

SUMMARY OF SAFETY AND EFFECTIVENESS (SSED)

I. GENERAL INFORMATION

Device Generic Name: Drug-Eluting Coronary Stent System (NIQ)

Device Trade Name:

TAXUS® Express²™ Paclitaxel-Eluting Coronary Stent System (Monorail) and
TAXUS® Express²™ Paclitaxel-Eluting Coronary Stent System (Over-the-Wire)

Applicant's Name and Address:

Boston Scientific Corporation
One Boston Scientific Place
Natick, MA 01760-1537
USA

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P030025/S028

Date of FDA Notice of Approval: September 24, 2008

Expedited: Not applicable

The original PMA (P030025) was approved on March 4, 2004 and is indicated for improving luminal diameter for the treatment of de novo lesions <28 mm in length in native coronary arteries >2.5 to <3.75 mm in diameter. The SSED to support the indication is available on the CDRH website and is incorporated by reference here: <http://www.fda.gov/cdrh/pdf3/P030025b.pdf>. Additionally, PMA supplement P030025/S021, approved September 24, 2008, expanded the indications of the product, specifically, for improving luminal diameter for the treatment of de novo lesions in native coronary arteries ≥ 2.25 to ≤ 4.0 mm in diameter in lesions ≤ 28 mm in length. The current supplement was submitted to further expand the indication for the TAXUS Express² Paclitaxel-Eluting Coronary Stent System to include in-stent restenosis (ISR).

II. INDICATIONS FOR USE

The TAXUS Express² Paclitaxel-Eluting Coronary Stent System is indicated for improving luminal diameter for the treatment of de novo lesions in native coronary arteries ≥ 2.25 to ≤ 4.00 mm in diameter in lesions ≤ 28 mm in length, and within bare metal stent restenotic lesions ≥ 2.5 to ≤ 3.75 mm in diameter and ≤ 28 mm in length.

III. CONTRAINDICATIONS

Use of the TAXUS Express² Paclitaxel-Eluting Coronary Stent System is contraindicated in patients with:

- Known hypersensitivity to paclitaxel or structurally-related compounds.
- Known hypersensitivity to the polymer or its individual components (see details in Section 1.2.2., Translute™ Polymer Carrier, Page 5 of labeling).

Coronary Artery Stenting is contraindicated for use in:

- Patients who can not receive recommended anti-platelet and/or anticoagulant therapy.
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery device.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the TAXUS Express² Paclitaxel-Eluting Coronary Stent System Directions for Use (DFU).

V. DEVICE DESCRIPTION

The TAXUS Express² Paclitaxel-Eluting Coronary Stent System is a device / drug combination product comprised of two regulated components: a device (Express² Coronary Stent System) and a drug product (a formulation of paclitaxel contained in a polymer coating). The components and characteristics of the TAXUS Express² Paclitaxel-Eluting Coronary Stent System are identical to the product approved in P030025 and updated in P030025/S021, which was an approval of the expanded sizes of 2.25 and 4.0 mm stents. Please refer to the original device description for additional details.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other treatment alternatives for coronary artery disease: drug therapy, percutaneous coronary interventions (such as angioplasty and placement of bare metal stents), and coronary artery bypass surgery (CABG). Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The TAXUS Express² Paclitaxel-Eluting Coronary Stent System has been approved for commercialization in the following countries:

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|-------------------|------------------|-----------|-----------|
| ▪ Algeria | ▪ Dominican Rep | ▪ Latvia | ▪ Qatar |
| ▪ Antigua/Barbuda | ▪ Dutch Antilles | ▪ Lebanon | ▪ Romania |
| ▪ Argentina | ▪ Ecuador | ▪ Lebanon | ▪ Russia |

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|------------------|-----------------|-----------------|------------------------|
| ▪ Armenia | ▪ El Salvador | ▪ Liechtenstein | ▪ Saudi Arabia |
| ▪ Aruba | ▪ Estonia | ▪ Lithuania | ▪ Scotland |
| ▪ Australia | ▪ Finland | ▪ Luxembourg | ▪ Serbia/Montenegro |
| ▪ Austria | ▪ France | ▪ Macau | ▪ Singapore |
| ▪ Bahamas | ▪ Georgia | ▪ Macedonia | ▪ Slovakia |
| ▪ Bahrain | ▪ Germany | ▪ Malaysia | ▪ Slovenia |
| ▪ Bangladesh | ▪ Great Britain | ▪ Malta | ▪ South Africa |
| ▪ Barbados | ▪ Greece | ▪ Martinique | ▪ Spain |
| ▪ Belarus | ▪ Guatemala | ▪ Mauritania | ▪ Sri Lanka |
| ▪ Belgium | ▪ Guyana | ▪ Mauritius | ▪ Suriname |
| ▪ Belize | ▪ Haiti | ▪ Mexico | ▪ Sweden |
| ▪ Bermuda | ▪ Honduras | ▪ Moldavia | ▪ Switzerland |
| ▪ Bolivia | ▪ Hong Kong | ▪ Myanmar | ▪ Thailand |
| ▪ Bosnia | ▪ Hungary | ▪ Nepal | ▪ Trinidad/Tobago |
| ▪ Brazil | ▪ Iceland | ▪ Netherlands | ▪ Tunisia |
| ▪ Brunei | ▪ India | ▪ New Zealand | ▪ Turkey |
| ▪ Bulgaria | ▪ Indonesia | ▪ Nicaragua | ▪ United Arab Emirates |
| ▪ Chile | ▪ Iraq | ▪ Norway | ▪ Uruguay |
| ▪ China | ▪ Ireland | ▪ Oman | ▪ Venezuela |
| ▪ Colombia | ▪ Israel | ▪ Pakistan | ▪ Vietnam |
| ▪ Costa Rica | ▪ Italy | ▪ Panama | ▪ West Bank Gaza Strip |
| ▪ Croatia | ▪ Jamaica | ▪ Paraguay | ▪ Yemen |
| ▪ Cyprus | ▪ Jordan | ▪ Peru | |
| ▪ Czech Republic | ▪ Kenya | ▪ Philippines | |
| ▪ Denmark | ▪ Korea | ▪ Poland | |

