Summary of Safety and Effectiveness Data

I. GENERAL INFORMATION

Product Generic Name:	Drug-Eluting Coronary Stent System (NIQ)
Product Trade Name:	TAXUS® Liberté® Paclitaxel-Eluting Coronary Stent System (Monorail) TAXUS® Liberté® 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
Premarket Approval Application (PMA) Number:	P060008
Date of Panel:	None
Date of Notice of Approval to Applicant:	October 10, 2008

II. INDICATIONS FOR USE

The TAXUS Liberté Paclitaxel-Eluting Coronary Stent System (Monorail and Over-the-Wire Systems) is indicated for improving luminal diameter for the treatment of de novo lesions in native coronary arteries ≥ 2.5 to ≤ 4.00 mm in diameter in lesions ≤ 28 mm in length.

III. CONTRAINDICATIONS

Use of the TAXUS Liberté 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 V B2. Inactive Ingredients** (Page 4).

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. WARNING AND PRECAUTIONS

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

V. PRODUCT DESCRIPTION

The TAXUS Liberté Paclitaxel-Eluting Coronary Stent System is a device / drug combination product comprised of two regulated components: a device (Liberté Coronary Stent System) and a drug product (a formulation of paclitaxel contained in a polymer coating). The characteristics of the TAXUS Liberté stent system are described in **Table 1**.

Table 1: TAXUS Liberté Stent System Product Description

	TAXUS Liberté Monorail® Stent Delivery System	**TAXUS Liberté Over-the-Wire Stent Delivery System**
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32	
Available Stent Diameters (mm)	2.50, 2.75, 3.00, 3.50, 4.00	
Stent Material	A 316L surgical grade stainless steel Liberté® stent	
Drug Product	A conformal coating of a polymer carrier loaded with 1μg/mm^2 paclitaxel in a slow release (SR)* formulation applied to the stent with a maximum nominal drug content of 229 μg on the largest stent (4.00 x 32 mm).	
Delivery System		
Working Length	140 cm	135 cm
Delivery System Y-Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 25 cm from tip. Designed for guidewire ≤0.014"	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤0.014"
Stent Delivery	A compliant balloon, nominally 0.3 mm longer than the stent, with two radiopaque markers.	
Balloon Inflation Pressure	Nominal Inflation Pressure: 9 ATM (Stent Diameter 2.50 mm) Nominal Inflation Pressure: 8 ATM (Stent Diameters 2.75 – 4.00 mm) Rated Burst Inflation Pressure: 18 ATM (stent Diameters 2.50 – 4.00 mm)	
Guide Catheter Inner Diameter	≥0.058"	≥0.066"
Catheter Shaft Outer Diameter	1.8F proximally and 2.7F distally: • On all balloon lengths with diameters up to 3.0 mm • On balloon lengths 8-20 mm with diameters of 3.5 mm • On Balloon lengths 8-16 mm with diameters of 4.0 mm 2.0F proximally and 2.7F distally: • On balloon lengths 24-32 mm with diameters of 3.5 mm • On balloon lengths 20-32 mm with diameters of 4.0 mm	3.2F proximally, 2.7F distally

*release rate is a function of weight/weight ratio of polymer and drug, and (SR) is the formulation that was studied clinically and is used in the marketed product

A. Device Component Description

The TAXUS Liberté Coronary Stent System consists of a balloon expandable Liberté stent, coated with paclitaxel in a slow-release (8.8% formulation) triblock copolymer system, and pre-mounted on either the Liberté Monorail™ or an Over-the-Wire (OTW) delivery system. TAXUS Liberté incorporates the identical bare Liberté stent component and a similar delivery system to that of Liberté Coronary Stent System (P040016, approved April 12, 2005), and the identical TAXUS technology as the TAXUS Express^2 Paclitaxel-Eluting Coronary Stent (P030025, approved March 4, 2004). The system is advanced over a guide wire through the coronary vasculature to deliver and dilate the stent at the target lesion location. Following stent deployment, the delivery balloon may be inflated with additional pressure in order to optimize the stent luminal diameter and strut apposition.

Liberté stents are manufactured from 316L stainless steel. The stent design consists of a dimensionally uniform pattern of radially expandable elements that share junctions with adjacent radially expandable elements. The TAXUS Liberté stent is available in 3 stent models each designed for specific diameters as follows:

- Small Vessel (SV): 2.50 mm
- Workhorse (WH): 2.75 - 3.50 mm
- Large Vessel (LV): 4.00 mm

B. Drug Component Description

The drug component of the TAXUS Liberté Paclitaxel-Eluting Coronary Stent System consists of paclitaxel (the active ingredient) and Translute™ polymer carrier (the inactive ingredient).

B1. Paclitaxel

The active pharmaceutical ingredient in the TAXUS Liberté stent is paclitaxel. It is a white powder, isolated from a spectrum of Taxus species and hybrids. The chemical name of paclitaxel is: Benzenepropanoic acid, β-(benzoylamino)-α-hydroxy-6, 12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a, 12b-dodecahydro-4, 11-dihydroxy-4a,8,12,12-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca{3,4}benz[1,2-b]oxet-9-yl ester, [2aR-[2aα, 4β, 4aβ, 6β, 9α (αr*, βs*) 11α, 12α, 12aα,12bα]]-.

Paclitaxel is a diterpenoid with a characteristic taxane skeleton of 20 carbon atoms, a molecular weight of 853.91 g/mol and a molecular formula of $C_{47}H_{51}NO_{14}$. It is highly lipophilic, insoluble in water, but freely soluble in methanol, ethanol, chloroform, ethyl acetate, and dimethyl sulfoxide.

The chemical structure of paclitaxel is shown in **Figure 1**. The nominal total loaded dose of paclitaxel per nominal stent length/diameter is shown in **Table 2**.

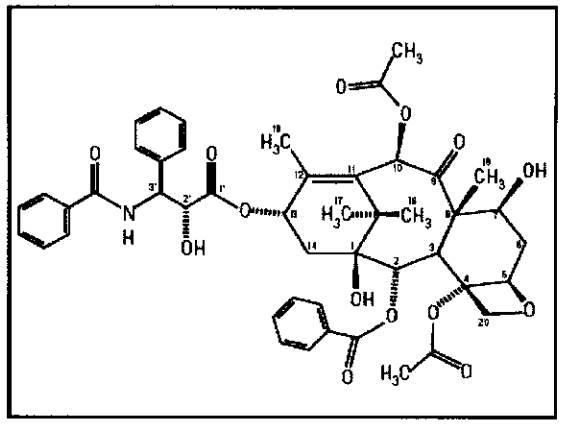


Figure 1: Chemical Structure of Paclitaxel

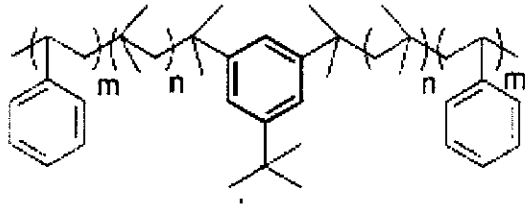
Table 2: Nominal Total Loaded Dose of Paclitaxel per Nominal Stent Length/Diameter

	Nominal Stent Length (mm)/ Stent Model	8	12	16	20	24	28	32
Total loaded dose Paclitaxel /Stent (µg)	SV	38	58	77	97	116	136	155
	WH	55	83	112	140	168	196	224
	LV	61	88	114	141	176	203	229

Small Vessel (SV): 2.50 mm; Workhorse (WH): 2.75-3.5 mm; Large Vessel (LV): 4.00 mm

B2. Inactive Ingredients

The only inactive ingredient in the TAXUS Liberté stent is SIBS [poly(styrene-b-isobutylene-b-styrene)], a tri-block copolymer (trade name: Translute™) that is composed of styrene and isobutylene units built on 1,3-di(2-methoxy-2-propyl)-5-tert-butylbenzene. It is a hydrophobic elastomeric copolymer with a molecular weight (Mn-number average molecular weight) of 80,000 to 130,000 g/mol and a polydispersity index of 1.0 to 2.0. The polymer is mixed with the drug paclitaxel and then applied to the stents. There is no primer or topcoat layer. The drug/polymer coating is adhered to the entire surface (i.e, luminal and abluminal) of the stent. The structural formula for the polymer is shown in **Figure 2** below.



m = repeating units of styrene
n = repeating units of isobutylene

Figure 2: The Chemical Structure of Translute™ Polymer Carrier

C. Mechanism of Action

The mechanism (or mechanisms) by which a TAXUS Liberté stent affects neointimal production as seen in clinical studies has not been fully established. Paclitaxel promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Treatment of patients with coronary artery disease may include exercise, diet, drug therapy, percutaneous coronary interventions (such as angioplasty, and placement of bare metal stents, coated stents, and other drug eluting stents), and coronary artery bypass surgery (CABG).

