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Quick Pulse

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Trends-in-Medicine

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BOSTON SCIENTIFIC'S TAXUS STENT GETS FDA PANEL RECOMMENDATION

The FDA's Circulatory System Devices Panel voted unanimously on Thursday, November 20, 2003, to recommend approval of Boston Scientific's Taxus (paclitaxel-eluting) stent. The panel put five conditions on approval:

1. Plavix/Ticlid continuation for six months.
(passed unanimously)
2. Wording in the label that the potential interaction between paclitaxel and stents eluting other compounds has not been studied.
(passed unanimously)
3. A mention in the label of the maximum expansion diameter of the stent.
(passed unanimously)
4. The rates in all tables to be corrected to reflect actual numbers.
(passed unanimously)
5. A change in the label to say Taxus "reduces restenosis compared to the comparator (a bare Express stent)." (NOTE: The label for the bare Express stent does not have a claim of reducing restenosis).
(passed by a vote of 5 yes, 4 no)

Three other conditions were suggested by panel members but rejected:

- a. Labeling that interaction between this and brachytherapy has not been studied. This was withdrawn because the language is already in the warning section.
- b. Deletion of a warning that patients with a Taxus stent can't undergo MIR because Taxus is a non-ferromagnetic stent. It was decided to leave this issue to the FDA.
- c. A modification to the label to change "de novo lesions" to "ischemic-driven de novo lesions." This was not passed.

Other conditions already have been worked out with the FDA, including:

- **Marketing study.** Boston Scientific and the FDA had previously agreed to a marketing study to begin before approval and continue after approval. This peri/post approval study will be in two parts. Phase 1 will be a pre-market Continued Access Study with up to 500 consecutive patients enrolled at 10 U.S. sites. Phase 2 is a post-marketing registry with 1,500 consecutive patients enrolled at 40 U.S. sites. Geographically diverse U.S. community-based facilities representing a variety of annual implant volumes will participate.
- **Overlapping stents.** Overlapping stents are not forbidden, but there will be wording saying they have not been evaluated.

➤ **Cytostatic agent.** Boston Scientific had sought – but isn't getting – the right to describe paclitaxel as a cytostatic agent rather than a cytotoxic agent. An FDA official said, "We talked with the company about that, and we don't think the data is there to support this...They may plan to address that at a future time." A Boston Scientific official said, "We removed that claim until we gather more data to support it."

Thus, the recommended label is:

Taxus Express² paclitaxel-eluting stents (over the wire and rapid exchange) are indicated for improving luminal diameter and reducing restenosis (more than the comparator) for the treatment of de novo lesions ≤ 28 mm in length in native arteries ≥ 2.5 - ≤ 3.75 mm diameter.

By comparison to the panel last year on Johnson & Johnson's sirolimus-eluting Cypher stent, this was a very friendly panel. Dr. Douglas Throckmorton, Director of the FDA's Division of Cardio-Renal Drug Products, CDER, participated actively in that panel, but he was noticeably absent at this Taxus panel. Panel members – and even some FDA staffers – praised Boston Scientific and the Taxus investigators for a good and thorough data presentation. Among their comments were:

- "What impressed me is that you didn't put together one team to do one study...This seems to be a very impressive effort with a lot of planning at each stage...It is a beautiful job."
- "Congratulations for the database presented...I'd like to take whoever chose this dose to Las Vegas with me the next time."
- "The sponsor brought a well-planned and well-managed study, and I complement the agency (FDA) for its precise and pertinent review."
- "I complement the company for the preparation of the overall package."

THE FDA POSITION

The FDA issued a Major Deficiency Letter to Boston Scientific on September 15, 2003, and the company began responding to the letter on September 30th, completing the response on November 5th. Those answers are currently under review by the FDA.

The FDA's lead reviewer for Taxus indicated there are really two out-standing issues:

1. **Whether Taxus clinical data adequately addresses concerns raised by animal studies.** This is what the panel discussed.

2. **Product stability testing.** The FDA reviewer said the company has set aside sufficient product for testing post-approval, and there is "no evidence of a problem."

The FDA staff also expressed some concern about PAM (parastrut amorphous material, also identified as "drug effect," strut fibrin, and thrombus), medial loss, and calcification with Taxus. Dr. Mary Russell, Medical Director and Vice President of Clinical Science at Boston Scientific, responded:

- There are more calcium deposits with Taxus than a bare stent, but the deposits are more diffuse with paclitaxel.
- There is medial cell loss, but it is replaced by structural fibrous tissue.
- There are rare microthrombi, but no evidence of gross thrombi.
- Neointima forms over, around and between struts. There are healthy endothelial cells and strut coverage by 28 days.