From January 1, 2007 - December 31, 2007, approximately 873,775 TAXUS Express² stents have been distributed worldwide. The TAXUS Express² Paclitaxel-Eluting Coronary Stent System is currently not approved in any other countries for the ISR indication.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse events (in alphabetical order) which may be associated with the use of a coronary stent in native coronary arteries include but are not limited to:

- Abrupt Stent Closure
- Acute myocardial infarction
- Allergic reaction to anticoagulants or antithrombotic therapy or contrast medium or stent materials including stent scaffold, polymer coating or drug
- Aneurysm (Coronary)
- Angina
- Arrhythmias, including ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Arteriovenous Fistula
- Cardiac Tamponade
- Cardiogenic Shock
- Death

- Dissection
- Emboli, distal (air, tissue, thrombotic, device materials or stent delivery system materials)
- Heart Failure
- Hematoma
- Hemorrhage, requiring transfusion
- Hypotension/Hypertension
- Infection, local and/or systemic
- Ischemia, myocardial
- Pain at the access site
- Perforation or Rupture of one or more coronary arteries
- Pericardial effusion
- Pseudoaneurysm, femoral
- Pulmonary edema
- Renal Failure
- Respiratory Failure
- Restenosis of stented segment
- Shock
- Stent embolization
- Stent migration
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident/Transient Ischemic Attack (TIA)
- Total occlusion of coronary artery
- Vessel Spasm
- Vessel trauma (dissection, perforation, rupture or injury, including coronary) requiring surgical repair or reintervention

Potential adverse events not captured above, that may be unique to the paclitaxel drug coating:

- Allergic/immunologic reaction to drug (paclitaxel or structurally-related compounds) or the polymer stent coating (or its individual components) or 316L stainless steel (or any of its components)
- Alopecia
- Anemia
- Blood product transfusion
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage or necrosis
- Myalgia / arthralgia
- Peripheral neuropathy

There may be other potential adverse events that are unforeseen at this time.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Biocompatibility Studies

The biocompatibility testing information included in the original PMA submission (P030025, approved March 4, 2004) and provided for the matrix expansion in Supplement 21 to P030025 are directly applicable to this PMA Supplement. Therefore, the information is not repeated herein.

B. In Vitro Engineering Studies

The non-clinical bench testing included in the original PMA submission (P030025, approved March 4, 2004) and provided for the matrix expansion in Supplement 21 to P030025 are directly applicable to this PMA Supplement. Therefore, only the information specific to the in-stent restenosis (ISR) indication is repeated herein (**Table 1**).

Table 1: In-Vitro Engineering Testing		
Stent, System and Coating Durability Testing		
Stress Analysis (FEA)	An in-depth analysis of the stent was conducted to ensure that the stent would not fail due to fatigue under implant conditions. The FEA evaluated the structural integrity of the stent and coating when subjected to the expected loading conditions generated in coronary arteries. The analysis took into account manufacturing, delivery, implantation and clinical loading over the implant life, and predicted that fatigue failures will not occur over 400 million cycles of loading.	Pass
Fatigue Analysis	Testing was conducted on the TAXUS Express ² stent and the stent coating to demonstrate that the stent and/or coating do not exhibit failure due to fatigue. All test samples met product specification.	Pass
Accelerated Durability Testing	Accelerated in vitro testing of approximately 10 years (400 million cycles) equivalent real time was conducted to ensure that the stents, when expanded to their largest intended diameters, will not show fatigue failure during simulated 10 year life span testing. All tested stents were free from fatigue induced surface defects, and there was no evidence of coating fatigue or corrosion. The stent met the 10 year accelerated fatigue resistance requirement of the product specification. Overlapping stents were also evaluated in an accelerated in vitro test of approximately 10 year equivalent real time and met visual requirements for coating integrity and strut damage.	Pass
Coating Durability	The coating durability of the TAXUS Express ² stent coating was assessed via a series of acute and long term in vitro and in vivo tests performed on the coated stent and the SIBS polymer. The test results demonstrate that the paclitaxel/SIBS coating displays good durability and coating integrity that will be maintained throughout the lifetime of the coated stent implant.	Pass

C. Coating and Characterization Testing

The Coating and Characterization information included in the original PMA submission (P030025, approved March 4, 2004) and provided for the matrix expansion in Supplement 21 to P030025 are directly applicable to this PMA Supplement. Therefore, only the information specific to the ISR indication is repeated herein (Table 2).