VII. MARKETING HISTORY

The TAXUS Liberté Paclitaxel-Eluting Coronary Stent System is commercially available in the following countries:

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

As of August 1, 2008, approximately 900,000 TAXUS Liberté stents have been distributed outside the U.S. No products have been withdrawn from the market in any country for any reason.

VIII. SUMMARY OF NON-CLINICAL STUDIES

A series of non-clinical laboratory studies were performed – those related to the stent and the stent delivery system [i.e. the stent on either the Monorail (MR) or Over-The-Wire (OTW) stent delivery system (SDS)], the polymer substance [i.e., polyisobutylene styrene (SIBS)], the drug substance (i.e., paclitaxel) and the finished combination product (i.e., TAXUS Liberté Paclitaxel-Eluting Coronary Stent).

A. Biocompatibility Studies

A series of biocompatibility tests and USP Physiochemical tests were conducted to demonstrate that the components of the TAXUS Liberté Paclitaxel-Eluting Stent System (Monorail and Over-The-Wire) are non-toxic. Tests were conducted on ethylene oxide-sterilized bare metal stents, stent delivery systems, polymer films, and polymer only coated stainless steel (SS) coupons. These test articles were processed in the same manner as the finished TAXUS Liberté product, except where polymers were present (i.e., films and coupons), the drug substance, paclitaxel, was not included in the polymer coating. With the exception of the inclusion of the drug substance, the surface treatment, coating processing, amount of coating per unit area, and sterilization processes were equivalent for both the stents and coupons utilized during testing. In all of these test systems, the materials were non-reactive and produced no greater response than then the negative control employed in each test system.

All biocompatibility testing was conducted in accordance with:

- FDA Guidance for Industry and Staff: Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, January 13, 2005
- ISO 10993-1, Biological Evaluation of Medical Devices: Evaluation and Testing (1997)

The biocompatibility studies are summarized in **Table 3**.

Table 3: Biocompatibility Test Summary

Test Name	Test Description	Test Article and Results
Cytotoxicity	ISO 10993-5: In Vitro Cytotoxicity (L929 MEM Elution)	▪ Stent and delivery systems: Pass (non-cytotoxic) ▪ Polymer-only coated 316L SS coupon: Pass (non-cytotoxic) ▪ Polymer-only coated stent: Pass (non-cytotoxic)
Sensitization	ISO 10993-10: Sensitization (Kligman Maximization)	▪ Stent and delivery systems: Pass (non-sensitizing) ▪ Polymer-only coated 316L SS coupon: Pass (non-sensitizing) ▪ Polymer-only coated stent: Pass (non-sensitizing)
Intracutaneous Reactivity	ISO 10993-10:Irritation (Injection)	▪ Stent and delivery systems: Pass (non-irritant) ▪ Polymer-only coated 316L SS coupon: Pass (non-irritant) ▪ Polymer-only coated stent: Pass (non-irritant)
Acute Systemic Toxicity	ISO 10993-11: Systemic Toxicity (Acute)	▪ Stent and delivery systems: Pass (non-toxic) ▪ Polymer-only coated 316L SS coupon: Pass (non-toxic)
Pyrogenicity	LAL	▪ Stent and delivery systems: Pass (non-pyrogenic)
	ISO 10993-11: Systemic Toxicity (Material-Mediated Rabbit)	▪ Polymer-only coated 316L SS coupon: Pass (non-pyrogenic)
Hemocompatibility	Direct Contact Hemolysis	▪ Stent and delivery systems: Pass (non-hemolytic) ▪ Polymer-only coated 316L SS coupon: Pass (non-hemolytic) ▪ Polymer-only coated stent: Pass (non-hemolytic)
	Lee and White Coagulation	▪ Stent and delivery systems: Pass (no change in coagulation time)
Implantation	14-days (Rabbit, Intramuscular)	▪ Stent and delivery systems: Pass (non-toxic)
	30-days (Rabbit, Intramuscular)	▪ Stent and delivery systems: Pass (non-toxic)
	14-days Repeat Dose Subchronic Toxicity (Mouse, Intravenous)	▪ Stent and delivery systems: Pass (non-toxic)
	90-Day Chronic Toxicity (Mouse, Intraperitoneal)	▪ Stent and delivery systems: Pass (non-toxic)
Genotoxicity	Bacterial Reverse Mutation Assay (Ames Test)	▪ Polymer-only coated 316L SS coupon: Pass (non-mutagenic)
	In Vitro Chromosomal Aberration (human blood lymphocytes)	▪ Polymer-only cast film: Pass (non-clastogenic)
	In Vivo Mouse Micronucleus Test	▪ Polymer-only cast films: Pass (non-mutagenic)
Volatile/Metal Extracts	USP Physiochemical Extracts	▪ Stent and delivery systems: Pass

A. Biocompatibility Studies, continued

Since the sponsor did not conduct the traditional battery of ISO10993 testing on the finished TAXUS Liberté stent (i.e., containing the drug substance), sub-chronic toxicity, thrombogenicity, and implantation of the TAXUS Liberté stent, containing all components and processing, were evaluated in porcine, rabbit, and canine models of stent-mediated vascular injury. The significant animal studies are summarized separately in Section VIII H. Animal Studies.

Complement activation testing was not conducted on the TAXUS Liberté stent. However, there is extensive clinical experience with the previous generation TAXUS Express^2 stent, which has the same materials and manufacturing processes, with no clinical reports to suggest that anaphylactic shock is a concern. Given that the TAXUS Liberté stent does not introduce any new materials or manufacturing processes that would suggest a new source for chemical anaphylatoxins, complement activation testing was determined not to be necessary.

The genotoxicity, carcinogenicity, and reproductive toxicity of TAXUS Liberté stents have not been evaluated. However, the genotoxicity, carcinogenicity, and reproductive toxicity of paclitaxel have been investigated in bacterial and mammalian cells in vitro and in laboratory animals in vivo. Paclitaxel was not mutagenic when tested in two gene mutation assays.

Formal carcinogenicity testing on the final TAXUS Liberté stent was not conducted. Because some paclitaxel remains on the product for an extended period of time, and the carcinogenic potential of the SIBS polymer coating had not previously been investigated, an appropriate rationale was provided to demonstrate that the carcinogenic potential of the TAXUS Liberté stent was minimal, based on the types and quantities of starting materials (including any manufacturing additives).

There is no evidence to suggest that any chemical interactions which would form a new intermediate or molecular entity occur between paclitaxel or the polymer carrier used in the TAXUS Liberté stents.

Long term biocompatibility of the drug/polymer coating of the stent in humans is unknown.

B. *In Vivo* Pharmacokinetics

B1. TAXUS Liberté Paclitaxel-Eluting Coronary Stent

Boston Scientific provided a letter from the drug substance manufacturer, authorizing access to a Drug Master File (DMF) in support of this application. The drug substance manufacturer produces a generic form of the drug Taxol®, a Bristol Myers Squibb drug product that is approved for injection of multiple oncologic indications. *In vivo* animal and *in vitro* pharmacology and toxicology studies, as well as *in vivo* and human pharmacokinetic studies, were conducted on Taxol to provide information about systemic, regional and local toxicity, dose-related toxicity, distribution profiles, end-organ disposition, drug metabolism and potential drug-drug interactions.