THE BOSTON SCIENTIFIC PRESENTATION

The principal investigator, Dr. Gregg Stone of Lenox Hill Hospital, presented the clinical results – and they did not differ in any way from the figures presented at TCT2003 from TAXUS-IV (*see the end of this report*). His emphasis was the amount of reduction, not the absolute figures, though those also were presented:

- a. 61% reduction in the primary endpoint of 9-month TVR
- b. 73% reduction in 9-month TLR
- c. 77% reduction in in-stent restenosis
- d. 70% reduction in in-segment restenosis
- e. 43% reduction in MACE at 9 months

Two issues that have been in the news recently with respect to Johnson & Johnson's Cypher sirolimus-eluting stent also were addressed – SATs and hypersensitivity. On drug hypersensitivity, Dr. Stone said there were two cases in the first 30 days in the TAXUS-IV trial, and neither was due to paclitaxel or to the Taxus stent. One was blamed on an allergic reaction

Taxus Stent Thromboses (SATs) through November 14, 2003

Studies	Number of patients	Total	≤ 30 days	31-180 days	>180 days
Completed trials	987	8	3	2	3
Ongoing studies -- TAXUS-V, TAXUS-VI, TAXUS-VI-ISR	1,747	13	12	0	1
Post-approval studies – WISDOM, MILESTONE-II	3,072	11	10	1	0
Investigator trials – TRUE, T-Search	932	7	---	---	---
Consumer reporting	69,126 stents sold	8	8	0	0
TOTAL	47 75,864 stents	47 (0.06%)	33	3	4

to clopidogrel (Sanofi's Plavix) and the other (swollen tongue/difficulty in breathing) to concomitant ACE inhibitor use. Each case resolved after the Plavix or ACE, respectively, was stopped.

THE PANEL DISCUSSION

The panel had questions for Boston Scientific, but they were mostly softballs with no sting. *Among the questions posed were:*

Endothelialization at 28 days. Boston Scientific was asked why the submission says there is partial endothelialization at 28 days, but company speakers said endothelialization was complete at 28 days. A Boston Scientific official said this had to do with statistical analyses. A panel member responded, "It bothers me when data is not congruous...The presentation says it is...I understand pathology is not black and white, but I think the presentation could have more clearly presented that."

Lack of dose-finding studies. Boston Scientific's Dr. Russell responded, "We are very confident of the reproducibility of our preclinical implant model for safety...but our model produces a very thin neointima which was inadequate for efficacy evaluations, so our dosing decision was made by establishing safe formulations by detailed histologic studies, and efficacy is being studied in the human atherosclerotic disease milieu." A Boston Scientific expert added, "We don't know the low end (for efficacy). We do know the high end (for safety)."

Plans for the MR dose. Dr. Russell said, "The IVUS findings were very similar between the SR and MR formulations...and the study was not powered to show a difference between SR and MR...but nonetheless the percent net volume obstruction was nearly identical at six months...We spent some time analyzing this, and our conclusion was: One possible explanation was that we had reached the dosing threshold with the SR, and there was no additional benefit for the 3-time higher release with the MR formulation in this standard, low-risk lesion set...So we actively pursued TAXUS-VI which includes higher risk lesions subsets -- longer lesions, more diabetics, etc...and we are awaiting the MR release results of those subsets to make a decision on whether MR has added value to SR in more complex lesions."

Comparison of Taxus MR and SR Formulations

Characteristic	Moderate Release	Slow Release
Dose density	1 µg/mm ²	1 µg/mm ²
Coating thickness	16-18 µm	6-8 µm
Drug distribution	Sparser	Denser
Paclitaxel/polymer ratio	Lower	Higher
Drug release <30 days	7.5%	21.9%

Long-term follow-up. Boston Scientific has committed to following the TAXUS-IV patients for five years. There are some animals that may be sacrificed at 24 months, though the

company Scientific was seeking guidance on whether it should wait and sacrifice them at 36 months instead.

Additional data was presented on events that occurred between nine and 12 months in TAXUS-IV, showing, what Dr. Stone called "a trend to less events with Taxus than control."