Table 2: Coating Characterization Testing

Test	Description of Test
Material Characterization	
Particulates	Particulate levels were evaluated for the TAXUS Express ² stent system post tracking and post deployment. The data demonstrated comparable results to the comparison devices.

D. Chemistry, Manufacturing and Controls Testing

The CMC information included in the original PMA submission (P030025, approved March 4, 2004) and provided for the matrix expansion in Supplement 21 to P030025 are directly applicable to this PMA Supplement. Therefore, the information is not repeated herein.

E. Stability

Site-specific stability studies were conducted to establish a shelf life/expiration date for the TAXUS Express² Coronary Stent System. Based on these studies, a shelf life of 12 months is appropriate.

F. Sterilization

The TAXUS Express² Coronary Stent System is sterilized using ethylene oxide sterilization, and has been validated per AAMI/ISO 11135:1994 "Medical Devices - Validation and Routine Control of Ethylene Oxide Sterilization."

Results obtained from the sterilization studies show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6} .

The amount of bacterial endotoxins was verified to be within the specification limit for TAXUS Express² Coronary Stent Systems.

G. Animal Studies

The non-clinical studies included in the original PMA submission (P030025, approved March 4, 2004) and provided for the matrix expansion in Supplement 21 to P030025 are directly applicable to this PMA Supplement. Therefore, only additional information supportive of the ISR indication is repeated herein (**Table 3**).

Table 3: Summary of Supportive Animal Studies

Study #	Type/# of Animals	Timepoints	Objective/Study Design	Key Endpoint Results
RVF03-082*	Domestic Swine- 2 overlap pairs/animal; 55 animals total	28, 90, 180, 360 days	<ul style="list-style-type: none"> Evaluated histology, mortality, myocardial effects at 30, 90, 180 and 360 days Test and Control overlapping stent pairs in each animal Total 55 animals 	<ul style="list-style-type: none"> No mortality (cardiac, stent-related or non-stent related) or histologic myocardial infarcts No downstream effects in myocardium, kidney, liver All vessels patent, no gross or microthrombus <p>Conclusion: Confirms and extends safety observations regarding TAXUS Slow Release Formulation.</p>
BS5P	Domestic Swine - 2 overlap pairs/animal; 37 animals total	30, 90, 180 days	<ul style="list-style-type: none"> Established safety margin using moderate release formulation for clinical formulation in overlap stent Evaluated histology, mortality, and myocardial effects at 30, 90, and 180 days Test and Control overlapping stent pairs in each animal Total 37 animals 	<ul style="list-style-type: none"> No stent-related mortality, distal myocardial effects, or gross or microthrombi, all vessels patent Intimal thickness lower for TAXUS overlap segments as compared to Controls, difference diminished by 90 days as expected in healthy swine model No aneurysmal dilatation of stented vessels <p>Conclusion: Safety Margin for Slow Release and safety of overlapping Moderate Release stent configuration established.</p>
RVF 02-069*	Domestic Swine- 2 overlap pairs/animal 11 animals total	180 days	<ul style="list-style-type: none"> Evaluated mortality, morphology, morphometry, myocardial effects at 180 days Test and Control overlapping stent pairs in each animal Total 11 animals 	<ul style="list-style-type: none"> No stent-related mortality, distal myocardial effects, total occlusions, or thrombi Endothelial cell coverage in TAXUS overlap segment comparable to Control in overlap and non-overlap segments Widely patent vessels All struts covered by mature neointima No safety issues <p>Conclusion: Extends observations from the Moderate Release overlapping stent study to the Slow Release formulation.</p>

* These studies were conducted using the Slow Release Formulation

These data demonstrate a consistent and positive safety profile of the TAXUS coronary stent.

H. In Vivo Pharmacokinetics Studies

The non-clinical chemistry study information included in the original PMA submission (P030025, approved March 4, 2004) and provided for the matrix expansion in Supplement 21 to P030025 are directly applicable to this PMA Supplement. Therefore, the information is not repeated herein.

