall, we are still below 2.0. My sense is that the total number will go up slightly."

Doctors questioned at TCT estimated that they are using, on average, 1.4 bare stents per patient and 1.2 Cyphers. Most sources predicted those ratios would remain fairly constant – because they are making a concerted effort to keep them from rising. A New York doctor said, "We are trying to preferentially put drug-eluting stents in small vessels and control the number we use because we lose money when we use more than 1.5 per-patient." A California doctor said, "Personally, I avoid drug-eluting stents because of the cost, so we use about 1.25 drug-eluting stents per patient. We try to keep it under 1.3 because that's all reimbursement covers."

The most commonly used bare stents, by these doctors, are Guidant's Zeta, followed by Boston Scientific's Express stent. A few are using a mix of several stents, and one is using a lot of Medtronic S-stents. Doctors like Guidant's Vision stent, but the price (~$1,500) has caused them to restrict its use. An Ohio doctor said, "We have Vision available, and it is very good, but it is overpriced. It is kept in a different closet for use only when nothing else works." A New York doctor said, "We plan to start using Vision, but our use will be limited by the cost."

Bare and drug-eluting stents generally are not mixed and matched unless it become necessary due to (1) anatomy, (2) deliverability, (3) availability or (4) cost. A source estimated that about 20% of patients around the U.S. might fall into one of the first three categories. A California doctor said, "I mix and match – but not in the same vessel."

How Experts at a Boston Scientific-Sponsored Session Would Choose

Lesion/patients	Best Stent	Rationale
De novo focal lesions >3.5 mm	Bare metal stent	Can't beat the $400 price, and TLR <5%
Straightforward 2.5-3.5 mm vessel	Taxus or Cypher	Similar outcomes
Diabetics	Taxus	Lower restenosis
Tortuous approach	Taxus	More deliverable
ISR	?brachytherapy	For now, brachytherapy probably will be supplanted by drug-eluting stents
SVG	Taxus or Cypher	Extrapolating for native vessel results
Bifurcations	Taxus or Cypher	Neither is ideal. A dedicated stent is needed
Small vessels and longer lesions	Taxus	Data
Large, bulky vessels	Cypher	Closed-cell stent may be better for scaffolding

An expert offered these tips for use of drug-eluting stents:

- **Pre-dilatation.**
- **Stent selection and deployment**. He said, "Stent length sizing is critical, and longer is better."
- **Post-dilatation.** He advised, "Always use a balloon shorter than the stent."
- **Antithrombotics.** He said, "The choice of regimen is very controversial. We are shifting up to a 600 mg loading dose of Plavix (Sanofi, clopidogrel). Give Plavix at least six hours before (PCI). The current trend is prolonged clopidogrel (up to one year)."
- **IVUS** is helpful, particularly in the most difficult patients, but it isn't needed in all drug-eluting stent cases.

Another question is whether to use drug-eluting stents for all patients or only select patients. In Europe, the decision generally has been only select patients. In the U.S. supply limitations have caused many hospitals to put off this decision.

A TCT debate laid out the two arguments:

- **Pro selective use.** A speaker called it prudent to adopt a thoughtful and lesion-specific approach, "Why the enthusiasm? Are we saving lives? There is no difference in death in (any of the Cypher trials)…The difference is in revascularization, but death is worse than revascularization…In our hospital we use Cypher for 43% of cases, but we've see a 200% increase in cath lab costs."
- **Pro universal use.** A speaker said the evidence supports universal use – if not now, soon. He noted, "Drug-eluting stents are safe…and effective…The benefits are durable…The data is here – or on the way – and it is much more impressive than the IIb/IIIa data…The issue isn't data; it's all money. It is entirely an economic issue. Once drug-eluting stents are deemed affordable, they will be used in essentially all situations where bare metal stents are used today – band beyond." However, he admitted that the use of drug-eluting stents is not yet justified in SVG, unprotected left main, ISR, branches of bifurcations, AMI and thrombus-containing lesions.

Following is a detailed look at the some of the major drug-eluting stent programs.

ABBOTT LABORATORIES' ABT-578

Abbott chose the 10 µg dose of ABT-578 for its drug-eluting stent program, and an investigator explained that this was chosen based on animal tests. A speaker reviewed the first-in-man PREFER trial with the BiodivYsio stent, which has a phosphorylcholine coating:

- The coating does not retard endothelialization; at five days, there is 91% coverage of the stent.
- PREFER was to be a 50-patient study, but the trial was stopped after only 11 subjects for "internal company reasons" – described as laboratory errors. There were no aneurysms, no SAT and no malapposition.

PREFER Results at 90 Days

Measurement	Results
Non-q wave MI	One patient
Death	0
TLR	0
% neointimal volume by IVUS	2.6%
Restenosis	0

BIOSENSORS' Biolimus A9

After selling its everolimus-eluting, bioerodable stent to Guidant, Biosensors continued working on drug-eluting stents with an everolimus analog that used to be called everolimus-plus and is now called biolimus. A speaker said, "Biolimus is highly lipophilic. It is a small molecule with a weight similar to sirolimus, but it elutes from resorbable polymers more rapidly than sirolimus – 85% in eight hours compared to 66% in eight hours with sirolimus -- and it stays resident in tissue for a very, very long time."

The Biolimus program uses the company's S-stent coated asymmetrically with a biodegradable PLA polymer. Reportedly, more than 50% of the coating, by weight, is drug.

In a study of nine pigs, there was no late loss at 28 days. Recruitment for a Phase I human trial, STEALTH-1 has begun. This is a 100-patient, multi-center, single-arm, single-dose safety trial in de novo lesions <24 mm, with a diameter of 2.75-4.0 mm, comparing the A9 to historical control. The primary endpoint is late loss vs. the bare meal S-stent. Data is expected at EuroPCR in May 2004. A Biosensors official said the company plans to see if the FDA will accept this trial as the pilot so that the company next could move to an IDE for a pivotal U.S. trial. He added, "Cypher isn't the last word on the 'limus' class."

BOSTON SCIENTIFIC

Boston Scientific executives were ecstatic with the results of TAXUS-IV. CFO Larry Best said, "We hit every element of our wish list…The results are even beyond our expectations." Boston Scientific Vice President for Cardiovascular Affairs (and TAXUS chief) Dr. Mary Russell said, "TAXUS-IV rocks and rolls…We leveled the playing field and paved the way…for a totally new arena in the treatment of restenosis." Dr. Jeff Popma of Brigham & Women's Hospital, which was the core lab, said, "TAXUS-IV is a home run." Another expert said, "We thought TAXUS-IV would be slightly worse than Cypher, and it actually appears slightly better."

The pivotal TAXUS-IV trial reported:

- Binary restenosis of 7.9% in-segment and 5.5% in-stent, compared to a restenosis rate of 3.2% in-stent and 8.9% in-segment in SIRIUS.
- The primary endpoint, TVR, was met -- 4.7% vs. 12.0% for control.
- TVF of 7.6% vs. 14.4% in control.
- An apparently stronger benefit in diabetics than Cypher.
- No edge effect, as occurred with Cypher in the SIRIUS trial.

TAXUS-IV was a well-blinded, prospective randomized trial of the slow-rate release, polymer-based, paclitaxel-eluting Taxus stent (Express^2 coated with 1 μg/mm^2 paclitaxel) in 1,314 patients at 73 U.S. sites. Co-principal investigator Dr. Greg Stone of Lenox Hill Hospital concluded Taxus:

(1) Is safe, with no increased risks of stent thrombosis.

(2) Markedly reduces clinical restenosis, resulting in reduced rates of bypass graft surgery and repeat percutaneous intervention.

(3) Is effective in a wide range of complex patients and lesions, including small vessels, long lesions, and patients with diabetes.

Safety also was good. Dr. Stone said, "There were no aneurysms, and malapposition was even less than in control…This is a major step forward in the field in that the results are certainly as good as Cypher, and, with a more deliverable stent, it will be a highly desirable stent in the marketplace. It is an alternative, and that is always good for patient care."