TAXUS-IV: 9 to 12 Month Safety Results

Adverse Event	Control	Taxus	p-value
Cardiac death	0.2%	0	Nss
MI	1.1%	0	p<.007
TLR	4.0%	1.4%	p<.003
TVR	5.8%	2.4%	p<.002
MACE	6.3%	2.4%	p<.0006
TVF	6.1%	2.4%	p<.0006

Diabetics. There was a discussion as to whether there were sufficient diabetics in the trials, and the panel seemed to accept that there were.

Paclitaxel remaining on the stent after 30 days. A panel member commented, "My concern is with the paclitaxel left on the stent. Wouldn't it be better to get rid of it?"

CVAs and hematologic dyscrasias. A panel member was concerned with the small but real incidence of these side effects. Dr. Stone responded, "There is no real pathophysiologic relationship between stent implantation and stroke...We don't think emboli are forming in the stent and moving to the circulation...I can't think of a paclitaxel relationship to stroke, especially since there are no detectable systemic levels...The p-value is not statistically significant for the dyscrasias, and we don't think there should be any systemic accumulation in the bone...And there are things paclitaxel could do like rash, that we saw less of." Boston Scientific's Dr. Russell added, "We actually looked at the individual reports for those 10 events...5 or 6 of them were formal CVAs, the others were TIAs...Of the five, one occurred in a patient who, against protocol, had a history of recurrent CVAs, and another was in a patient who had a stroke post-knee replacement surgery...That is fairly anecdotal, but that is the breakdown, and we did look at that closely...On the hematologic dyscrasia -- a scary word that reflects how reporting was done -- ...the majority of them were bruising and rashes...and we have the superimposed complexity of the antiplatelet therapy."

Polymer safety. A panel member commented, "We shouldn't glibly expect (the issue) to just be paclitaxel...It could be the polymer...and we don't have huge experience with the polymer." A Boston Scientific official said, "With the low drug:polymer ratio, we would very much expect to see some drug retention...so we did some very extensive testing...and there was no change in chemical properties...and no difference between polymer and bare stent...The polymer is very biostable."

Short (8-12 mm) stents. These were not studied in TAXUS-IV, but the panel felt they should be approved anyway. Dr. Stone said, "Given the fact that we did see benefits in all lesion lengths, I think it is reasonable to include all lengths... One of drawbacks, if any, in this trial was we didn't have shorter stents available...We have a lot of experience with bare 8 mm and 12 mm stents, and we know those are appropriate, so while there is no data yet, this is an extension of reasonable clinical experience, and, given the dose is less, it should be safe and effective." Dr. Russell said, "No issues were identified with longer stents, so it is unlikely there will be issues with smaller stents." A panel member said, "I defer to the interventional cardiologists, but I would see frequently multiple stent usage if this is approved." The panel chairman said, "You are encouraging people to cover dissections by asking for this...and the vast majority of the literature says to leave edge dissections alone – whether it's a drug-eluting stent or a bare stent."

THE FDA'S QUESTIONS

After the presentations and discussion, the FDA posed the following series of questions for the panel to discuss. The panel's consensus is listed in red at the end of each, followed by selected panel and FDA comments.

1. Does the combination of 9 month clinical data from the pivotal TAXUS IV (SR formulation) study and the adjunctive data from TAXUS I (SR formulation) and TAXUS II (SR and MR formulations) adequately address the potential concerns raised by the animal studies? YES

The panel chairman said, "I think the consensus of the panel is that, at the 9-month clinical endpoint, the data is convincing, but none of us are comfortable with a 9-month cutoff to establish safety, certainly not with respect to those issues raised by the animal studies. We would like to see a longer term study... We are all in accord with safety out to nine months, but we await additional long-term clinical data to be fully assured (of the safety)."

2a. Are the clinical studies presented adequate to address concerns about possible adverse effects from interactions with drugs typically administered to the target patient population? YES

There was a member of the panel who felt there are theoretical consideration of drug/drug interaction that have not been evaluated, but the rest of the panel did not believe there are any serious drug/drug interactions, though they cannot be certain.

2b. Please comment on whether the clinical studies adequately address other drug interactions that are likely to be important or of interest. If not, what other information or studies should be provided? Specifically,

please consider the potential for the following types of interactions: with anti-neoplastic agents or with chemotherapeutic agents (where a hypersensitivity reaction could be induced). NO, but this was not an area of major concern for the panel.