X. SUMMARY OF PRIMARY CLINICAL STUDY

TAXUS V – IN-STENT RESTENOSIS INDICATION EXPANSION CLINICAL TRIAL

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of coronary drug-eluting stent implantation with the TAXUS Express² Coronary Stent System for use within bare metal stent restenotic lesions ≥ 2.5 to ≤ 3.75 mm in diameter and ≤ 28 mm in length. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

Study Design

TAXUS V – In-stent restenosis (ISR) was a prospective, randomized, open-label, controlled, multicenter study conducted in the U.S. The study objective was to demonstrate a non-inferior or superior 9-month target vessel revascularization (TVR) rate for the TAXUS Express slow-release (SR) Stent compared to intra-coronary brachytherapy (beta source) for the treatment of in-stent restenosis (ISR) in a previously implanted bare metal stent in a single native coronary vessel (cumulative target lesion length ≤ 46 mm, baseline reference vessel diameter ≥ 2.5 mm to ≤ 3.75 mm).

Patients were to be randomized (1:1) to receive either the TAXUS Stent or brachytherapy (using any FDA-approved beta source intra-coronary brachytherapy system approved for use at the study center). Enrollment of 488 patients at 40 clinical sites was planned. Due to sites reporting lack of use and technical support for current brachytherapy systems, FDA granted permission for the sponsor to stop enrollment in the brachytherapy arm and enroll an additional 25 patients in the TAXUS Stent group as a single arm registry. A total of 421 patients [220 TAXUS Stent (includes the 25 registry patients), 201 brachytherapy] enrolled at 37 sites in the U.S. and Canada are included in the Intent-To-Treat (ITT) analysis. While all 220 TAXUS Stent patients are represented in this document, for scientific publication and presentation purposes, the trial Principal Investigators presented only the 195 randomized TAXUS Stent patients.

Aspirin treatment was mandated for 9 months after the procedure, and recommended indefinitely. Antiplatelet treatment (clopidogrel or ticlopidine) was mandated for 6 months post-procedure in all patients (recommended for 12 months), and mandated for 12 months in any brachytherapy patient also receiving a new stent.

Follow-up was performed at 1, 4, 9, and 12 months post-procedure with yearly follow-up for clinical parameters through 5 years. After the 1-year follow-up, the TAXUS V ISR study population was reduced to a pre-specified cohort (Safety Population), which consists of all patients who received a study treatment (TAXUS stent implanted or delivery of brachytherapy) at the index procedure.

Angiographic follow-up at 9 months was to be completed for all patients. A subset of 250 patients was to be enrolled into the IVUS substudy and undergo IVUS imaging at baseline and 9 months to identify potential safety concerns and understand the impact of the protocol-mandated angiography on clinical revascularization rates. For patients treated with TAXUS stents, angiographic assessments were performed for the area of the vessel within the TAXUS stent margins (in-stent) and for the area within the TAXUS stent margins plus the area immediately 5 mm proximal and distal from the TAXUS stent margins (analysis segment). For patients treated with brachytherapy, angiographic assessments were performed for the radiation segment plus 5 mm on both the proximal and distal edges of the radiation segment.

This trial utilized a clinical events committee (CEC) to adjudicate potential Major Adverse Cardiac Events (MACE) including all reported death and stent thromboses. During the course of the trial, the data monitoring committee (DMC) reviewed accumulating safety data to monitor for incidence of MACE and other trends that might warrant modification of the trial. Core labs were used for central assessment of angiography, IVUS, ECG and blood lab data, and were blinded to treatment assignment.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the TAXUS V ISR study was limited to patients who met the following inclusion criteria:

1. Patient was ≥ 18 years old
2. Eligible for percutaneous coronary intervention (PCI)
3. Documented stable angina pectoris (Canadian Cardiovascular Society Classification 1, 2, 3, or 4) or unstable angina pectoris with documented ischemia (Braunwald Class IB-C, IIB-C, or IIIB-C), or documented silent ischemia
4. Left ventricular ejection fraction of $\geq 25\%$
5. Acceptable candidate for CABG
6. Patient (or legal guardian) understood the study requirements and the treatment procedures and provided written Informed Consent before any study-specific tests or procedures were performed
7. Patient was willing to comply with all specified follow-up evaluations

Patients were not permitted to enroll in the TAXUS V ISR study if they meet the following exclusion criteria:

1. Known hypersensitivity to paclitaxel
2. Any previous or planned treatment with a non-study anti-restenotic drug-coated or drug-eluting coronary stent in the target vessel. (Note: previous or

planned treatment with heparin or phosphorylcholine coated stents was acceptable, as long as the procedure with the non-study stent met the protocol-defined criteria for staged procedures.)