9-Month TAXUS-IV Angiographic Results

Measurement	Control	TAXUS	p-value
Angiographic Follow-up	267	292	---
Restenosis			
Restenosis: in-stent	24.4%	5.5%	p<.0001
Restenosis: in-segment	26.6%	7.9%	p<.0001
Restenosis by Subgroups			
No diabetes	24.4%	8.5%	p<.001
Diabetics (oral meds)	29.7%	5.8%	p=.003
Diabetics (insulin)	42.9%	7.7%	p=.007
Lesions <10 mm	18.9%	5.6%	p=.01
Lesions 10-20 mm	25.8%	7.2%	p<.0001
Lesions >20 mm	41.5%	14.9%	p=.004
Late Loss			
In-segment	0.61 mm	0.23 mm	p<.0001
Proximal edge	0.27 mm	0.15 mm	p<.0001
In-stent	0.92 mm	0.39 mm	p<.0001
Distal edge	0.17 mm	0.05 mm	p<.0007

9-Month TAXUS-IV Clinical Results

Measurement	Control	TAXUS	p-value
Number of patients	652	662	---
# of stents implanted	1.09	1.08	---
TLR and TVR			
TLR	11.3%	3.0% (73% reduction)	p<.0001
TLR-PCI	8.7%	2.4%	p<.0001
TLR-CABG	3.1%	0.6%	p<.0008
Primary Endpoint: TVR	12.0%	4.7%	p<.0001
TVR (non-TLR)	1.1%	1.7%	p=.48
TVR-CABG	3.4%	1.1%	p=.005
TVR-PCI	9.0%	3.6%	p=.0001
TVF	14.4%	7.6%	p=.0001
9-Month MACE			
Cardiac death	1.1%	1.4%	Nss
MI	3.7%	3.5%	Nss
MACE	15.0%	8.5%	p=.0002
Thrombosis (SAT)	0.8%	0.6%	Nss
TLR by Subgroups			
Diabetics (oral meds)	17.4%	4.8%	p=.004
Diabetics (insulin)	13.05	5.9%	Nss
Lesions <10 mm	9.3%	3.3%	p=.01
Lesions 10-20 mm	10.5%	2.8%	p=.0001
Lesions >20 mm	18.6%	3.3%	p=.0009
Restenosis: in-stent	24.4%	5.5%	p<.0001
Restenosis: in-segment	26.6%	7.9%	p<.0001
Short stents	9.2%	3.5%	p<.05
32 mm stents	17.9%	2.6%	p<.05
Single stent	10.9%	3.0%	p<.05
Multiple stents (84 patients)	20.5%	0	p=.001

Johnson & Johnson has sued Boston Scientific for patent infringement, and is seeking an injunction to prevent Taxus from coming to market. A ruling from federal judge Sue Robinson in Wilmington, DE, could come any day.

J&J has about two years left on the so-called '762 patent, which is already licensed to the other major stent manufacturers -- Guidant, Medtronic, Abbott Laboratories and Cook. But J&J doesn't want to license it to Boston Scientific unless it can't get an injunction – and then the royalty fee could be punitively high.

But injunctions before trial are extraordinary remedies. Most experts thought an injunction was a long-shot even before the TAXUS-IV data was released, but in August 2003 an appellate court ruling gave support to the J&J position. To gain an injunction, J&J reportedly must show that:

1. Taxus will do irreparable harm to J&J.
2. A pretrial injunction wouldn't weigh unduly on Boston.
3. The public's interest would be served.
4. J&J would ultimately win its patent claim at trial. And this is the most important.

Taxus performance in diabetics may make an injunction impossible because keeping Taxus off the market might be construed as against the public interest. Yet, the number of diabetic patients in both TAXUS-IV and SIRIUS were small. A Boston Scientific official said, "It is erroneous to draw conclusions...The sample size is too small to draw significant conclusions…There is a nice feasibility trend, but we need more data…but the trends look quite compelling, so I would have to speculate that there may be differences in the insulin-dependent signaling pathways where paclitaxel has the ability to block those, where the more selective pathways interrupted by rapamycin would not be interrupted. More basic science looking at the pathways is needed to decipher if there is much

underlying this." Another Boston Scientific official said, "If there is a sustainable benefit for a device that treats diabetics differently, I think it will have a significant advantage and, like the positive edge effect, I can't say if it is a property of diffusion...but it will carry considerable weight. The one drug that is fundamentally different in its mechanism of action appears to be potentially separating itself in that regard."

TAXUS-IV IVUS Results at 9-Months

Measurement	Control n=87	Taxus n=91
Vessel area	286	288
Stent area	147	150
Lumen area	106	131
Neointimal volume	41	18
% in-stent net volume obstruction	29.4%	12.2% (p<.001)
Aneurysms		
Post-procedure	0.6%	1.3%
9-month follow-up	0.7%	0.7%
Resolved	0.4%	1.0%
Persistent	0.4%	0.7%
Late acquired	0.4%	0
Incomplete Apposition		
Post-procedure	6.4%	11.6%
9-month follow-up	3.0%	4.0%
Resolved	5.4%	6.4%
Persistent	1.1%	3.2%
Late acquired	2.2%	1.1%

* IVUS was conducted on 178 of 268 patients from pre-selected sites, where all patients were mandated to undergo IVUS.

Lack of Confounders in TAXUS-IV

Measurement	Control	Taxus
Non-study bare metal	0	0
No study stent placed	0	2 patients
Gap stenosis	0	0
Non-restenotic TLR	3 patients	1 patient
Edge stenosis	2 patients	3 patients
Total	5 patients	6 patients

Protocol change

The original protocol for TAXUS-IV called for nine-month angiographic follow-up on the first 500 patients. However, **the protocol was changed during the trial** to include QCA on another 232 patients who got the longest (32 mm) stent, for a total of 732 patients. Researchers reported on nine-month QCA follow-up of 569 patients.

TAXUS-IV originally was planned to include 1,174 patients, but another 152 were added to include more 32-mm stents, so the trial had 1,326 patients, and 12 of these never were randomized, giving a trial total of 1,314 patients. Dr. Stone offered this explanation, "1,172 patients would give 85% power to show a 40% relative reduction in TVR…but we guaranteed 216 patients stratified to small vessels and 216 with 32-mm stents…It turned out the 32-mm stents didn't become available until the latter part of the trial, so we expanded the trial to 1,326 patients per protocol to be sure we got the 216 32-mm stents." There were 536 pre-specified patients for whom angiography was intended, and there was follow-up on 432 (82.5%) of these. Another 196 patients with 32-mm stents were added to the prospective analysis, and 117 (59.7%) of these had angiography. This should lessen some concerns with the change in protocol."

Among the questions raised by this protocol change are:

- **Lack of FDA approval for the protocol change.** Reportedly, the FDA was not consulted about the protocol change. An FDA official called this "problematic" and said this means the company will have to submit a per-protocol analysis as well, and the agency's focus would be on the per-protocol analysis. It is unclear what the results were in the per-protocol analysis since that was not presented.
- **Timing**. A Boston Scientific official said the decision to add the extra 32-mm patients to the angiography group had nothing to do with early results from SIRIUS, "We finished enrollment on June 1, and then finished 32-mm enrollment on July 3rd, and the Cypher results had nothing to do with how the investigators performed, in my opinion. We were all over the investigators on our criteria…I don't think there was much of a learning curve from SIRIUS." However, some SIRIUS data -- a preliminary analysis of the 8-month angiographic and IVUS results of SIRIUS plus 9-month clinical results from the first 400 of the 1,101 SIRIUS patients – was presented in May 2003 at EuroPCR.
- **Impact of adding longer stents.** An investigator said, "We did an analysis that will be shown looking at stent-to-lesion length ratio to see if that made a difference, and we couldn't show a strong relationship there."

Analysis of TAXUS-IV Protocol Change

Measurement	Original Protocol	Patients Added (32 mm stents)	Total
Number of patients in trial	1,172	154	1,326-12 non-registered = 1,314
QCA pool	First 500 patients	232	732
Adjusted QCA pool	536	196	732
Actual QCA follow-up	442 (82.5% of 536 pool; 37.6% of protocol)	117 (59.7% of 196 pool)	559 (42.5% of 1,314, 76.4% of 732 pool)
TVR	Not Computed	---	4.7%

➢ **Percent of patients undergoing angiography.** Far fewer patients underwent angiographic follow-up in TAXUS-IV than in SIRIUS. Experts speculated that this lowered the restenosis rate because angiography itself is known to increase the restenosis rate by (a) finding things that clinical follow-up do not and (b) causing some injury itself. An expert said, "How the FDA will interpret this is uncertain. The agency will be very concerned that there was only ~40% angiographic follow-up when SIRIUS had close to 70% angiographic follow-up." Another expert said, "The strongest predictor of events is the percentage of patients who get angiographic follow-up because they have a much higher frequency of intervention on the lesion. So, the low TVR (in TAXUS-IV) was driven by the very low angiographic follow-up, which was by design."