Given that the polymer coating and drug component of the TAXUS Liberté Paclitaxel-Eluting Coronary Stent System is identical to that of the TAXUS Express^2 Paclitaxel-Eluting Coronary Stent System (P030025), the evaluation of the TAXUS Express^2 Stent System is applicable. In the clinical studies, TAXUS I, II, and III, which evaluated the TAXUS Express^2 Stent System, no paclitaxel levels were detected after stent implantation using an analytical method with a lower limit of quantification (LLOQ) of 10 ng/ml. These findings were confirmed in preclinical studies using multiple stents with total loaded doses above the clinically available stent system and an assay with an LLOQ of 0.03 ng/ml. Hence, in the absence of systemically detectable levels, standard pharmacokinetic parameters were not established.

B2. Drug Interactions

Paclitaxel is metabolized in the liver via CYP2C8 to 6-alpha-hydroxypaclitaxel and via CYP3A4 to 3'-p-hydroxypaclitaxel and 6-alpha, 3'-p-dihydroxypaclitaxel. Paclitaxel is a substrate of P-glycoprotein. Because metabolism appears to play an important role in the elimination of paclitaxel, agents that could compete with or inhibit the CYP2C8 and CYP3A4 isoenzymes may increase paclitaxel plasma levels. Potential drug interactions may occur with any drug that affects these isoenzymes.

Formal drug interaction studies have not been conducted with the TAXUS Liberté Stent. Consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place a TAXUS Liberté Stent in a patient who is taking a drug with known interactions to paclitaxel or when deciding to initiate therapy with such a drug in a patient that has recently received a TAXUS Liberté stent.

C. *In Vitro* Engineering Testing

In vitro engineering testing, in accordance with FDA "Guidance for Industry and Staff: Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems", January 13, 2005, was conducted on the TAXUS Liberté stent and TAXUS Liberté stent delivery systems, as applicable.

Where appropriate, in vitro engineering testing was conducted on the uncoated, bare version of the Liberté stent mounted on either the MR or OTW delivery catheters, which were approved in P040016. Additional engineering testing was also performed on the TAXUS Liberté™ stent mounted on the delivery catheters. Some testing was not repeated since there was no change to the stent substrate, and where the effect of the coating did not impact test results; for the tests that were repeated, the results demonstrated adequate performance.

The in vitro engineering studies conducted are summarized in **Table 4**. "Pass" denotes that the test results met product specifications and/or the recommendation in the above-referenced guidance document.

Additional testing was conducted to support the integrity of the coating on the TAXUS Liberté stent as shown in **Section VIII D. Coating Characterization Testing**.

Table 4: Stent and Delivery Catheter Engineering Testing

Test	Description of Test	Conclusion
Material Characterization		
Material Composition	Chemical analysis was conducted on the stainless steel ingot provided by the material supplier to confirm both chemical analysis and inclusion/impurity content as provided by ASTM F138-00 "Standard Specification for Wrought 18 Chromium-14 Nickel-2.5 Molybdenum Stainless Steel Bar and Wire for Surgical Implants (UNS S31673)."	Pass
Stent Corrosion Resistance	TAXUS Liberté stents were tested according to ASTM F2129-01 "Standard Test Method for Conducting Cyclic Potentiodynamic Measurements to Determine the Corrosion Susceptibility of Small Implant Devices" to demonstrate that the finished stents exhibit corrosion and repassivation characteristics comparable to or better than marketed 316L bare metal coronary stents. The results indicated that the corrosion resistance met product specification. Testing included assessment of Pitting (Potentiodynamic), Crevice, Fretting, Galvanic Corrosion.	Pass
Surface Contamination	TAXUS Liberté stents were examined via SEM at 500X and 2000X to detect evidence of surface contamination or impurities on the stent material not removed by cleaning processes. Results of SEM evaluation showed no evidence of contamination above the specified limits.	Pass
Stent Dimensional and Functional Attributes		
Dimensional Verification	Testing was conducted to measure and optically inspect the stent to document that stent dimensional measurements do not deviate from product specifications. All products met specifications.	Pass
Percent Surface Area	Stent surface coverage as a function of stent diameter was calculated for the TAXUS Liberté stent. The percent surface area at each diameter is determined by dividing the total artery contact surface area of the coated stent by the surface area of the artery at any given nominal stent diameter. The highest percent surface area is 25.6% found for the 2.75 mm diameters stent, i.e. the smallest diameter WH stent.	Pass
Foreshortening	The length of the stents were measured prior to and after expansion to the largest nominal diameter. All stents met product specifications.	Pass
Recoil for Balloon Expandable Stents	Testing was conducted to quantify the amount of elastic recoil for the stent and correlate this parameter to the recommended sizing procedures. Results indicated that product specifications were met.	Pass
Stent Integrity	Testing was conducted to determine whether the deformation experienced by the stent undergoing expansion above the maximum rated diameter gives rise to stent or coating fractures. No stent exhibited any strut fracture or indications of coating integrity issues when visually examined at 32X following over-expansion.	Pass
Radial Stiffness and Radial Strength	Testing was conducted to determine the ability of the TAXUS Liberté stent to resist collapse under short term and long term loads.	Pass
Compression Resistance	Testing was conducted to determine the radial resistance of the TAXUS Liberté stent to external compression.	Pass
Mechanical Properties	Ultimate tensile strength, yield strength and elongation testing was performed on tubing (pre-processing) used to fabricate the stents as well as the stent component post-processing. Ultimate tensile strength, yield strength and elongation on pre-processed tubing met product specification. Testing on stent components determined that mechanical properties were not altered by processing.	Pass

Table 4: Stent and Delivery Catheter Engineering Testing, continued

Test	Description of Test	Conclusion
Stent Dimensional and Functional Attributes, continued		
Magnetic Resonance Imaging (MRI) Safety and Compatibility	Through non-clinical testing, the TAXUS Liberté Stent has been shown to be MR Conditional (poses no known hazards under specified conditions). The conditions are as follows: • Field strengths of 3 Tesla or less. • A maximum whole body averaged specific absorption rate (SAR) of 2.0 W/kg or less for a total active MR scan time (with RF exposure) of 15 minutes or less. • Maximum Spatial Field Gradient of 70 mT/cm or less. • A rate of change of magnetic field (dB/dt) of 60 T/s or less. The TAXUS Liberté Stent should not migrate in this MRI environment. MR imaging within these conditions may be performed immediately following the implantation of the stent. This stent has not been evaluated to determine if it is MR Conditional beyond these conditions. Boston Scientific conducted tests using both single stents and overlapped stents. The maximum temperature rise was less than 2.0 degrees Celsius in all cases. The effect of heating in an MRI environment for stents with simulated fractures has been tested and found to be similar to single stents. In vivo, local SAR depends on MR field strength and may be different than the estimated whole body averaged SAR, due to body composition, stent position within the imaging field, and scanner used, thereby affecting the actual temperature rise. MR imaging quality may be compromised if the area of interest is in exactly the same area or relatively close to the position of the stent.	Pass
Radiopacity	Testing was conducted on the bare metal stent as the addition of the coating did not add or detract from the radiopacity of the stent in clinical use.	Pass
Stent Conformability	Testing was conducted to determine the conformability (axial flexibility) of the stent in its expanded state by determining the pure bending moment of the stent. All diameters of stents were tested and met specifications.	Pass
Stent Delivery System Dimensional and Functional Attributes		
Delivery, Deployment and Retraction	The delivery, deployment and retraction of the TAXUS Liberté Stent System was assessed by testing system track, crossing profile, stent deployment, guidewire movement at rated burst pressure and balloon withdrawal from a stent and into the guide catheter. Testing demonstrated that the TAXUS Liberté stent system could be delivered to the target location, deployed, and retracted, thus met required product specifications.	Pass
Balloon Rated Burst Pressure (RBP)	TAXUS Liberté stent systems were tested to failure to demonstrate that the stent system met rated burst pressure. All stent systems met specification and demonstrated with 95% confidence that at least 99.9% of balloons will not experience loss of integrity at or below the rated burst pressure.	Pass
Balloon Fatigue	TAXUS Liberté stent systems across the range of stent/balloon lengths and diameters were required to complete 20 pressurization cycles to Rated Burst Pressure (RBP). The results show statistically that, with 95% confidence, 90% of the catheters will not experience balloon, shaft, or proximal/distal seal loss of integrity at or below the maximum recommended rated balloon burst pressure.	Pass
Stent Diameter vs. Balloon Pressure (Compliance Chart)	Testing was performed to determine how the diameter of a deployed balloon varies with applied balloon pressures. The stent sizing results verify that the stent systems meet the labeled compliance values.	Pass