3. Previous external radiotherapy to the heart or target vessel area
4. Known genetic radiation sensitivity disorders (i.e. ataxia-telangiectasia, etc.)
5. Planned use of both the assigned study treatment and a non-study stent (i.e., commercial stent) in the treatment of the target vessel
6. Previous or planned treatment with non-study intra-coronary brachytherapy in the target vessel
7. Recent MI (Symptom onset ≤ 72 hours prior to randomization)
8. CK-MB $> 2x$ the local laboratory's upper limit of normal (refers to a measured value on the day of the index procedure as drawn per protocol). A CK-MB or normal troponin laboratory result was to be available on the day of the procedure prior to randomizing the patient for patients with recent MI or unstable angina. Patients with stable angina could be randomized without lab results being received for the baseline troponin or CK-MB drawn immediately pre-procedure.
9. Cerebrovascular accident within 6 months of randomization
10. Planned CABG ≤ 9 months post index procedure
11. Acute or chronic renal dysfunction (creatinine > 2.0 mg/dl or > 177 $\mu\text{mol/L}$)
12. Leukopenia (leukocyte count $< 3.5 \times 10^9$ /liter)
13. Thrombocytopenia (platelet count $< 100,000/\text{mm}^3$) or thrombocytosis ($> 750,000/\text{mm}^3$)
14. Active peptic ulcer or active gastrointestinal bleeding, or previously active within 6 months
15. Known allergy to stainless steel
16. Any prior true anaphylactic reaction to contrast agents; defined as known anaphylactoid or other non-anaphylactic allergic reactions to contrast agents that could not be adequately pre-medicated prior to the index procedure
17. Contraindication to ASA or to both clopidogrel and ticlopidine
18. Patient was currently on warfarin or it was anticipated that treatment with warfarin would be required during any period within 6 months post the index procedure
19. Patient was currently or had been treated with paclitaxel or other chemotherapeutic agents within 12 months of the index procedure
20. Anticipated treatment with paclitaxel, oral rapamycin or colchicine during any period in the 9 months post index procedure
21. Male or female with known intention to procreate within 3 months post index procedure
22. Female of childbearing potential unless a pregnancy test (serum and/or urine) was negative within 7 days before the index procedure
23. Lactating female
24. Life expectancy of less than 24 months due to other medical conditions

25. Co-morbid condition(s) that could limit the patient's ability to participate in the study, limit compliance with follow-up requirements or impact the scientific integrity of the study
26. Planned surgical procedure requiring withdrawal of any anti-platelet therapy within 6 months post index procedure
27. Currently participating in another investigational drug or device study that had not completed the primary endpoint or that clinically interfered with the endpoints of this study

2. Follow-up Schedule

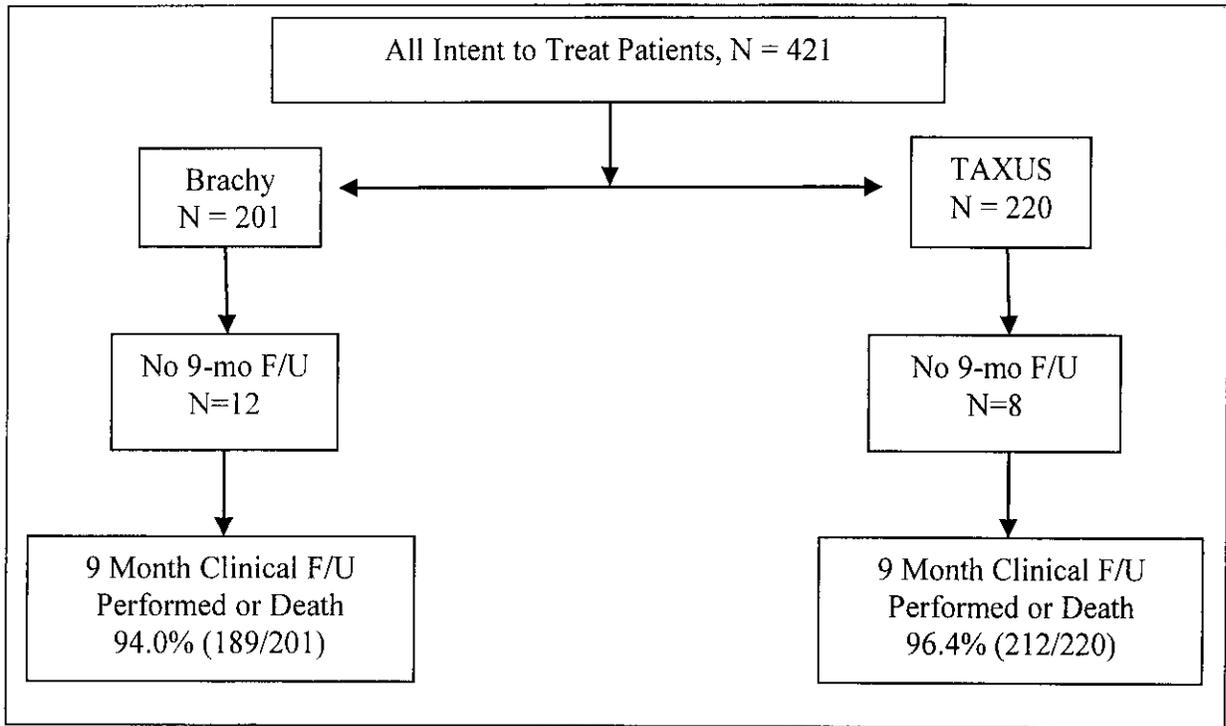
Follow-up included clinical assessments at 1, 4, and 9 months. In addition, patients agreed to annual telephone follow-up for clinical parameters through 5 years post-procedure. After the 1-year follow-up, the TAXUS V ISR study population was reduced to a pre-specified cohort (Safety Population), which consists of all patients who received a study treatment (TAXUS stent implanted or delivery of brachytherapy) at the index procedure. Follow-up through 24 months is currently available.