Boston Scientific rebutted this argument with a subset analysis comparing TVR and TLR in patients who underwent angiography to all Taxus patients.

Other Taxus issues

A number of other questions have been raised about the TAXUS-IV results, including:

➢ **Late Loss.** In-stent late loss was significantly higher in TAXUS-IV than SIRIUS – 0.39 mm vs. 0.17 mm, and there was a large standard deviation (0.5). Boston Scientific officials defended the late loss, suggesting that the company's internal studies indicate that the probability of restenosis or TLR is minimal with a late loss of <0.6 mm. One Boston Scientific official explained, "Late loss is a weak predictor of TLR…I don't know what late loss means…I'm very interested in learning what it means…We are doing a lot of late loss analysis unknown to the rest of the community to see what it looks like in different quartiles, and what is the optimal amount of late loss…We are happy with the late loss we've had. There is no clinical indication of a disadvantage of late loss of 0.3 to 0.4, and we are actively studying this in TAXUS-II with two-year follow-up."

Measurement	All Taxus patients in TAXUS-IV	All angiography patients in TAXUS-IV
TLR	3.0%	3.8%
TVR	4.7%	6.2%
TVF	7.6%	7.5%
Late loss in-segment	.23 mm	.61 mm
Late loss in-stent	.39 mm	.92 mm

Dr. Bram Zuckerman, head of Cardiovascular Devices at the FDA's CDRH, indicated he is thinking about the late loss argument proposed by Boston Scientific, but he does not yet appear convinced. However, the theory has helped put off, at least for now, acceptance of late loss as a surrogate endpoint.

Experts seemed to accept this theory. Their comments included:

- "Maybe paclitaxel is not as antiproliferative as sirolimus…It doesn't inhibit the neointimal hyperplasia as much…The .39 mm late loss in-stent may mean the tissue inhibition is not quite as strong…but it is the totality of the delivery system and the drug that determine the late restenosis rate."
- "I came to this meeting thinking lower is better, and then when I saw the TAXUS-IV data and dissected it, some of those concepts weren't changed but were refined. (Boston Scientific) put together a nice regression model that found the average late loss for a bare stent is about 1.0 mm and that gave a (restenosis) risk of 25%…There is a very steep curve…so if there is 0.4 mm or 0.5 mm late loss, your risk of restenosis is very low…(A colleague) still thinks late loss is the most important variable…so there will be a healthy debate on whether absolute late loss or clinical outcomes are the most important…I thought you would have to get to 0.2 mm or 0.1 mm late loss, but the data suggest 0.6 mm late loss is an indicator. Below that, there is not much restenosis…so, the range of 0.3-0.4 mm is quite acceptable...so the fundamental premise that the lower the late lumen loss, the better, is not quite so clear…If you want to measure which drug is biologically the best the in-stent late lumen loss is the best…Sirolimus is a better antiproliferative drug than paclitaxel, but you can't get the drug there without the stent and delivery system…so we need to see if in-stent late lumen loss is the pertinent clinical variable."
- "We are not treating late loss but clinical symptoms…0.1 mm or 0.3 mm doesn't mean anything…If it is 0.4 mm, and the patient is asymptomatic, we don't see the patient. Because of the trials, these numbers are important….but I would not over-interpret these results…We know from TAXUS-IV that late loss is not predictable of future restenosis…Does paclitaxel work? I guess it does."

➢ **Overlapping stents.** The Canadian label is for single stenting, and most experts believe that will be the case in the U.S. as well. At the FDA's direction, overlapping stents were kept to a minimum in TAXUS-IV. Only 4% of stents were overlapping, so few conclusions can be made about the viability of overlapping Taxus stents. An expert said, "When I pick a stent, I try to pick one so I don't need to overlap...My intention is never to overlap stents…Obviously, we worry about toxicity for a double dose...but no aneurysms have been seen in TAXUS-VI (an international trial of the moderate-release paclitaxel formulation in the treatment of lesions ≥18 mm in 448 patients, with multiple stents permitted)."

➢ **Polymer "bonding" and "webbing."** A J&J expert said that a scanning electron microscope comparison of the polymers used on 10 Cyphers and on eight Taxus stents indicate the Taxus polymer is a combination of polymers

similar to that found in a Goodyear tire, "It is more like rubber, with significantly higher tackiness, and stickiness. It's been used in orthopedic implants...Bonding happens when a polymer sticks to itself, forming a bridge when the tent expands. Webbing is the polymer pulling away from the expanding stent due to the polymer sticking to itself. Both webbing and bonding were zero with Cypher but are common in Taxus. Though there have been no clinical sequelae, I can't speak to the meaning of whether the durability of the results are comparable…It is an unusual polymer formulation to maintain most of the dose on the polymer for an indefinite period of time…Unless we see a clinical impact that is negative, I'm not sure what this means."

Will the moderate-release (MR) dose be superior to the slow-release (SR) dose used in TAXUS-IV?

A Boston Scientific official said, "That is the million dollar question...I can hardly wait to see the TAXUS-VI data."

Were the TAXUS-IV results due to the slower release of paclitaxel than sirolimus?

An investigator said, "There is an early phase burst with paclitaxel in the first six to 12 hours, then a slow release. The drug overall releases significantly slower than sirolimus, so that at 30 days much of it is sequestered away in the polymer. Both (drugs) are effective."

Are there any safety concerns to ~90% of the paclitaxel remaining on the stent permanently – or at least indefinitely?

Asked how Boston Scientific can be sure the remaining paclitaxel won't elute in the future, an official said that is proprietary information, and he wouldn't reveal it, but he indicated the FDA does have that information. Another Boston Scientific official said, "The FDA was concerned...They said, 'Get the drug out.' And we tried…We started with individual extreme conditions – non-physiologic things like lowering pH, increasing the temperature, adding various detergents, and the thing that allowed the largest amount of drug to come off was to put it in 100% organic solvents...but until we got to 100%, the drug did not come off, without regard to how long we left it in, stirred it, etc…Of course, when we did that, the physical properties of the polymer were destroyed, and it became tacky…After going through that for four to six months, we decided that was non-physiologic…and it was highly unlikely that the drug would come off after the burst phase." A Taxus investigator said, "I'm a little biased…I have a PhD in biochemistry…If you feel there is no elution from the stent, and it is biologically inert, then there shouldn't be any legitimate concerns...assuming nothing is eluting from the stent, that the polymer coating has been rendered biologically inert."

Doctors questioned about this issue generally were not concerned about residual paclitaxel. One said, "It's just not an issue."

What questions did the FDA pose for the Advisory Committee review?

Boston Scientific officials declined to outline these, but one official commented, "Our team is on top of the questions, and it doesn't appear they are overwhelmed by the questions." Another official said, "The questions are very manageable.

The FDA asked for our answers in a week. They want to send the briefing package to the panel members eight weeks in advance." A third official said that over the years the agency has wanted to know:

- What happens to drug retained in the stent?
- What is the kinetic release profile?
- Is there a routine, useful, and reproducible assay in the manufacturing environment?
- Would you tabulate the data in a different way – across various studies and formats and at the edges of the stent?

An expert at a Boston-sponsored session said that if he were on the advisory panel he would want more information on overlapping stents, "I think the labeling may say that Taxus is only for single stent use…What happened with Cypher was that when things were asked for, that had not been studied, additional data had to be presented…I would want to make sure the labeling said the appropriate subsets were studied in a trial…I'd also want to know the worst case with four overlapping drug-eluting stents and systemic levels."