Table 4: Stent and Delivery Catheter Engineering Testing, continued

Test	Description of Test	Conclusion
Stent Delivery System Dimensional and Functional Attributes, continued		
Catheter Bond Strength	Representative sizes of the TAXUS Liberté stent delivery system were tested to determine the balloon bond and full unit tensile strength of the delivery system. All stent systems exceeded the minimum specifications for full unit tensile and balloon bond.	Pass
Crossing Profile	Stent systems for each diameter balloon were tested to determine the non-deployed stent/balloon profile. All samples met the product specification.	Pass
Balloon Inflation and Deflation Time	TAXUS Liberté delivery systems across the range of balloon lengths and diameters were tested for inflation/deflation times, and all stent systems met specifications.	Pass
Stent Securement for Unsheathed Stents	Testing was conducted to assess the forces required to displace a crimped TAXUS Liberté stent from the delivery systems (1) directly from the balloon catheters, (2) after tracking through a simulated tortuous artery model and (3) after tracking through a simulated tortuous artery model and then through a simulated lesion. All stent systems met the stent securement specification.	Pass
Balloon Catheter Withdrawal Resistance	Testing was conducted to verify that the TAXUS Liberté stent system can be safely withdrawn back into the recommended guide catheter sizes both before and after stent deployment. All samples met the product specification.	Pass
Dye Flow	Testing was conducted to assess dye flow while the TAXUS Liberté Stent system is positioned in a guide catheter. Results demonstrated that dye flow met product specification.	Pass
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 Liberté 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. The stents were dynamically cycled over simulated vessel conditions for 400 million cycles. Following cycling, stents were visually inspected using 40X optical microscopy. No signs of strut cracking or breaking were detected. Additionally, eight stents (four coated and four with coating removed after fatigue testing) were randomly analyzed using SEM. 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 2 year equivalent real time and met visual requirements for coating integrity and strut damage.	Pass
Coating Durability	The coating durability of the TAXUS Liberté 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

D. Coating Characterization Testing

The coating characterization testing conducted on the TAXUS stent coating is summarized in **Table 5**.

Table 5: Coating Characterization Testing

Test	Description of Test
Material Characterization	
Materials Analysis – Polymer	Polymer components were tested to ensure conformity to raw material specifications and incoming inspection procedures.
Chemical Analysis-Polymer	Assays were conducted to determine Mw, Mn, polydispersity, monomer content, presence/formation of oligomers and free monomers.
Chemical Analysis - Drug	Drug substance was tested to ensure conformity to incoming Certificate of Analysis.
Drug Content	Assay was conducted to quantitatively determine the total amount of the drug substance, paclitaxel, on the TAXUS Liberté stent.
Dose Density	Dose per unit area was calculated.
Drug Content Along Stent Length	Testing was conducted to characterize the uniform distribution of drug along the length of the TAXUS Liberté stent.
Coating Uniformity/Reproducibility	Testing was conducted to verify the reproducibility of coating uniformity from stent to stent and batch to batch.
Impurities/Degradation Products	Assays were conducted to quantitatively determine the type and amount of impurities and degradation products on the TAXUS Liberté stent.
In vitro Elution	Assay was developed to measure the *in vitro* release kinetics of paclitaxel off the TAXUS Liberté stent.
Particulates	Particulate levels were evaluated for the TAXUS Liberté stent system post tracking and deployment.

E. Chemistry Manufacturing and Controls (CMC) Testing

Each batch of finished devices undergoes CMC testing. This testing is summarized in **Table 6**. Where applicable, the test methods follow International Conference on Harmonization (ICH) Guidelines. Information to support the stability of the TAXUS Liberté Stent is summarized separately in **Section VIII F – Stability** below.

Table 6: CMC Release Testing

Test	Description of Test
Material Analysis - Polymer	The polymer was tested to ensure conformity to specifications. The polymer met specifications prior to utilization in finished goods.
Drug Identity	Assay is conducted to verify the identity of the drug substance, paclitaxel, in the TAXUS Liberté stent.
Drug Content/Impurities	Assays are conducted to quantitatively verify the amount of drug and the type and amount of impurities on the TAXUS Liberté stent.
Drug Content Uniformity	Multiple stents are assayed to verify the uniformity of the drug content between individual stents is within specifications established for the TAXUS Liberté stent.
Residual Solvents	Assay is conducted to verify that residual levels of solvents used in the manufacturing process are below acceptable limits established for the TAXUS Liberté stent.
In vitro Drug Elution	The *in vitro* release profile of paclitaxel is measured to verify that the drug release is within the specifications established for the TAXUS Liberté stent.
Particulates	Particulate counts are measured to verify that they remain below acceptable levels established for the TAXUS Liberté stent.

F. Stability

Stability studies were conducted to establish a shelf life/expiration date for the TAXUS Liberté Paclitaxel-Eluting Coronary Stent System. Testing to establish package integrity and functional testing of the stent system were conducted on aged product. Testing evaluation included drug identity, assay, degradants, *in vitro* elution, particulates, sterility, drug content uniformity, residual solvents and endotoxin. Appropriate engineering tests were also performed on aged product to ensure that the TAXUS Liberté Stent System continues to meet specification throughout its shelf life. The data generated support a shelf life of 18 months.

In addition, the stability of the drug substance and inactive polymer has been independently verified.

G. Sterilization

The TAXUS Liberté Paclitaxel-Eluting Coronary Stent System (Monorail and Over-The-Wire) is sterilized using ethylene oxide sterilization and has been validated per AAMI/ISO 1135:1994 "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 endotoxin was verified to be within the specification limit for TAXUS Liberté stent delivery systems.

H. Animal Studies

Detailed arterial histopathology and histomorphometry can not be obtained through human clinical trials, so a series of animal studies were conducted to evaluate safety, efficacy (proof of concept), and overall product performance.

The intravascular safety and biocompatibility of paclitaxel-eluting stents were evaluated in a series of animal studies in a porcine model of stent mediated vascular injury. Studies were conducted in accordance with §21 CFR 58 (Good Laboratory Practices) with the exception of study number S5458-123131. This study was not conducted in accordance to Good Laboratory Practices (Code of Federal Regulations 21:58). The data generated was collected under independent Quality Assurance oversight in strict accordance to the study protocol and site Standard Operating Procedures (SOPs) to ensure the integrity of the data and conclusions.

The results of these tests support the safety and biocompatibility of the TAXUS Liberté Stent. Summaries of these studies are included in **Table 7**.