3. Clinical Endpoints

The primary endpoint of the study was a comparison of the rate of TVR through 9 months post-index procedure between groups. In the protocol, TVR was to be ischemia-driven, based on the presence of symptoms, positive functional testing, or Quantitative Coronary Angiography (QCA) severity of restenosis. The study was designed to sequentially test non-inferiority and then superiority of the TAXUS stent vs. brachytherapy for TVR rates at 9 months.

Major secondary endpoints included cumulative MACE rates at each follow-up time point and detailed QCA and IVUS analysis at 9 months. Additional secondary endpoints included stent thrombosis, TVF, clinical procedural and technical success rates, and binary restenosis rates.

A. Accountability of PMA Cohort



B. Study Population Demographics and Baseline Parameters

The ITT population was predominantly male (66%), past or present smokers (67%), with a history of hyperlipidemia and hypertension requiring treatment (91% and 81%, respectively). Medically-treated diabetics accounted for approximately 34% of ITT patients, and the proportion of ITT patients requiring insulin was approximately 14%. The treatment groups were well matched on baseline demographic, clinical and lesion characteristics. Statistically significant differences were observed for insulin-requiring diabetics (10.4% Brachy, 18.2% TAXUS, $P=0.0243$), lesion calcification (15.4% Brachy, 7.3% TAXUS; $P=0.0084$), and ISR pattern ($P=0.0082$) with more focal lesions in the Brachy group and more diffuse lesions in the TAXUS group.

C. Safety and Effectiveness Results

The primary endpoint of the study was met, with the superiority of the TAXUS stent demonstrated by a lower TVR rate for the TAXUS group versus the Brachytherapy group (9.7% TAXUS and 17.5% Brachytherapy; $p=0.0206$). This difference was driven by a lower target lesion revascularization (TLR) rate for the TAXUS group versus the Brachytherapy group (6.0% TAXUS and 13.9% Brachytherapy; $p=0.0071$).

Additionally, similar rates between groups for the primary safety endpoint (including cardiac death and MI) suggest comparable safety profiles at 9 months post-procedure.

Safety (Tables 4 & 5)

- MI rates (both Q-wave and non-Q wave) were comparable between the two groups at 9 months (overall MI rate was 3.7% in the TAXUS group as compared to 4.6% in the Brachy group, P=0.64).
- No cardiac deaths occurred in the TAXUS group while one cardiac death occurred in the Brachy group through 9 months post index procedure (P=0.47).
- Stent thrombosis occurred in three patients in the TAXUS group for a rate of 1.4%.

Efficacy Results (Tables 4 & 5)

- TAXUS was shown to be superior to Brachy based on the results for the primary endpoint of 9-month TVR (9.7% in the TAXUS group versus 17.5% in the Brachy group; P=0.0206).
- Reductions in TVR were driven by a significantly lower rate of target lesion revascularization (TLR) in the TAXUS group (6.0%) as compared to Brachy (13.9%) (P=0.0071).
- 9-month MACE and TVF rates were statistically significantly lower in the TAXUS group as compared with the Brachy group (45% relative reduction [P=0.0117] and 43% relative reduction [P=0.0168], respectively).
- Statistically significant differences favoring TAXUS patients over Brachy patients at 9 months were noted for MLD, %DS, Binary Restenosis (P<0.0001 for all) and Late Loss (P=0.0163) with no negative edge effects observed.

Angiographic and IVUS Results (Table 6)

A summary of the angiographic and IVUS results are provided in Table 6.

Subgroup Analyses

There were no subgroup analyses performed for the TAXUS V ISR clinical study.

Table 4: TAXUS V ISR Clinical Results

	9 months (ITT Population)			2 years (latest available follow-up) (Safety Population)		
	TAXUS (N=220)	Brachy (N=201)	P-Value	TAXUS (N=217)	Brachy (N=193)	P-Value
EFFICACY						
TVR, Overall[§]	9.7% (21/216)	17.5% (34/194)	0.0206 ^a -2.3% ^b	16.7% (35/209)	27.6% (51/185)	0.0095
TLR, Overall	6.0% (13/216)	13.9% (27/194)	0.0071	9.6% (20/209)	21.6% (40/185)	0.0009
TLR, PCI	4.2% (9/216)	12.4% (24/194)	0.0023	7.2% (15/209)	20.5% (38/185)	0.0001
TLR, CABG	2.3% (5/216)	2.6% (5/194)	1.0000*	2.9% (6/209)	3.2% (6/185)	0.8300
Non-TLR, Overall	4.6% (10/216)	6.2% (12/194)	0.4851	9.1% (19/209)	10.3% (19/185)	0.6923
Non-TLR, PCI	2.8% (6/216)	3.6% (7/194)	0.6318	5.7% (12/209)	6.5% (12/185)	0.7577
Non-TLR, CABG	1.9% (4/216)	2.6% (5/194)	0.7409*	3.3% (7/209)	3.8% (7/185)	0.8161
SAFETY						
Total Death	0.0% (0/216)	0.5% (1/193)	0.4719*	1.0% (2/210)	1.1% (2/185)	1.0000*
Cardiac Death or MI	3.7% (8/216)	5.2% (10/194)	0.4740	4.8% (10/209)	7.6% (14/185)	0.2491
Cardiac Death	0.0% (0/216)	0.5% (1/194)	0.4732*	0.5% (1/209)	1.1% (2/185)	0.6025*
MI	3.7% (8/216)	4.6% (9/194)	0.6352	4.3% (9/209)	6.5% (12/185)	0.3363
Q-wave MI	0.5% (1/216)	0.0% (0/194)	1.0000*	0.5% (1/209)	0.5% (1/185)	1.0000*
Non-Q-wave MI	3.2% (7/216)	4.6% (9/194)	0.4654	3.8% (8/209)	6.5% (12/185)	0.2302
Per Protocol Stent Thrombosis**	1.4% (3/216)	NA	NA	1.9% (4/208)	NA	NA
Non-Cardiac Death	0.0% (0/216)	0.0% (0/193)	Undef	0.5% (1/209)	0.0% (0/183)	1.0000*