Comparison of Taxus and Cypher

How do Taxus and Cypher compare? A Boston Scientific official said, "They both had superior clinical outcomes, both showed superior angiographic restenosis rates, and both had acceptable safety profiles. But TAXUS-IV showed excellent stent performance, consistent benefits, and advantages at the edges." Dr. Russell said, "The TAXUS-IV results are a mirror image of TAXUS-II, both on angiography and IVUS, so I think that there is an edge benefit. It is small but the significance is real. Reasons? Anything is pure speculation. I don't know the reason. It does look like, given how reproducible it is, there may be some, call it diffusion, of the drug, or maybe localization of the drug, or how the vessel responds in general and paclitaxel's ability to reduce recoil and fibrotic responses throughout the entire vessel. It is restricted on IVUS to the first 1 mm, and in TAXUS-II it was the first 3 mm of 5 mm on the distal side and 1 mm on the proximal side, so it is a fairly contained edge benefit." Another official said, "I believe stent performance and system play a major role in getting very good edge data – and there are no negative factors from the drug or polymer that make performance go worse. So you can expect some positive effect from the drug (paclitaxel)."

An independent head-to-head study done at a hospital in India compared Taxus and Cypher in 100 patients, all of whom had angiography. A researcher concluded: Late loss and restenosis were comparable with Taxus and Cypher. The

pattern and location of the restenosis was different. There was more edge effect with Cypher."

Cypher vs. Taxus in India

Measurement	Cypher	Taxus	p-value
Diabetics	44%	38%	---
Lesion length ≥ 20 mm	19.5%	16.4%	p=.02
RVD ≤2.75 mm	2.8%	3.%	p=.007
Late loss	19.6%	25%	p=.69
Restenosis	10.7%	11.4%	p=1.0
TLR	7.1%	6.8%	Nss
Location of late loss	Mostly peripheral	Mostly in-stent (27% non-focal)	---
Restenosis attributable to stent	80%	66.7%	---

Although investigators warned against direct comparisons of TAXUS-IV and SIRIUS and of the Cypher and Taxus stents, most doctors were doing just that. A Taxus investigator said, "It is difficult to compare study to study. What we need to do is focus on the outcomes of this stent. In concert with its deliverability and flexibility, these results set a new standard for drug-eluting stent technology – and for improved outcomes for patients…It's always a mistake to compare the results of one trial to another. The core labs were the same, but the operators and techniques were different, so I would try not to read too much into a comparison."

An Expert's Comparison of Taxus and Cypher

Feature	Taxus/TAXUS-IV	Cypher/SIRIUS
Stent platform	Express	BX Velocity
Stent lengths	6, 24, 32	8, 18
Randomization	Pre-dilatation	Post-dilatation
Blinding	All hospital personnel	Billing staff unblinded
Non-target vessel stenting	Allowed	Prohibited

The apparent advantages of Taxus over Cypher are:

➢ **A lower restenosis rate.** However, even some Taxus investigators called the results "equivalent" to Cypher. One said, "Many people will consider this equivalent data."

➢ **Better stent deliverability and ease of use.** A Taxus investigator said, "As interventionalists look at the data, they will say Cypher is as effective as Taxus…Maybe there is some play for Taxus in diabetics…but I think it will come down to issues of deliverability because the efficacy of both is within a close ballpark, and it will come down to deliverability." Another expert said, "The paclitaxel on (the Taxus) platform is very effective in diabetes, which we never expected. Why? We don't know yet. But we need to look beyond the drug to the delivery system. It looks like the delivery system is very important and might make a difference."

However, TAXUS-IV used the Express stent, not the new and improved Express^2 which is in use in Europe, and sources pointed out that there are differences between Taxus and Express^2. A J&J official said, "In our testing, and from the international feedback we've received, Taxus does not perform the same as Express^2 because of the polymer…The polymer does impact the performance of the Express^2 stent, so if you are comparing Cypher vs. Taxus, that's what has to be compared (not Cypher and Express^2)…We find Cypher equivalent if not better…We have some data points with direct stenting with Cypher, and you can't do that with Taxus." European doctors who have used Taxus agreed that the handling is different from both Express and Express^2, and there is a small learning curve – but they still concurred that Taxus is a very deliverable stent.

Even though Taxus utilizes the Express platform, some sources pointed out that Taxus delivery is not the same as the bare Express or Express2 – that the coating affects the deliverability, at least to some extent, though there was little doubt among experts that Taxus is more deliverable than Cypher.

Low restenosis in diabetics. Doctors were very impressed with how Taxus performed in diabetics, and the numbers looked much better than for Cypher. A source said, "The data on sirolimus in diabetics is very questionable." Another commented, "In SIRIUS, we obliterated in-stent restenosis in diabetics; it was the edges that got worse…Wherever we got drug without injuring the artery, the drug did well…It may be the drug is okay; that it is the delivery platform that is the issue."

➢ **No edge effect.**

The Future of Taxus

There will be one-year data from TAXUS-IV at the American Heart Association meeting in November 2003. Then, on Thursday, November 20, the FDA's Circulatory Systems Advisory Panel will meet to consider its recommendation on Taxus. A Boston Scientific official indicated the FDA "does not want a long gap between the advisory panel and approval." Thus, Boston Scientific officials are hoping that Taxus will be approved as early as January 2004, but other sources thought a February or March 2004 approval might be more realistic. There will be TAXUS-VI data at EuroPCR in May 2004.

Although J&J is conducting a head-to-head trial of Cypher and Taxus, Boston Scientific does not plan to run any head-to-head trials. A Boston Scientific official said, "You would need huge numbers to show superiority, and I don't even know if you could do it…We have two datasets that look very comparable to me…I don't see the value to the clinical community. If there were a niche where it was not clear which drug was better and we needed to answer that, it would

be important for clinicians, and then maybe I would change my opinion."

Liberté: Next generation paclitaxel-eluting stent

Liberté is the next generation Taxus stent, and it has a very different geometric design. Boston Scientific got an IDE for Liberté in 1Q03, and "most" of the patients are already enrolled, with enrollment expected to be complete in 4Q03. CE Mark is expected in 4Q03, and the PMA submission is planned for 1Q04. Boston Scientific said the data the FDA requires for Liberté will depend on the label the company is seeking, "The FDA wants a lot of preclinical data…They want safety and efficacy data…If it is just a workhorse stent, then, given the vastness of our data, the requirement may be only for a single arm registry. If we want to strengthen indications, then they would want a solidly-designed study to support that."

GUIDANT

By early 2004, Guidant should have four different everolimus trials running: two with standard polymers, and two with different bioresorbable polymers.

1. Tru-Coat polymer with everolimus
2. Another polymer with everolimus
3. Two bioabsorbable polymers
   a. Polylactic acid (PLA) on Champion stent and eventually on the Vision stent. This has a high drug-loading capability. It is a stainless steel stent, coated on the outside of the struts rather than circumferentially. This is the FUTURE trial program.
   b. PolyEster Amide polymer, an amino acid/fatty acid-based polymer obtained with the MediVas acquisition. It can bind two different drugs and two different sites. The first embodiment was the Temp Coating (PEA-Tempo coating) used in Blue Medical's nitrous oxide-eluting NOBLESSE trial, which had a four-month restenosis rate of 9.5% and a late loss of 0.69 mm. Reportedly, Guidant is repeating the two-week and six-week animal studies that MediVass did with this coating, but can use that data as the basis for starting human clinical trials.

With the FUTURE program, Guidant is doing a modular filing for a CE Mark. The first module was filed August 28, 2003 with the six-month FUTURE-I data. There will be two other modules – the FUTURE-I one-year data, and the FUTURE-II six-month data. A Guidant official said, "Publicly, we are not counting on that yielding a CE mark, though that is possible…We expect it to be available somewhere in the world in 2005, and we expect FDA approval in late 2005 or early 2006…We expect to be in human clinicals with this in 1Q04, and we haven't decided whether it will be U.S. or OUS."

Guidant got FUTURE drug/stent system from Biosensors and now manufacturers the system itself under the Champion name, using a different delivery system (the same one used for its Vision stent). Thus, Guidant has total quality and manufacturing control of the system. A Guidant official said, "It is the S-stent…All we are doing is taking manufacturing inside Guidant and putting it on a new balloon dilatation catheter…We see a broad spectrum of activity. The nice thing about the PLA polymer is it has the capacity to load a lot of drug, even with a thin layer…It also is applied on the OD of the stent, so a lot of drug is directed to vessel wall rather than the ID of the stent." An investigator said, "The S-stent has been used in Asia, but is not so popular in Europe. In Asia, the registry is out, and it proved to be very successful…It was performing well and delivering well. The three sites in Europe that used it were happy; they had no failures, and the delivery success will be high." Another expert said, "The delivery system is paramount."