Table 7: Summary of Major Supportive Animal Studies

Study #	Stent Design	Type/# of Animals	# of Stents	Timepoints	Endpoints
RVF03-082 GLP: Yes	Test Article: TAXUS Liberté 3.0x16, 3.5x16 Control: Bare Liberté 3.0x16, 3.5x16	Domestic Swine- 2 overlap pairs/animal; 55 animals total Vessels: LAD, LCX, RCA	Test: 69 pairs Control: 38 pairs	28, 90, 180, 360 days	▪ Histologic and histomorphometric evaluations ▪ Evaluation of degree of re-endothelialization by SEM ▪ Chronic Vascular Response
RVF03-115 GLP: Yes	Test Article: TAXUS Liberté 2.0x12, 2.5x20 Control: Bare Liberté 2.25x16, 2.5x16	Domestic Swine - 2 stents/animal; 30 animals total Vessels: LAD, LCX, RCA, OM 10 animals/time-point	Test: 30 Control: 30	30, 90, 180 days	▪ Histologic and histomorphometric evaluation ▪ Evaluation of degree pf re-endothelialization by SEM ▪ Chronic Vascular Response
S5458-123131 GLP: No	Test Article: TAXUS Liberté MR & OTW models Control: NA	Domestic Swine- 4 animals total Vessels: LAD, LCX, RCA	Test: 13 MR & 13 OTW Control: NA	Acute – Implant and deployment procedure	▪ Acute evaluations included the performance assessment of the stent delivery system and stent deployment characteristics
BJAW-0171 GLP: Yes	Test Article: TAXUS Liberté 2.75x8 Control: TAXUS Express 2.75x8	Rabbit- single test and control stent/animal; 110 animals total Vessels: Right and Left Iliac 10 animals/time-point	Test: 110 Control: 110	2, 4, 10, 20, 30, 45, 60, 90, 135, 180, and 270 days	▪ Residual Stent drug content and tissue drug content comparison between the Liberté and Express stent platforms.

Stent Fractures:

Stent fractures were identified in the animal study results of evaluations to support the TAXUS Liberté Stent System. In order to better understand the significance of stent fractures in the animal studies, a root cause investigation with respect to stent fractures was conducted. In a total of 6 studies conducted in domestic swine (some of which were not used in support of this application), a total of 530 Liberté and TAXUS Liberté stents were examined by Faxitron analysis and 25 stents had fractures (4.72%). In an analysis of 607 additional Liberté, TAXUS Liberté and polymer coated Liberté stents from 4 studies conducted in Yucatan mini-swine (some of which were not used in support of this application), no fractures were identified. The overall stent fracture rate for the Liberté stent platform is 2.20% (25/1137), when combining all 10 studies. The majority of stent fractures (19/25) were identified between 180 and 580 days post-implant. In addition, 16/25 (64%) stent fractures were identified in stents in an overlapping configuration. Because these animal studies were designed to evaluate cardiac function and vascular safety and not *in vivo* device durability, it is unclear how the study results correlate to the clinical use of the device.

In order to better understand the clinical implications of stent fracture, an analysis was conducted of the incidence of stent fracture obtained from study angiograms evaluated by the core lab in the TAXUS ATLAS study. A total of 867 patients received a TAXUS Liberté stent during the index procedure. From this group, 863 angiographic films were able to be analyzed, with a total of 932 study stents implanted in these patients. No stent fractures were detected during or immediately following the index procedure. A sub-set of patients (n=543) were randomized to have follow-up angiography at 9-months post-procedure. From this subset, 454 patients returned for an angiogram and were evaluated for stent fracture. There were a total of 497 study stents implanted in these patients, and no stent fractures were detected. An analysis of angiographic data on 568 patients with 623 stents implanted was also conducted after 9 months follow-up. In this group there was one stent fracture identified; however, the core lab was unable to determine if the fracture occurred in the study stent or a commercially available stent which was used to treat in-stent restenosis in this patient. Based on this data available from the clinical study, a stent fracture rate of 0.18% per patient (1/568) or 0.16% (1/623) was observed.

Durability of the TAXUS Liberté Stent System was also evaluated as part of the *in vitro* engineering testing. Pulsatile fatigue testing was conducted on TAXUS Liberté stents in a straight configuration, both single and overlapping stents, to the equivalent of 10 years (400 million cycles). In addition, TAXUS Liberté stents were evaluated for pulsatile fatigue on a curve to the equivalent of two years (80 million cycles). No stent fractures were identified in any test samples.

As a condition of approval, additional testing to evaluate pulsatile fatigue on a curve to 400 million cycles will be conducted.

IX. OVERVIEW OF CLINICAL STUDIES

The TAXUS Liberté clinical development program consists of a series of single-arm, historically-controlled, multicenter trials designed to assess the risk/benefit profile of the polymer-controlled, paclitaxel-eluting TAXUS Liberté stent. The specific goal of the TAXUS Liberté clinical trial program is to demonstrate that the TAXUS Liberté stent performs as well as the TAXUS Express stent to safely and significantly reduce the need for revascularization compared to bare metal stents within defined target lesions. The TAXUS Liberté clinical trial program was specifically designed to start with relatively simple lesions, and progress to increasingly more complex lesions, patient populations and procedures. This overview will focus on data generated with the pivotal TAXUS ATLAS trial comparing the TAXUS Liberté stent to a historical control population of TAXUS Express patients treated in the TAXUS IV and TAXUS V de novo clinical trials. A summary of the designs of these studies is presented in **Table 8**.

A. TAXUS ATLAS

TAXUS ATLAS[1] is a multi-center, single-arm trial to evaluate the safety and efficacy of the 1 $\mu g/mm^2$ (loaded drug/stent surface area) slow-release (SR) formulation TAXUS Liberté stent in the treatment of *de novo* coronary lesions compared with the TAXUS Express Paclitaxel-Eluting Coronary Stent System (case-matched historic control data derived from the TAXUS IV and TAXUS V *de novo* studies). A total of 871 patients at 61 clinical sites were enrolled in this study. The primary endpoint for the study was the 9-month ischemia driven target vessel revascularization (TVR) rate. Secondary endpoints included 9-month clinical assessments for all patients and analysis of angiographic and intravascular ultrasound (IVUS) parameters in a subset of patients. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for at least 6 months. Follow-up through 1 year is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

The objective of TAXUS ATLAS was to demonstrate non-inferiority of clinical and angiographic outcomes for TAXUS Liberté when compared to TAXUS Express. Therefore, the treatment group is compared to a case-matched Control group derived from TAXUS IV and TAXUS V *de novo*. In order to case-match the Control group, all TAXUS IV and V patients randomized to the TAXUS Express group with (1) a reference vessel diameter (RVD) by visual estimate $\geq$2.5 mm and $\leq$4.0 mm, (2) a lesion length by visual estimate $\geq$10 mm and $\leq$28 mm, and (3) receiving 1 planned study stent were included. This resulted in inclusion of all 662 patients randomized into the TAXUS Express treatment arm of TAXUS IV and 329 out of 577 patients randomized into the TAXUS Express treatment arm of TAXUS V *de novo*.

[1] Turco MA, Ormiston JA, Popma JJ, et al. Polymer-based, paclitaxel-eluting TAXUS Liberté stent in de novo lesions: The pivotal TAXUS ATLAS trial. J Am Coll Cardiol. 2007;49(16):1676-1683.

B. TAXUS IV

TAXUS IV[2] is a randomized, double-blind, controlled pivotal Phase III U.S. study of the safety and performance of the SR formulation TAXUS® Express™ Paclitaxel-Eluting Coronary Stent System in patients with low risk, *de novo* coronary artery lesions. A total of 1,326 patients at 73 U.S. sites were enrolled with patients randomized 1:1 to the TAXUS Express stent or the uncoated Express™ control stent. The primary endpoint for the study was the 9-month ischemia driven TVR rate. Secondary endpoints included 9-month clinical assessments for all patients and analysis of angiographic and IVUS parameters in a subset of patients. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for at least 6 months. Follow-up through 4 years is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

C. TAXUS V

TAXUS V de novo[3] is a randomized, double-blind, controlled, expansion study of the safety and performance of the SR formulation TAXUS® Express[2]™ Paclitaxel-Eluting Coronary Stent in de novo lesions in small and large diameter vessels, as well as long lesions. TAXUS V de novo was designed to expand the data set beyond the standard-risk, de novo coronary artery lesions studied in the pivotal TAXUS IV trial. A total of 1172 patients at 66 U.S. sites were enrolled with patients randomized 1:1 to the TAXUS Express Stent System or the uncoated Express control stent. The primary end point was the incidence rate of ischemia-driven TVR through 9 months post-index procedure. Secondary end points included the cumulative major adverse cardiac event (MACE) rate at follow-up and detailed quantitative coronary analysis (QCA) and IVUS analysis in pre-specified subgroups at 9 months. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for at least 6 months. Follow-up through 2 years is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

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[2] Stone GW, Ellis SG, Cox DA, et al. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation.* 2004;109(16):1942-1947.
Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med.* 2004;350(3):221-231.