Patients who did not receive a study treatment were not followed beyond one year.

[§] Primary Endpoint at 9 months.

^a p-value for two-sided Z test

^b 95% upper one-sided confidence bound for TAXUS - Brachy

Decision rule:

- Superiority shown if two-sided p-value ≤ 0.05 and TAXUS < Brachy.
- If not superior, non-inferiority shown if 95% upper 1-sided confidence bound < 10%.
- Neither proved if neither of above two conditions are met.

* p-values are two-sided from Fisher's exact test; p-values without * are from the Chi-square test.

P-values are not adjusted for multiple comparisons.

This trial was not adequately powered to compare the rate of low frequency events to Brachytherapy, nor was it sized to determine the rate of low frequency events with a pre-specified precision.

** Per protocol, stent thrombosis (in target vessel) was defined as either:

Table 4: TAXUS V ISR Clinical Results

1. angiographically confirmed - thrombus detected in any stent placed in the target vessel(s), or
2. non-angiographically confirmed - death (without other obvious cause) within the first 30 days after the index procedure and/or acute MI in the distribution of the target vessel(s)

Table 5: TAXUS V ISR Major Adverse Cardiac Events (MACE) From Post-Procedure to Latest Follow-Up

	TAXUS V ISR to 2 Years*	
	TAXUS Express	Brachy
In-Hospital MACE	1.4% (3/220)	1.5% (3/201)
Cardiac Death or MI	1.4% (3/220)	1.0% (2/201)
Cardiac Death	0.0% (0/220)	0.0% (0/201)
MI	1.4% (3/220)	1.0% (2/201)
Q-Wave MI	0.0% (0/220)	0.0% (0/201)
Non-Q-Wave MI	1.4% (3/220)	1.0% (2/201)
TVR, Overall	0.0% (0/220)	0.5% (1/201)
TVR, TLR	0.0% (0/220)	0.5% (1/201)
TVR, Non-TLR	0.0% (0/220)	0.5% (1/201)
In-Hospital Per Protocol Stent Thrombosis	0.0% (0/220)	NA
30-Day MACE, overall	2.3% (5/219)	2.5% (5/199)
Cardiac Death or MI	1.8% (4/219)	1.5% (3/199)
Cardiac Death	0.0% (0/219)	0.0% (0/199)
MI	1.8% (4/219)	1.5% (3/199)
Q-Wave MI	0.5% (1/219)	0.0% (0/199)
Non-Q-Wave MI	1.4% (3/219)	1.5% (3/199)
TVR, Overall	0.9% (2/219)	1.5% (3/199)
TVR, TLR	0.9% (2/219)	1.0% (2/199)
TVR, Non-TLR	0.0% (0/219)	1.0% (2/199)
30-Day Per Protocol Stent Thrombosis	0.5% (1/219)	NA
6-Month MACE, overall	4.6% (10/216)	10.7% (21/197)
6-Month Per Protocol Stent Thrombosis	1.4% (3/219)	NA
9-Month MACE, overall	11.1% (24/216)	20.1% (39/194)
Cardiac Death or MI	3.7% (8/216)	5.2% (10/194)
Cardiac Death	0.0% (0/216)	0.5% (1/194)
MI	3.7% (8/216)	4.6% (9/194)
Q-Wave MI	0.5% (1/216)	0.0% (0/194)
Non-Q-Wave MI	3.2% (7/216)	4.6% (9/194)
TVR, Overall	9.7% (21/216)	17.5% (34/194)
TVR, TLR	6.0% (13/216)	13.9% (27/194)
TVR, Non-TLR	4.6% (10/216)	6.2% (12/194)
9-Month Per Protocol Stent Thrombosis	1.4% (3/216)	NA
1-Year MACE	16.4% (35/214)	24.9% (47/189)
Cardiac Death or MI	4.2% (9/214)	6.3% (12/189)
Cardiac Death	0.5% (1/214)	0.5% (1/189)
MI	3.7% (8/214)	5.8% (11/189)
Q-Wave MI	0.5% (1/214)	0.0% (0/189)
Non-Q-Wave MI	3.3% (7/214)	5.8% (11/189)
TVR, Overall	14.5% (31/214)	22.2% (42/189)
TVR, TLR	8.4% (18/214)	16.9% (32/189)
TVR, Non-TLR	7.0% (15/214)	9.5% (18/189)