Guidant's only data at TCT were from the FUTURE-I and FUTURE–II trials which used Biosensor's everolimus-eluting stent with a bioerodable polymer. These new results presented at TCT included:

- In the 42-patient FUTURE-I trial, there was no new MACE between the previously-reported six-month results and the one-year data shown at TCT2003. FUTURE-I excluded diabetics.
- In the 64-patient FUTURE-II trial, six-month angiographic gave more confidence that this drug/polymer combination may work. The 4.8% MACE was due to one patient with proximal edge stenosis. FUTURE-II had 23% diabetics. Dr. Eberhard Grube, the principal investigator, said, "Diabetics in FUTURE-II looked exactly the same as non-diabetics."

On the polymer side, is the SPIRIT program. It is unclear whether this will be with the Tru-Coat polymer or the alternative polymer. In SPIRIT-I, the first patients should be enrolled before the end of 2003. Then a Phase I European trial will be considered and a SPIRIT IDE trial for U.S. approval.

JOHNSON & JOHNSON

Just before TCT, J&J released the results of NEW-SIRIUS, a pooled analysis of the E-SIRIUS (Europe) and C-SIRIUS (Canada) trials. Restenosis was 5.1%, TLR 4.0%, and late loss 0.18 mm.

NEW-SIRIUS Results

Measurement	Cypher	Control
% patient angiographied	87%	
Late loss	.18 mm	1.04 mm
In-Segment Restenosis		
In-segment	**5.1%**	**44.2%**
Small vessels	7.7%	49.4%
Medium vessels	7.5%	49.4%
Long vessels	9.0%	39.0%
In-Stent Restenosis		
In-stent	3.1%	42.7%
Proximal edge	2.1%	7.4%
Distal edge	1.5%	N/A
Small vessels	3.8%	46.9%
Medium vessels	4.5%	42.4%
Long vessels	N/A	N/A
Diabetics		
Angiography	105 patients	
In-segment	10.8%	56.4%
In-stent	5.4%	54.5%
TVR	4.7%`	N/A
MACE	71.%	N/A

Comparison of New-SIRIUS, SIRIUS and TAXUS-IV Results

Measurement	NEW-SIRIUS Cypher	SIRIUS Cypher	TAXUS-IV Taxus
Number of patients	225	533	662
In-segment restenosis	5.1%	8.9%	7.9%
Late loss	0.18 mm	0.17 mm	0.33 mm

J&J also tried to pre-empt some of the Taxus news at TCT with a pre-meeting press conference that included three Cypher patients who told their stories and humanized the drug-eluting stent story.

a. A man who was the first patient in the First-in-Man trial. He has been followed out to 45 months with excellent results. However, I would point out that his stenosis was not severe (61%) when Cypher was put in.
b. A middle-aged man who had a heart transplant 15 years ago. He is believed to be the first heart transplant patient to get a Cypher. He got it the day Cypher was approved, and he is still doing very well.
c. A 75-year-old Florida woman who got two Cyphers over a year ago. She appeared typical of elderly, restenotic patients.

There is wide variation in the U.S. from hospital to hospital in how many patients get Cypher stents. At one East Coast hospital, >95% of patients get a Cypher, and in Dr. Eduardo Sousa's hospital in Brazil 75% of patients get a drug-eluting stent (but only 10% of patients overall in Brazil get a Cypher).

At a Florida hospital, about 50% of patients get Cyphers. A prominent interventional cardiologist argued guidelines to restrict use of drug-eluting stents, saying, "It is easy to promulgate guidelines based on approvals...but we have yet to find a group that doesn't benefit from this technology…We are administering a medication here…And when drug-eluting stents are restricted at one hospital, patients will just go to another hospital where they can get them…There are institutions that restrict use to one drug-eluting stent per patient, and that allocation is not fair to patients."

Patients in the SECURE (compassionate use) registry reportedly are doing well, and these include 58 SVGs. An investigator said, "The results seem pretty competitive to FIM, RAVEL or SIRIUS. Obviously, some patients will fail, but the results so far are pretty impressive."

Comparison of SIRIUS and TAXUS-IV Results

Measurement	SIRIUS Cypher	TAXUS-IV Taxus
Number of patients	533	662
Diameter stents used	2.5 - 3.0 mm	2.5 - 3.5 mm
Duration of antiplatelet therapy	2 months	6 months
Reference vessel diameter	2.61 mm	2.75 mm
Average lesion length	14.8	13.4
Diabetics	20.0%	23.4%
Stent/lesion length	1.7	1.9
IIb/IIIa use	24%	58%
Overlapping stents	34.7%	6.8%
In-segment restenosis	8.9%	7.9%
Late loss	0.17 mm	0.33 mm

Cypher Issues

Lymphoma. On the last day of TCT, a surprise presentation reported a single case of 4 cm B-cell lymphoma surrounding a Cypher stent. The patient reportedly had no lymphoma markers in his bone marrow and no lymphoma risk factors, so it appeared to be a local event. A source said, "Immuno-suppressants used to be given subcutaneously but they aren't any longer because of the incidence of local B-cell lymphomas." A J&J official said, "There have been cases published in the literature that tumors can be associated with coronary devices, but it is unusual and usually fibrotic in nature…It is also unusual for the lymphoma to have developed in such a short time (five months) post-procedure. More than 250,000 patients have been treated with Cypher stents world-wide, and this is the only report." However, the company notes there is no conclusive association between the lymphoma and the Cypher stent, and J&J is following the case carefully.

Supply. J&J officials insisted U.S. supply problems are over, but there is still some backlog in Europe, though that is

expected to be resolved soon. An official cited the earlier-than-expected launch of the 3.5 mm Cypher as proof that U.S. inventory problems have been resolved; the 3.5 was planned for a September 2003 launch but released a few weeks earlier than that. One official said, "Today, there are no allocations or order restrictions for Cypher stents in the U.S…Given the supply and clinical outcomes, we believe drug-eluting stent usage will continue to increase. There is no reason a patient should receive a bare metal stent today." Another official said U.S. supply needs were not met by shorting Europe; European manufacturing is separate and has different issues.

However, U.S. doctors said they are still seeing inventory shortages, and some sources were critical of J&J trying to block Taxus from coming to the U.S. market through patent litigation if J&J can't supply the country's needs.

SAT warning letter. At the time the Cypher warning letter went out to doctors, the SAT rate was 0.085%, and a J&J official said it is now 0.10%. He described this slight increase as a blip due to increased reporting after the letter. He also said that there are still problem centers that have worse SAT rates. Sources agreed there is no evidence that the SATs are related to use of bivalirudin (The Medicine Company's Angiomax), but some sources believe at least some cases may be due to clinical cardiologists stopping the antiplatelet regimen (Plavix) earlier than recommended, and J&J is working to educate interventional cardiologists to be sure patients understand that their clinical cardiologists must not stop their antiplatelet medication early. Even a Taxus investigator denied that Cypher stents are causing excessive thrombosis, commenting, "We haven't been able to detect a real problem, but it certainly bears watching."

Technique matters. Lack of technique is primarily to blame for the SATs seen with Cypher, experts insisted. Dr. Marty Leon of Lenox Hill Hospital said, "It was a mistake to simply assume this was just another generation stent and the technique should be the same as with bare metal stents. We learned that, particularly in more difficult patients – diabetics, small vessels, etc. -- technique is more important, needs to be more precise, with longer stents, expansion, prep, etc. So, it requires extra attention, meticulous attention to get the optimal out of the stent. The stent and the drug are terrific, and sometimes it is the physician that doesn't allow the device to behave up to its limits of safety and efficacy." Asked if the SATs and technique issues are unique to Cypher, Dr. Leon said, "No, it is general to drug-eluting stents. It is not just a Cypher issue."

Shelf life. Current shelf life is six-months in the U.S. and 12 months in Europe. J&J has tests underway and plans to submit for an extension of the U.S. shelf life. The relatively short U.S. shelf life has resulted in some returns due to out-dating, but an official said this was minimal. He explained, "We have had hospitals with expired Cyphers, and we take them back and give them credit, but it was a minimal amount, nothing material to the company."

Pricing. J&J lowered the $3,200 U.S. price of the Cypher stent in early September, so that hospitals now pay from $2700 (low volume) to $2,250 (high volume) for the stent. J&J officials claimed the price reduction is simply hospitals being able to take advantage of the volume discounts that have been unavailable because of supply constraints, not an attempt to block some of the price discounting that was expected from Boston Scientific.