[3] Stone GW, Ellis SG, Cannon L, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: A randomized controlled trial. JAMA. 2005;294(10):1215-1223.

Table 8: Comparison of TAXUS Clinical Studies

	TAXUS ATLAS	TAXUS IV (Pivotal)	TAXUS V de novo (Expansion)
Study Type	Multi-center, single-arm registry study	Prospective, multicenter, randomized, double-blind	Prospective, multicenter, randomized, double-blind
Number of Patients (ITT)	Total: 871 TAXUS Liberté Stent: 871 Blended TAXUS IV & V de novo historical control: 991	Total: 1314 TAXUS Express Stent: 662 Uncoated control: 652	Total: 1156 TAXUS Express Stent: 577 Uncoated control: 579
Dose Release Formulation	Slow Release (SR) (1 $\mu g/mm^2$)		
Lesion Criteria: Vessel Diameter (by visual estimate)	≥2.5 mm to ≤4.0 mm	≥2.5 mm to ≤3.75 mm	≥2.25 mm to ≤4.0 mm
Lesion Criteria: Lesion Length (by visual estimate)	≥10 mm and ≤28 mm	≥10 mm and ≤28mm	≥10 mm and ≤46 mm
Product Used	Liberté™ stent on the Maverick™ Monorail Stent Delivery Balloon Catheter	Express™ Stent on the Maverick™ Monorail Stent Delivery Balloon Catheter	Express™ Stent on the Maverick™ Monorail Stent Delivery Balloon Catheter
Antiplatelet Therapy	Aspirin indefinitely and clopidogrel or ticlopidine for 6 months		
Follow-Up	30 days: clinical 4 months: clinical 9 months: clinical (all), QCA and IVUS (subset) 1 – 5 years: clinical		

Abbreviations: ITT=intent-to-treat; IVUS=intravascular ultrasound; QCA=quantitative coronary angiography; SR=slow-release

X. POTENTIAL ADVERSE EFFECTS OF THE PRODUCT ON HEALTH

A. Observed Adverse Events

Observed adverse event experience comes from three clinical studies: TAXUS ATLAS, TAXUS IV and TAXUS V de novo. Principal adverse events for these trials are shown in **Table 9**. Stent apposition data for TAXUS ATLAS is presented in **Table 10**.

Table 9: TAXUS ATLAS, TAXUS IV, and TAXUS V *de novo* Major Adverse Cardiac Events (MACE) From Post-Procedure to Latest Follow-Up

	TAXUS ATLAS to 1 Year*		TAXUS IV to 4 Years**		TAXUS V de novo to 2 Years†	
	TAXUS Liberté	TAXUS Express Control	TAXUS Express	Uncoated Control	TAXUS Express	Uncoated Control
In-Hospital MACE	2.4% (21/871)	2.6% (26/991)	2.4% (16/662)	2.1% (14/652)	4.0% (23/577)	3.1% (18/579)
30-Day MACE, overall	2.8% (24/870)	3.3% (33/987)	2.9% (19/662)	2.5% (16/652)	5.1% (29/569)	3.6% (21/576)
9-Month MACE, overall	11.0% (95/862)	10.5% (102/974)	8.5% (56/662)	15.0% (98/652)	15.0% (84/560)	21.2% (120/567)
Cardiac Death	0.8% (7/862)	0.9% (9/974)	1.4% (9/662)	1.1% (7/652)	0.5% (3/560)	0.9% (5/567)
MI	3.7% (32/862)	3.9% (38/974)	3.5% (23/662)	3.7% (24/652)	5.4% (30/560)	4.6% (26/567)
Q-Wave MI	0.7% (6/862)	0.6% (6/974)	0.8% (5/662)	0.3% (2/652)	0.5% (3/560)	0.2% (1/567)
Non-Q-Wave MI	3.0% (26/862)	3.3% (32/974)	2.7% (18/662)	3.4% (22/652)	4.8% (27/560)	4.4% (25/567)
TVR, Overall	8.0% (69/862)	7.1% (69/974)	4.7% (31/662)	12.0% (78/652)	12.1% (68/560)	17.3% (98/567)
TLR, Overall	5.7% (49/862)	4.5% (44/974)	3.0% (20/662)	11.3% (74/652)	8.6% (48/560)	15.7% (89/567)
Non-TLR, Overall	3.2% (28/862)	2.7% (26/974)	1.7% (11/662)	1.1% (7/652)	4.8% (27/560)	4.2% (24/567)
1-Year MACE	12.5% (106/851)	12.3% (118/957)	10.6% (70/662)	19.8% (129/652)	18.9% (105/556)	25.9% (146/563)
2-Year MACE	NA	NA	14.7% (95/645)	25.2% (161/640)	22.1% (120/542)	29.2% (159/544)
3-Year MACE	NA	NA	18.9% (116/614)	29.0% (178/613)	NA	NA
4-Year MACE	NA	NA	22.1% (133/601)	31.5% (190/604)	NA	NA
Cardiac Death	NA	NA	3.0% (18/601)	4.0% (24/604)	NA	NA
MI	NA	NA	7.2% (43/601)	7.1% (43/604)	NA	NA
Q-Wave MI	NA	NA	1.3% (8/601)	1.0% (6/604)	NA	NA
Non-Q-Wave MI	NA	NA	6.0% (36/601)	6.5% (39/604)	NA	NA

Table 9: TAXUS ATLAS, TAXUS IV, and TAXUS V *de novo* Major Adverse Cardiac Events (MACE) From Post-Procedure to Latest Follow-Up

	TAXUS ATLAS to 1 Year*		TAXUS IV to 4 Years**		TAXUS V de novo to 2 Years†	
	TAXUS Liberté	TAXUS Express Control	TAXUS Express	Uncoated Control	TAXUS Express	Uncoated Control
TVR, Overall	NA	NA	16.0% (96/601)	26.0% (157/604)	NA	NA
TLR, Overall	NA	NA	7.8% (47/601)	20.2% (122/604)	NA	NA
Non-TLR, Overall	NA	NA	9.0% (54/601)	9.3% (56/604)	NA	NA
4-Year Stent Thrombosis	NA	NA	1.6% (9/579)	1.1% (6/569)	NA	NA

* After 9 months, the TAXUS ATLAS study population was reduced to a pre-specified cohort (per protocol population), which consists of all patients who received a study stent at baseline.
** After 2 years the TAXUS IV study population was reduced to a pre-specified cohort, which consists of all patients who received a study stent at baseline (Safety Population). At 4 years, the safety population is comprised of 1290 (n=649 for TAXUS, n=641 for Control).
† After 1 year the TAXUS V de novo study population was reduced to a pre-specified cohort, which consists of all patients who received a study stent at baseline (Safety population).
NA= Not Applicable; variable and/or time point not calculated.

In TAXUS ATLAS, a pre-specified subset of patients underwent IVUS evaluation of the treated lesion immediately after treatment and as a part of a scheduled angiographic evaluation at 9 months. **Table 10** presents incomplete apposition rates by treatment group for the IVUS subset (n=610), based on core lab identification of one or more struts not apposed to the vessel wall, with evidence of speckling indicative of blood flow. There were no statistically significant differences between treatment groups with respect to percent of patients with incomplete apposition post-procedure (P=0.7260). However, the rate of late incomplete apposition at 9-month follow-up was significantly lower in the TAXUS Liberté group than in the TAXUS Express control group (p=0.0461). Paired IVUS analysis for both post-procedure and 9 months was available for 285 patients. In this patient group, the rates were comparable between TAXUS ATLAS and Control with regard to resolved (present post-procedure, absent at 9 months), persistent (present post-procedure and at 9 months), or late-acquired (absent post-procedure, present at 9 months) incomplete apposition.