	TAXUS V ISR to 2 Years*	
	TAXUS Express	Brachy
1-Year Per Protocol Stent Thrombosis	1.4% (3/213)	NA
2-Year MACE	18.7% (39/209)	29.7% (55/185)
Cardiac Death or MI	4.8% (10/209)	7.6% (14/185)
Cardiac Death	0.5% (1/209)	1.1% (2/185)
MI	4.3% (9/209)	6.5% (12/185)
Q-Wave MI	0.5% (1/209)	0.5% (1/185)
Non-Q-Wave MI	3.8% (8/209)	6.5% (12/185)
TVR, Overall	16.7% (35/209)	27.6% (51/185)
TVR, TLR	9.6% (20/209)	21.6% (40/185)
TVR, Non-TLR	9.1% (19/209)	10.3% (19/185)
2-Year Per Protocol Stent Thrombosis	1.9% (4/208)	NA

* After 1 year the TAXUS V ISR study population was reduced to a pre-specified cohort (Safety Population), which consists of all patients who received a study treatment at baseline.

Table 6: TAXUS V ISR 9- Month Angiographic and IVUS Results

	TAXUS (N=220)	Brachy (N=201)	P-Value
QCA			
MLD (mm), In-stent			
Post-Procedure	2.52±0.40 (216)	NA	NA
9-Month	2.17±0.59 (191)	NA	NA
MLD (mm), Analysis Segment			
Post-Procedure	2.15±0.46 (218)	1.87±0.44 (200)	<0.0001
9-Month	1.92±0.62 (191)	1.46±0.66 (170)	<0.0001
% DS, In-stent			
Post-Procedure	7.60±9.74 (216)	NA	NA
9-Month	20.63±20.18 (191)	NA	NA
% DS, Analysis Segment			
Post-Procedure	21.72±10.15 (218)	30.22±10.66 (200)	<0.0001
9-Month	30.22±19.67 (191)	44.61±22.89 (170)	<0.0001
Late Loss			
In-stent (mm)	0.36±0.49 (191)	NA	NA
Analysis Segment (mm)	0.26±0.53 (191)	0.40±0.58 (170)	0.0163
Binary Restenosis (%)			
In-stent (%)	6.8% (13/191)	NA	NA
Analysis segment (%)	13.6% (26/191)	31.2% (53/170)	<0.0001
IVUS			
Neointimal Volume (mm ³)			
Post-Procedure	0.01±0.04 (44)	47.56±48.83 (47)	<0.0001
9-Month	23.99±24.17 (47)	55.93±40.53 (43)	<0.0001
% Net Volume Obstruction			
Post-Procedure	0.00±0.02 (38)	30.11±13.26 (38)	<0.0001
9-Month	13.01±10.62 (45)	32.35±11.74 (41)	<0.0001
Incomplete Apposition			

Table 6: TAXUS V ISR 9- Month Angiographic and IVUS Results

	TAXUS (N=220)	Brachy (N=201)	P-Value
Late (9 months)	5.9% (3/51)	NA	NA
Late Acquired	2.6% (1/39)	NA	NA

P-values for continuous variables are two-sided from Student's t-test.

P-values are not adjusted for multiple comparisons.

This trial was not adequately powered to compare the rate of low frequency events to a bare metal control group, nor was it sized to determine the rate of low frequency events with a pre-specified precision.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA did not require advisory panel input.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Non-clinical studies of the TAXUS Express² Paclitaxel-Eluting Coronary Stent System demonstrate that the stent is adequate for its intended use. Clinical study data demonstrates that the TAXUS Express² Paclitaxel-Eluting Coronary Stent System is both safe and effective for its intended use in patients followed through 9 months. The superiority of the TAXUS stent TVR rate observed for the 9-month primary endpoint was maintained through 2 years for this study population. The reduction in TVR was reflected in a significantly lower rate of TLR in the TAXUS group compared to vascular brachytherapy.

XIII. CDRH DECISION

CDRH issued an approval order on September 24, 2008. The final conditions of approval cited in the approval order are described below.

1. The applicant should collect and report to the Agency on an annual basis clinical outcomes through 5 years post-procedure on at least 80% of patients enrolled (excluding those discontinued due to death) from the TAXUS V ISR study. When appropriate or as requested by FDA, the applicant should submit PMA supplements requesting approval to update your IFU to include these data.
2. The applicant should comply with the commitments made in Amendment 6 related to confirmatory particulate matter testing in simulated use and chronic conditions as well as updating particulates specifications as appropriate.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.