Future Drug-Eluting Stent Plans

Data will continue to be reported and new trials started, including:

- There will be a New England Journal article with SIRIUS data in the next couple of months.
- Four-year (45-month) data will be complete in December 2003 on all the First-in-Man patients in Brazil, but the ones who have been examined (by angiography and IVUS) so far have demonstrated no aneurysms, pseudo-aneurysms, perforations or other systemic disorders.
- Studies for a Cypher label expansion to include 2.25 mm and 4.0 mm diameter stents will start in late September 2003, and the company is projecting approval toward the end of 2004 or early 2005.
- The REALITY trial, which is comparing Cypher head-to-head with Taxus, started enrollment at the end of August 2003, and J&J hopes to complete enrollment by the end of this year. There will be more than 1300 patients, all OUS.

J&J plans to launch its next general sirolimus stent, Cypher Select in Europe at the end of September 2003 (it already has CE Mark) and in the U.S. in 2004. Cypher Select will be on the Sonic delivery system (still a Guidant delivery system); J&J plans to introduce its own delivery system in late 2005. An official said, "This is a derivative of the BX Velocity, but with an adjustment to the flex segments. We changed the geometry to greatly improve the deliverability, and we put it on the next generation delivery system. It is still a closed-cell stent." Another official said, "Cypher Select has an improved tip design that facilitates crossing. It has a shorter, formed tip. There is also a shortened balloon overhang (<0.5 mm)."

After Select, will come the sirolimus-eluting Steeplechaser, a chromium cobalt stent using the same SurModics coating. J&J plans to continue using SurModics coatings, though it has looked at other polymers for coronary stents, nothing has been found to replace the SurModics coating. However, the non-coronary polymer is from a different firm.

MEDTRONIC

Medtronic's Endeavor stent is a chromium cobalt Driver stent with a phosphorylcholine-coating that elutes ABT-578, a sirolimus analog. A 10 µg/mm of stent length was chosen after animal studies found no difference in efficacy from 10 µg to 30 µg. The elution profile is very quick – comparable to the Cypher fast-release – with >95% eluted within several days.

Four-month data from the 100-patient non-randomized ENDEAVOR-I trial, conducted in Australia and New Zealand, looked very good. The late loss was higher than Cypher but slightly below TAXUS-IV, so sources did not appear concerned with this, especially in light of the new theory about late loss proposed by Boston Scientific (*See page 7*). The interesting thing about ENDEAVOR-I was that 99% of patients received follow-up angiography. Diabetics comprised 16% of the patients. The remaining endpoints are TVF and TLR at nine months and late loss at 12 months.

ENDEAVOR-II, a multinational trial, is already underway, and 132 of the ~1,200 patients had been enrolled by the time of TCT. Enrollment is expected to be completed in late 2003. Stent diameters of 2.25-3.5 mm and lengths of 18-30 mm for de novo lesions of 14-27 mm will be used, with pre-dilation required. The primary endpoint is TVF at nine months. It will compare the Endeavor stent to the bare Driver stent. This trial is not considered a necessary step for obtaining CE Mark or for starting a U.S. trial. A Medtronic official said, "Our intent is to have 80%-90% angiographic follow-up on a pre-specified number of patients, but that needs to be worked out with the executive committee of the trial." About 300 of these patients will be followed with IVUS. Dr. Popma who headed the core lab for both SIRIUS and TAXUS-IV will be in charge of the core lab for ENDEAVOR-II, and he said, "It is a subtle question about trial design…We know that sometimes we are influenced by the angiogram we see...The higher the level of angiographic follow-up designed in the trial, the more potential risk of ocular stenotic reflex…so you can either go 100% as in ENDEAVOR-I or design a trial with enough patients to tell you what you want, and then the rest of the trial is to see how patients do clinically without the pollution of an angiogram."

ENDEAVOR-III is due to start soon. This is a confirmatory U.S. trial comparing Cypher and Endeavor in 300-480 U.S. patients. Stent diameters of 2.25-3.5 mm and lengths of 18-30 mm for de novo lesions of 14-27 mm will be used, with pre-dilation required. The primary endpoint was supposed to be late loss at eight months by QCA, but Medtronic officials suggested that may be changed, given the results of TAXUS-4. Before ENDEAVOR-III can start, the FDA needs a full package on ABT-578 from Abbott, plus the preclinical work, which Medtronic officials said is complete.

Medtronic is investing substantially to expand its manufacturing capacity in Ireland where it will manufacture the Endeavor stent. An official said, "On pricing, I was encouraged by Taxus because it puts products on a more level playing field, so the value of the technology may be recognized by the marketplace."

ENDEAVOR-I Results

Measurement	30 days	4-Months
MACE	1% **Primary endpoint**	2%
Death	0	0
Non-q-wave MI	1%	1%
TLR	0	1%
TVR (non-TLR)	0	0
Late loss in-stent	---	.33
Late loss in-segment	---	.20 **Primary endpoint**
Late loss index in-stent	---	.17
Late loss index in-segment	---	.11
Binary restenosis	---	2.1%

SAHAJANAND MEDICAL TECHNOLOGIES' INFINNIUM

This paclitaxel-eluting stent from India could become the spoiler for Boston Scientific. The company plans to bring it to Europe and the U.S. – at a much lower price than Taxus. Safety and efficacy appear comparable to Cypher and Taxus, and a prospective multi-center trial is planned to start in 4Q03, and it reportedly will include at least one U.S. site.

Infinnium uses a Millennium stent, which has a slotted tube design, coated with a biodegradable polymer. There are actually four different layers of polymer on the stent, each with a different composition and different drug concentration:

1. 1% protective coating
2. 33% fast release (15 µg/day for the first four days)
3. 30% moderate release (9 µg/day for the next five days)
4. 36% slow release (3 µg/day for the next 37 days)

Data was presented from the 282-patient SIMPLE-I trial, which had 33.3% diabetics. A total of 318 stents were placed, for an average of 1.13 per patient. The trial found no edge phenomenon.

Phase I SIMPLE-I Trial Results

Measurement	Infinnium
Number of patients	282
Number of stents placed	318
Stents per patient	1.13
Diabetics	33.3%
Stents ≤16 mm	69.8%
Angiographic follow-up	33% *
TVR	0.7% **
30-Day MACE	
Overall MACE	2.1%
MI	0.35%
SAT	2.1%
6-month MACE	
TVR	2.83%
MI	1.06%
Overall MACE	4.96%
SAT	4 patients ***
Event-free survival	95%
In-stent Angiographic Results (90 patients)	
Late loss	0.2 mm
Diameter stenosis	18.8%
Restenosis	5.9%
In-segment Angiographic Results (90 patients)	
Late loss	0.12 mm
Diameter stenosis	28.6%
Restenosis	8.9%

* 94% of first 100 patients
** One MI that died and another death
*** All SATs occurred when antiplatelet therapy was stopped in violation of the protocol.

MISCELLANEOUS STENT NEWS

SORIN'S Janus tacrolimus-eluting carbostent

Following a successful pig study, Sorin is starting the JUPITER-I trial of this closed-cell stent in 30 patients with de novo lesions at several centers in Italy.

Sirolimus analogs

A number of companies are working on "limus" analogs, also dubbed rapalogs (rapamycin analogs). These include Ariad's AP-23573, which is in Phase I trials for treating glioblastoma and is being evaluated as a potential agent for drug-eluting stents.

THE REGULATORY PERSPECTIVE

Hurricane Isabel closed the federal government on September 18, 2003, but several FDA and CMS officials came to work anyway – to participate in an FDA Town Hall Meeting at TCT. They reviewed the current regulatory concerns, procedures and issues relating to drug-eluting stents, carotid stents, peripheral stents, and more. Some very interesting tidbits came out of these meetings.

CENTERS FOR MEDICAID AND MEDICARE SERVICES (CMS)

CMS is considering a national coverage decision that could limit, not expand, use of drug-eluting stents.

The CMS standard for Medicare reimbursement of a device/procedure are different from those used by FDA for approval. CMS is particularly concerned with:

1. Quality of the evidence
2. Outcomes studied
3. Generalizability
4. Expert opinions

Some of the thinking that is helping to shape CMS decisions right now includes:

- **Less generalization.** Was the device/procedure testing in a sufficiently broad age group? A CMS official cited the example of bone morphogenic protein (BMP): "BMP was all done on patients under age 50 except for two patients age 65…We had concerns about whether older patients would respond the same as younger patients...We closely looked at the data and asked companies for more data before we made a decision."