Table 10: Frequency of Incomplete Stent Apposition

Incomplete Apposition (IA)	TAXUS ATLAS (N=327)	Control (TAXUS IV & V) (N=283)
Early (Post-Procedure)	8.7% (22/254)	7.3% (14/191)
Late (9-Month)	4.3% (9/209)	10.1% (14/139)
Paired Data		
Resolved	3.4% (6/177)	2.8% (3/108)
Persistent	2.3% (4/177)	3.7% (4/108)
Late Acquired	1.7% (3/177)	5.6% (6/108)

Resolved = # patients with BL IA and without FU IA ÷ # patients evaluable at baseline and follow-up.
Persistent = # patients with BL IA and with FU IA ÷ # patients evaluable at baseline and follow-up.
Late Acquired = # patients without BL IA and with FU IA ÷ # patients evaluable at baseline and follow-up.
Incomplete Apposition variables are from assessment by IVUS core laboratory

B. Potential Adverse Events

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

- Abrupt stent closure
- Acute myocardial infarction
- Allergic reaction to anti-coagulant and/or antiplatelet therapy, contrast medium, or stent materials
- Angina
- Arrhythmias, including ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Arteriovenous fistula
- Cardiac tamponade
- Cardiogenic shock/Pulmonary edema
- Coronary aneurysm
- Death
- Dissection
- Emboli, distal (air, tissue or thrombotic material or material from devices(s) used in the procedure)
- Heart failure
- Hematoma
- Hemorrhage, required transfusion
- Hypotension/Hypertension
- Infection, local or systemic
- Ischemia, myocardial
- Pain, at the access site
- Perforation or Rupture of coronary artery
- Pericardial effusion
- Pseudoaneurysm, femoral
- Renal Failure
- Respiratory Failure
- Restenosis of stented segment
- Stent emobolization or migration
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident /TIA
- Total occlusion of coronary artery
- Vessel spasm
- Vessel trauma 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)
- 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.

XI. SUMMARY OF CLINICAL STUDIES

A. TAXUS ATLAS Clinical Trial

Objective: The primary objective of this study was to demonstrate non-inferiority of the TAXUS Liberté Stent as compared to the TAXUS Express Stent with respect to target vessel revascularization rate (TVR) 9 months post-index procedure.

Design: TAXUS ATLAS was a multi-center, single-arm trial in patients at 61 sites. Eligible patients were those presenting for stenting of *de novo* lesions of a single native coronary artery (RVD of 2.5 to 4.0mm) with a target lesion of 10 to 28 mm in length and stenosis >50% in diameter (visual estimates) who are candidates for percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG), and had documented angina pectoris or functional ischemia.

A total of 871 intent-to-treat (ITT) patients were enrolled and evaluable in this study. The Control group (991 total ITT patients) was comprised of case-matched, historic data derived from the TAXUS IV and TAXUS V *de novo* studies. Multiple stenting was allowed for bail-out only. After the procedure, patients who received the assigned study stent (protocol population) were treated with aspirin indefinitely and clopidogrel or ticlopidine for at least 6 months.

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 9-month follow-up, the study population was reduced to a pre-specified cohort, which consists of all patients who received the assigned study stent at baseline (per protocol population). Follow-up through 1 year is currently available in 856/867 (98.7%) patients.

A subset of patients was pre-assigned to have angiographic (N=543) and IVUS (N=327) follow-up at 9 months. Angiographic assessments were performed for the area of the vessel within the stent margins (in-stent) and the areas immediately 5 mm proximal and distal from the stent margins (analysis segment).

Demographics: Patients were well-matched for baseline demographics. QCA analysis of the baseline lesion characteristics showed well-matched RVD (mean 2.75±0.50 mm versus 2.79±0.49 mm, p=0.1274) between TAXUS Liberté and the Control group. However, minimum lumen diameter (MLD) was smaller (mean 0.85±0.36 mm versus 0.92±0.34 mm, p<0.0001), % diameter stenosis was greater (mean 69.13±11.83 % versus 66.76±10.80 %, p<0.0001), and lesion length was longer (mean 14.76±6.61 mm versus 13.60±6.11 mm, p<0.0001) for TAXUS Liberté compared to the Control group. In addition, QCA parameters assessing baseline lesion complexity (bend, tortuosity, calcification, and presence of branch vessel disease) were significantly higher for TAXUS Liberté, resulting in a significantly higher proportion of lesions with AHA/ACC Type B2 or C lesion complexity (75.5% for TAXUS Liberté versus 61.2% for Control, p<0.0001). In the presence of rigid matching criteria, these differences indicate a change in clinical practice patterns from the TAXUS Express Control (enrolled 2 to 3 years ago) to the TAXUS Liberté treatment group.

Despite the higher lesion complexity, stent placement in the TAXUS Liberté group was accomplished with shorter procedure times (47.8±25.5 minutes versus 53.0±49.5 minutes, p=0.0052) and a lower incidence of geographic miss during the stent placement (5.6% versus 9.2%, p=0.0036).

Results: The primary endpoint data (9 months) and latest available follow-up (1 year) results are presented below (**Table 11**, **Table 12**, **Table 13**, **Table 14**, **Table 15**, **Table 16**, **Figure 3**, and **Figure 4**).

Conclusion: Overall, the primary and all prespecified secondary endpoints of TAXUS ATLAS were met. In studied patients, the TAXUS Liberté stent was associated with a non-inferior rate of 9 month TVR (primary endpoint) as compared to TAXUS Express. Quantitative coronary angiography (QCA) and IVUS analyses confirmed similar results for both groups with non-inferiority for binary restenosis rate, minimum lumen diameter (MLD), percent diameter stenosis (%DS), late loss, and % in-stent net volume obstruction between the groups. The results were achieved with similar rates and results for edge restenosis and late loss at the proximal and distal edges. There were comparable MACE rates, rates of stent thrombosis, aneurysm and incomplete stent apposition between groups, demonstrating the similarity of the TAXUS Liberté Stent to the TAXUS Express Stent.

Table 11: TAXUS ATLAS Clinical Results

	9 months (ITT population)				1 year (latest available follow-up) (per protocol population*)		
	TAXUS Liberté (N=871)	**Control (N=991)**	**P-Value**		**TAXUS Liberté (N=867)**	**Control (N=978)**	**P-Value**
EFFICACY							
TVR, Overall	8.0% (69/862)	7.1% (69/974)	0.4787		9.2% (78/851)	8.9% (85/957)	0.8334
TLR, Overall	5.7% (49/862)	4.5% (44/974)	0.2865		6.1% (52/851)	5.5% (53/957)	0.6035
TLR, PCI	5.3% (46/862)	3.9% (38/974)	0.1472		5.9% (50/851)	5.0% (48/957)	0.4203
TLR, CABG	0.3% (3/862)	0.6% (6/974)	0.5141		0.2% (2/851)	0.5% (5/957)	0.4579*
Non-TLR, Overall	3.2% (28/862)	2.7% (26/974)	0.4911		4.2% (36/851)	3.8% (36/957)	0.6111
Non-TLR, PCI	2.8% (24/862)	2.1% (20/974)	0.3596		3.5% (30/851)	2.8% (27/957)	0.3925
Non-TLR, CABG	0.5% (4/862)	0.6% (6/974)	0.7578		0.8% (7/851)	0.9% (9/957)	0.7894
SAFETY							
Total Death	1.2% (10/863)	1.8% (18/977)	0.2570		1.3% (11/854)	2.3% (22/961)	0.1110
Cardiac Death or MI	4.2% (36/862)	4.7% (46/974)	0.6510		4.5% (38/851)	4.7% (45/957)	0.8102
Cardiac Death	0.8% (7/862)	0.9% (9/974)	1.0000		0.8% (7/851)	1.0% (10/957)	0.6248
MI	3.7% (32/862)	3.9% (38/974)	0.9030		4.0% (34/851)	3.9% (37/957)	0.8879
Q-wave MI	0.7% (6/862)	0.6% (6/974)	1.0000		0.7% (6/851)	0.6% (6/957)	0.8383
Non-Q-wave MI	3.0% (26/862)	3.3% (32/974)	0.7901		3.3% (28/851)	3.2% (31/957)	0.9515
Stent Thrombosis	0.8% (7/858)	0.7% (7/966)	1.0000		0.9% (8/846)	0.7% (7/947)	0.6318

*After 9 months, the TAXUS ATLAS study population was reduced to a pre-specified cohort (per protocol population), which consists of all patients who received a study stent at baseline. Patients who did not receive a study stent were not followed beyond 9 months.