The chairman said, "We didn't spend a great deal of time on this...It is a small point, and we shouldn't hang ourselves up on this." A panel member agreed, "We don't have adequate information, but it shouldn't preclude availability of the product. (But) the panel wants to encourage long-term follow-up in animal studies." Another panel member said, "I don't think we are exposing patients to hypersensitivity...I don't think even on a theoretical basis that we should be concerned with drug/drug interaction when a second drug will be administered later." A third panel member said, "As a user myself, I would like to know if there is a potential problem, an unknown risk but perhaps a risk -- to raise that awareness." Dr. Bram Zuckerman, head of Cardiovascular Devices at the FDA's CDRH, concluded, "This whole issue needs to be better discussed with the sponsor."

3. Do the clinical data submitted from the pivotal TAXUS IV (SR formulation) study, plus the data from the adjunctive TAXUS I (SR formulation), and TAXUS II (SR and MR formulations) studies, provide reasonable assurance of safety? YES

The panel chairman said, "The panel is in agreement that there is a reasonable assurance of safety...but beyond 270 days, we need to be very, very circumspect."

4. Does the clinical data at 270 days presented on the TAXUS stent from the pivotal TAXUS IV study provide reasonable assurance of effectiveness? YES

5a. Does the evidence presented on the TAXUS product support the proposed labeling indication?

Not as originally proposed, but the panel

- a. Favored approval of the shorter (8-12 mm) stents anyway.**
- b. Favored inclusion of language claiming "reduction of restenosis" in the label**
- c. Wanted the reduction of restenosis clarified to say it was vs. a bare Express stent, not all bare stents.**
- d. Thought de novo lesions should be clarified to specify those with evidence of ischemia, but this idea was later dropped.**

A panel member said, "I want to give this issue the benefit of the doubt...I would want those (shorter lengths) on my shelf...It's the same stent, not a different device...The sponsor also is asking for a diameter that is not tested, but cutting it shorter just means less drug delivered, so the whole risk might be a loss of efficacy or less dose, but I don't see how it would increase risk or make it unsafe...and I don't see any evidence

of unsafety... If the sponsor hadn't asked for shorter lengths, I would be asking them to cut them up and give me shorter ones."

Other comments included:

- "As a clinician I agree, but does the data support that? We have to say, no."
- "I'd like to point out there is no evidence presented on this."
- "I think we'd be hampering clinicians if they didn't have access to all the lengths requested." The FDA's Dr. Zuckerman concluded, "I think we've heard your opinion, and we'll act accordingly."
- "If we don't provide 8 mm stents, people will take longer stents and have a longer overlap, which I would argue is worse...From a practical, real world point of view, you have to make the shorter lengths available."

5b. Please comment on whether the labeling should specify that multiple stents should only be used for bailout purposes (e.g., dissection, insufficient lesion coverage) and whether in these cases the shortest stent available (i.e., 8 mm) should be used. NO

The chairman said, "We feel that the 8-1 mm stents should be approved for reasons of expedience, convenience and general availability, not necessarily for coverage of dissections for which there was not enough documentation in this particular protocol."

5c. Please comment on whether the labeling should address the potential combination of the TAXUS stent with an additional drug-eluting stent in the same vessel. YES

5d. Please comment on whether the labeled recommendation for post-procedural antiplatelet regimen is appropriate, and whether additional recommendations on procedural anticoagulation regimens are warranted. YES, according to the trial protocol (6 months clopidogrel and aspirin indefinitely)

5e. Please comment on any other aspects of the product labeling, such as

(1). Contraindications – The ones used in the trial be accepted, including history of allergy to nickel or stainless steel.

(2) Warnings/Precautions (such as use with brachytherapy, conjunction with other procedures, etc.). A warning against use in brachytherapy patients should be included, and a caution should be included that there is no data on combining two different drug-eluting stents.

A panel member explained, "Clinicians should be aware this has not been studied, and there is no information and should be taken under advisement in selecting a product."

6. Please discuss long-term adverse effects that may be associated with TAXUS™ stents, and whether the proposed 5-year follow-up on the clinical trial cohorts and the proposed pre/post-marketing study are appropriate to evaluate the chronic effects of the implantation of the TAXUS™ stent. If not, what additional information should be collected? Specifically, discuss how long patients should be followed, and what endpoints and adverse events should be measured.

5 year follow-up is absolutely mandatory.

The FDA's Dr. Zuckerman said, "We have safety data to 270 days, and in the ideal setting we might want 10 years, but there are pre- and post-approval bounds...The sponsor gave an indication of the main safety problems they would be looking at, and the Agency is in general concurrence."

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
<i>Primary Endpoint:</i> 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

TAXUS-4 IVUS Results at 9-Months *

Measurement	Control n=80	Taxus n=81
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.

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