- **Restricting who can do specific procedures.** CMS wants to know where Medicare beneficiaries get the best results from the technology. The agency has a "growing" concern about who is doing procedures, and the trend is likely to include restrictions on which doctors/specialists can perform specific procedures. An official explained, "We want to know where our can beneficiaries get the best results from the technology. For example, for lung reduction, we said we won't pay for it except at certain facilities. We need evidence that other facilities can perform the procedure…and that will be a factor more in the future."

- **Preference for reimbursement only for on-label use of products.** CMS is moving toward greater emphasis on approved indications, making reimbursement of off-label use less certain. In a reference to the recent warning letter Johnson & Johnson issued about thromboses related to the Cypher stent, a CMS official commented, "There is a concern that off-label use of drug-eluting stents may have caused harm to patients…The data is not clear on that yet...but we have that concern…so we will look carefully when making decisions about whether we are going to broadly or narrowly cover something….On drug-eluting stents, we didn't limit that because we thought the evidence at the time did not call for that…Where mortality is very high, we will very narrowly cover (products). If risks are low, the indications will be less narrow." This official said that doctors will not be required to submit pre-payment reviews, but if uncovered off-label use is found in a post-payment review, the doctor/hospital could be required to reimburse Medicare.

➢ **Possible National Coverage Decision (NCD) for drug-eluting stents.** CMS issued a reimbursement rate for drug-eluting stents, but the decision on whether or not to pay was left to the local carriers. Now, CMS is considering making a National Coverage Decision on drug-eluting stents. Convening a panel on this would help air the issues related to off-label use of drug-eluting stents, an official said. It also could lead to a federal mandate that carriers only cover stents reimbursed when used on-label. A CMS official said, "We are currently considering whether we should open a discussion on off-label use of drug-eluting stents…One outcome could be a national coverage discussion of the adverse events around drug-eluting stents…We are very pleased with the sharing of information by Cordis (Johnson & Johnson) on that…So for coronary drug-eluting stents our concern at the present is: Should we address something around adverse events?"

➢ **More emphasis on patient outcomes.** With diagnostic tests, for instance, CMS wants to know something actually has an impact on patient outcomes – that the information has clinical utility – before covering it. An official cited the example of PET scanning for Alzheimer's Disease, saying, "PET may be better...but what you can do for those patients is minimal. So we asked for more information before we decide to pay for that." This has implications for screening patients for vulnerable plaque and other conditions if the tests do not lead to different treatment of a patient.

➢ **Reduction of DRGs for drug-eluting stents.** CMS added special DRGs for drug-eluting stents and would like to phase those out as soon as possible, returning to simply two stent DRGs. A CMS official said, "Next year when we go to re-weight the DRG, we will have data on cases getting drug-eluting stents, so we can get payment weights based on that and begin to evaluate whether and when to reconsolidate the DRGs so that there are basically only two, as before drug-eluting stents, which is more consistent with the design of the system…If drug-eluting stents do reduce bypass procedures, certainly it will be picked up in our Medicare database, and would be something we certainly would be wiling to consider if the evidence shows it would have a dramatic effect on the payments we currently are making."

➢ **Greater collaboration with the FDA.** A CMS official said, "With this collaboration we don't think we will create a bigger bureaucracy…It will just make it more simultaneous." An FDA official said, "We have a wonderful working relationship with CMS...our ability to understand the other parts of HHS, specifically CMS, over last few years has improved dramatically." With respect to drug-eluting stents, the FDA official commented, "(Drug-eluting stents) are not just a CDRH product, even though we are the lead agency. These are complex products that include a substantial drug review because we are dealing with drugs that have some interesting safety profiles."

➢ **Multi-stenting not ready for Medicare reimbursement.** An official said, "I'm not sure we are at the point where we should be reimbursing for multi-stenting. That is sort of the agency viewpoint."

➢ **CMS stimulating data collection.** An official said, "The agency is extremely interested in how we've become players or stimulators of the collection of data…We do have a stick, and I'm not sure how we wield that stick."

➢ **Voluntary registries may become less voluntary.** A CMS official said, "Voluntary registries are problematic...Is there some way for us to encourage that data collection to be less voluntary?...We will make attempts in the near future to do that, but I'm not sure how that will float."

FOOD AND DRUG ADMINISTRATION (FDA)

FDA officials also pointed to several hot buttons with their agency right now, including:

➢ **Better science.** FDA officials have been pounding the table all year on this topic, asking and demanding better science in the data submitted to the agency, and they said there is still room for improvement.

➢ **Primary endpoints need to be met, with rare exceptions.** Close is just that – close.

➢ **Surrogate endpoints for drug-eluting stent trials not ready for prime time yet.** In January 2003, an FDA official indicated that the agency might consider surrogate endpoints once the first drug-eluting stent was approved: "There is a potential to design an equivalence trial with co-primary endpoints – one QCA and the other TVF with a moderate-sized delta -- so the sample size would not be 10,000 patients…(BUT there are some) caveats to utilization of QCA as a key primary endpoint. Angiographic follow-up has (historically) been less than ideal. There have been even more problems, in some cases, getting QCA follow-up on subgroups." The guidance was that QCA would have to be in a high rate percentage (≥70%) of patients in a trial to allow the use of surrogate endpoints.

A theory was proposed at TCT that late lumen loss does not correlate with restenosis until it is ≥0.6, far higher than previously thought. What does this mean for the use of late loss as a QCA surrogate endpoint? An FDA official said, "We have to be sure we choose the right surrogate endpoint. Surrogate endpoints are not ready for prime time yet."

➢ **Overdosing studies are mandatory.** An official said, "Many people still don't get the idea that we need overdosing studies (3x-10x)."

➢ **PK studies** are handled by CDER, but CDRH "takes them seriously."

➢ **Vulnerable plaque measuring devices probably will require a PMA, not a 510K submission.**

➢ **Among key data concerns are:**

- Studies with "best" risk patients rather than those who are sicker.
- Post hoc analyses, especially if the primary endpoint is missed.
- Failure to address missing data. An official said, "There is a big problem when there is a lot of missing data…or trials with large drop-out rates."
- Suggestions that post-market studies will solve study problems. An official commented, "They won't. We have to have real data on safety and efficacy, not just the promise that eventually some post-marketing study might be done."
- Public presentation ignoring unfavorable data.
- Lack of confidence limits/error bars.
- Confusing quantity with quality.

OTHER CLINICAL TRIALS OF INTEREST

An FDA official said there was no good trial data presented at TCT. She thought all of the drug-eluting stent trial data was presented in a biased way. She was very concerned with the quality of the data. She and Zuckerman both confirmed that Boston Scientific will have to provide a per-protocol analysis of the TAXUS-IV data to the FDA, and that analysis will supercede the analysis they presented at TCT.

Several FDA official expressed concern with the off-label product "promotion" at TCT, citing PFO closure for migraine headaches as perhaps the most egregious.
No company was mentioned by name.

REPLACE-2: The Angiomax Results Hold Up

When the 30-day results of REPLACE-2 were presented at the American Heart Association, The Medicine Company's Angiomax (bivalirudin) was shown to be non-inferior – and perhaps even superior – to heparin, but some cardiologists wondered if the results would hold up over time. The six-month results from REPLACE-2 were presented at TCT, and they were virtually identical to the 30-day results. The REPLACE-2 data confirm the shorter-term findings that Angiomax is a safe and effective replacement for heparin in combination with anti-platelet drugs, but the data did not show a superiority benefit.

There had also been a concern about a numerically higher rate of MI with bivalirudin at 30-days, even though the difference was not statistically significant (7.0% vs. 6.2% with heparin). At six-months, there continued to be the same spread in MI between bivalirudin and heparin (8.2% vs. 7.4%), leading the principal investigator, Dr. A. Michael Lincoff to conclude, "The difference is entirely peri-procedural."

At a Medicine Company-sponsored, symposium, a doctor said his East Coast hospital is using bivalirudin for 85% of cases. He said, "Clearly, the myth that IIb/IIIas are the only thing that reduce mortality is pretty much out the window…We seem to be getting our cake and eating it too with this compound." A West Coast doctor, whose hospital is using Angiomax for 80% of its PCI patients, said, "In 2003, using bivalirudin, you can reduce CKMB elevation, reduce mortality, and reduce bleeding complications."

A speaker also addressed some of the issues that have been raised about Angiomax:

➢ Complications. "We do get bleeding complications (with PCI), especial in the groin – e.g., hematomas – and I worry about coronary perforation. IIb/IIIa inhibitors reduce ischemic complications, but IIb/IIIa inhibitors increase bleeding complications."

➢ ACT measurement. "It really isn't true – the ACTSs weren't significantly higher (in REPLACE-2) than in other trials."

➢ CKMB, which trended higher in the Angiomax arm, compared to ReoPro (Lilly, abciximab). "That's true, but looking at the new six-month data…you see a small but not statistically significant trend toward increased CKMB elevation with ReoPro, but not with Integrilin (Millennium,

REPLACE-2 30-Day and Six-Month Results

Measurement	30-day Data		Six-Months	
	Heparin 65 U/kg	Bivalirudin .75 mg/kg bolus and 1.75 mg/kg-hr during PCI	Heparin 65 U/kg	Bivalirudin .75 mg/kg bolus and 1.75 mg/kg-hr during PCI
Primary endpoint: composite of death, MI, urgent revascularization, and major in-hospital hemorrhage	10.0%	9.2% (p>.05)	Not reported	Not reported
Death	0.4%	0.2%	1.35%	0.95% (p=0.15)
MI	6.2%	7.0% (nss)	7.4%	8.2% (p=0.24)
Urgent revascularization	1.2%	1.4%	11.36%	12.06% (p=0.45)

eptifibatide)…But mortality is trending lower…We are not claiming this drug saves lives, but it is trending towards benefiting patients who receive bivalirudin…If you have a non-Q-wave MI, it is better to have bivalirudin for some reason."

Among the ongoing Angiomax trials are:

- ADEST, a 1,175-patient study already underway at nine sites implanting Cypher stents with Angiomax as the anti-coagulant. The endpoints are death, MI, ischemic revascularizations and bleeding. A speaker said, "So far, there is no difference. If anything, bleeding goes in the right direction…The bivalirudin seems as effective as an anticoagulant with Cypher stents as with bare metal stents."
- PRIM, a safety study being conducted at Lenox Hill Hospital, comparing Angiomax with bare metal stents to historical control.
- ACUITY, which will look at the efficacy of Angiomax on patients with acute coronary syndrome, unstable angina or NSTEMI. One patient has already been enrolled, and the trial will enroll more than 13,000 moderate-to-high risk patients.
- HORIZONS, an AMI trial. This trial reportedly makes ACUITY look like a simple trial. It will compare 3,400 randomized patients undergoing primary PCI with bivalirudin and either a bare Boston Scientific Liberté stent or a Taxus Liberté paclitaxel-eluting stent. This trial will start in 1Q04 or 2Q04.
- STEALTH-1, testing Angiomax in patients getting Biosensor's biolimus-eluting stents.

A debate on antithrombotic therapy focused on the use of Angiomax.

Pro: Direct antithrombins are all that are needed. A speaker said, "All I need is bivalirudin, clopidogrel, aspirin and – in about 2% of my cases, a IIb/IIIa inhibitor…In the 1990s we used IIb/IIIas in 62% of cases, but in the last five large, randomized trials, IIb/IIIas have not measured up…Bivalirudin has a very short half life...and there is no late price for use of bivalirudin…The additional cost (for bivalirudin) is $377, so for every six patients treated with bivalirudin instead of heparin, you can buy a drug-eluting stent…Bivalirudin is safe, effective, simple and saves money…If bivalirudin had been the standard of care and someone came along with heparin plus IIb/IIIa, would anyone have switched?"

Con: It is criminal to dismiss IIb/IIIa inhibitors. A speaker said, "(With bivalirudin), on balance, per 1,000 patients undergoing PCI, you would trade eight MIs, for three transfusions…The success of bivalirudin is inextricably linked to provisional use of IIb/IIIas…The duration of treatment (in REPLACE-2) with bivalirudin was a median of 44 minutes, which implies a median procedure time of approximately 35 minutes, and that indicates mild-moderate, not complex, procedures." The moderator said, "The totality of data says bivalirudin is a replacement for a large number of patients…but my preference is not to dismiss IIb/IIIas in high risk patients where there is overwhelming data on the benefits of IIb/IIIas…there is a role for both strategies and a stratified approach." Another expert said, "There is only one randomized trial on bivalirudin and lot of information on IIb/IIIas…so at present, I am impressed with REPLACE-2, but there is still a place for IIb/IIIas in high risk patients."

COOL-MI

Cooling patients before PCI sounds like a great idea, but the theory wasn't proven in the most recent trial – COOL-MI. This study of the value of cooling AMI patients as adjunctive therapy prior to PCI failed to show a benefit to cooling. Patients who had an acute infarct were randomized to either primary PCI or Primary PCI+endovascular cooling.

Researchers concluded:

- Mild systemic hypothermia is safe and well tolerated.
- Cooling – at least as administered in this trial -- did not result in a reduction of infarct size.
- Patients with an anterior MI who are cooled to ≤35°C appear to have a large reduction in infarct size.

However, the problem in the trial may be that it takes longer to cool a body to the target temperature than it does to get a patient into the cath lab and a PCI started. It takes an average of 31 minutes from the time of onset to achieve a temperature <35°C, but it only takes 18 minutes for a patient to arrive at the hospital and be prepped for PCI. An investigator concluded, "I don't think, based on this, that the company can get FDA approval, and it is still a little early to do this in clinical practice, but I am very, very optimistic that future studies will show positive results."

COOL-MI Results

Measurement	Cooling n=177	Control n=180	p-value
Primary Endpoint #1: Infarct size at 30 days (by PECT)	13.8%	14.1%	Nss
Infarcts size in anterior MI patients	9.3% (n=16)	18.2%	p=.05
Primary Endpoint #2: MACE at 30 days	3.9%	6.2%	Nss
Death	2.2%	3.4%	Nss
Re-infarct	1.7%	0.6%	Nss
Peak CK-MB	49.8	46.9	Nss

Reliant's Reprieve Endovascular Temperature Therapy System was used for the cooling. Reprieve is a closed loop heat exchange catheter that is placed into the inferior vena cava. Cool saline is circulated through the catheter to cool the patient's blood and thereby reduce core temperature. As part of the cooling protocol, patients were administered oral buspirone (60 mg) and meperidine infusion at 25-30 mg/hour

to control shivering. A forced air blanket was also used to warm the patient's chest and further suppress shivering.

One of the things investigators will be exploring in the future is ways of getting a person's temperature down quicker – or, perhaps, delaying the PCI until the patient is cooled sufficiently. An investigator said, "The company will look at methods of improving the speed of cooling…and we think getting the body cooled quicker will be important…It will be an interesting question whether we can delay opening an artery in order to cool the patient before PCI…There is a concern that doctors wouldn't sit with a wire or balloon waiting for the cooling, but, based on this, we think a strategy of waiting 10-15 minutes may be efficacious."

One option may be to use contact cooling in the ambulance to start the cooling process. An expert said, "Contact surface devices might be a good start, but they take 90-120 minutes to achieve therapeutic cooling."

NON-INVASIVE CARDIAC IMAGING

Are new, non-invasive cardiac imaging modalities – PET, CT angiography, MRI -- ready for prime time? Most sources didn't think so – but it is improving and holds promise for the future. Following are some comments made about these technologies:

- **MRI angiography.** One speaker said, "MRI will help identify infarcts in ways not previously possible...but it has a long way to go…The problem is with the false positives…It has high sensitivity but low specificity…MIR can identify plaque." Another speaker said, "MRI can give spectacular pictures of the coronary anatomy, but it requires a perfectly regular heart rhythm."
- **Coronary CT angiography.** A speaker said, "The detail can be exquisite…It is good for identifying calcified lesions." Another speaker said, "We will be going to multi-slice (spiral) CT...but we are not there yet….We can get useful information with certain selected patients with CT." A third expert said, "It is clear that we need to have conjunction of CT and MRI…but, in my opinion, probably the cath lab of the future will do functional assessment with MRI but first do a multiscan CT." ♦