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.

Table 12: TAXUS ATLAS Primary Endpoint

Per Protocol Population	TAXUS Express Control (N=980)	TAXUS Liberté (N=867)	Difference [Upper 1-Sided 95% CI]	p-Value	Δ
9-Month TVR	7.01% (67/956)	7.95% (68/855)	0.94% [2.98%]	0.0487[a]	3.0%
Intent-to-Treat Population	**TAXUS Express Control (N=991)**	**TAXUS Liberté (N=871)**	**Difference [Upper 1-Sided 95% CI]**	**p-Value**	**Δ**
9-Month TVR	7.14% (69/967)	8.03% (69/859)	0.90% [2.94%]	0.0454[a]	3.0%

[a] P-values represent unadjusted results from non-inferiority testing.

Table 13: TAXUS ATLAS Secondary Endpoints

Per Protocol Population	TAXUS Express Control (N=980)	TAXUS Liberté (N=867)	Bonferroni Adjusted Upper 1-Sided 95% CI[b]	p-Value[c]	Δ
In-Stent Percent Diameter Stenosis	18.80±19.44 (486) (-23.34, 100.00)	21.04±21.40 (448) (-21.01, 100.00)	2.24 [5.35]	0.0006**	6.6%
In-Stent Binary Restenosis	8.64% (42/486)	11.38% (51/448)	2.74% [7.32%]	0.0354	6.3%
In-Stent MLD[a] (mm)	2.28±0.66 (486) (0.00, 4.08)	2.19±0.71 (448) (0.00, 4.23)	-0.09 [-0.19]	0.0316*	-0.17 mm
In-Stent Late Loss (mm)	0.42±0.54 (484) (-0.85, 2.71)	0.41±0.54 (446) (-0.77, 2.55)	-0.01 [0.07]	<0.0001*	0.18 mm
% In-Stent Net Volume Obstruction	12.26±13.73 (139) (-27.01, 53.96)	13.92±11.30 (209) (-8.77, 50.96)	1.66 [4.80]	0.0021**	5.7%

*Variances equal: Pooled t statistic

**Variances unequal: Satterthwaite's approximate t statistic

[a] Lower 1-Sided 95% CI is reported for In-Stent MLD.

[b] Bonferroni Adjusted Upper 1-sided 95% CI calculated using a 1-sided 99% CI.

[c] P-values represent unadjusted results from non-inferiority testing.

Table 14: TAXUS ATLAS Procedural Results

Procedural Outcomes	TAXUS Express Control (N=991)	TAXUS Liberté (N=871)	P-Value
Procedure Time	53.0±49.5 (991)	47.8±25.5 (870)	0.0052
Geographic Miss	9.2% (91/985)	5.6% (49/869)	0.0036

P-values are not adjusted for multiple comparisons.

Table 15: TAXUS ATLAS 9-Month Angiographic and IVUS Results

Angiographic Outcomes [a]	TAXUS Express Control (N=704)	TAXUS Liberté (N=543)	P-Value
MLD (mm), In-stent			
Post-Procedure	2.70±0.45 (484)	2.60±0.46 (446)	0.0006
9-Month	2.28±0.66 (486)	2.19±0.71 (448)	0.0541
MLD (mm), Analysis Segment			
Post-Procedure	2.28±0.50 (484)	2.22±0.51 (447)	0.0615
9-Month	2.01±0.61 (486)	1.97±0.67 (449)	0.3132
% DS, In-stent			
Post-Procedure	4.43±10.29 (484)	7.30±8.87 (446)	<0.0001
9-Month	18.80±19.44 (486)	21.04±21.40 (448)	0.0934
% DS, Analysis Segment			
Post-Procedure	19.77±9.97 (484)	21.30±9.47 (447)	0.0169
9-Month	28.47±17.24 (486)	29.15±19.06 (449)	0.5688
Late Loss, In-stent (mm)	0.42±0.54 (484)	0.41±0.54 (446)	0.6872
Late Loss, Analysis Segment (mm)	0.27±0.46 (484)	0.25±0.50 (447)	0.5889
Binary Restenosis			
In-stent restenosis	8.6% (42/486)	11.4% (51/448)	0.1893
Analysis segment restenosis	12.1% (59/486)	14.3% (64/449)	0.3836
IVUS Outcomes [b]	**TAXUS Express Control (N=283)**	**TAXUS Liberté (N=327)**	**P-Value**
Neointimal Volume (mm^3) (9 months)	21.6±25.0 (140)	24.9±24.1 (209)	0.2089
% Net Volume Obstruction (9 months)	12.3±13.7 (139)	13.9±11.3 (209)	0.2197
Incomplete Apposition			
Late (9 months)	10.1% (14/139)	4.3% (9/209)	0.0461
Late Acquired	5.6% (6/108)	1.7% (3/177)	0.0871

[a] Includes all patients in the angiographic subset.
[b] Includes all patients in the IVUS subset.
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.

Table 16: TAXUS ATLAS Stent Thrombosis

Per Protocol Population	TAXUS Express Control (N=978)	TAXUS Liberté (N=867)	P-Value
Protocol Defined Stent Thrombosis [a]			
Cumulative through 1 year	0.7% (7/947)	0.9% (8/846)	0.6318
Acute ST (≤24 hrs)	0.2% (2/978)	0.0% (0/867)	0.5015*
Subacute ST (>24 hrs and ≤30 days)	0.3% (3/976)	0.2% (2/865)	1.0000*
Late ST (>30 days and ≤12 months)	0.2% (2/972)	0.7% (6/863)	0.1583*

Table 16: TAXUS ATLAS Stent Thrombosis (continued)

Per Protocol Population	TAXUS Express Control (N=978)	TAXUS Liberté (N=867)	P-Value
ARC Definite & Probable Stent Thrombosis [b]			
Cumulative through 1 year	0.8% (8/947)	1.2% (10/846)	0.4745
Acute ST (≤24 hrs)	0.2% (2/978)	0.0% (0/867)	0.5015*
Subacute ST (>24 hrs and ≤30 days)	0.3% (3/976)	0.2% (2/865)	1.0000*
Late ST (>30 days and ≤2 months)	0.3% (3/972)	0.9% (8/863)	0.0868

To be included in the calculation of stent thrombosis rate for a given interval, a patient either had to have a stent thrombosis during the interval (e.g. 31-365 days inclusive) or they had to be stent thrombosis-free during the interval with last follow-up on or after the first day of the given interval (e.g. 31 days).

[a] Per protocol, stent thrombosis is defined as the occurrence of any of the following:

1. Clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis:
   a) Angiographic documentation of a complete occlusion (TIMI flow 0 or 1) of a previously successfully treated artery (TIMI flow 2 to 3 immediately after stent placement and diameter stenosis ≤30%) and/or
   b) Angiographic documentation of a flow-limiting thrombus within or adjacent to a previously successfully treated lesion.
2. Acute MI of the distribution of the treated vessel.
3. Death within the first 30 days (without other obvious cause) is considered a surrogate for stent thrombosis when angiography is not available.

[b] Academic Research Consortium (ARC) stent thrombosis is defined as follows[4]:

1. Definite ST is considered to have occurred after intracoronary stenting by either angiographic or pathologic confirmation of stent thrombosis.
2. Probable ST is considered to have occurred after intracoronary stenting in the following cases:
   a) Any unexplained death within the first 30 days following stent implantation.
   b) Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of St and in the absence of any other obvious cause.

After 9 months, the TAXUS ATLAS study population was reduced to a pre-specified cohort (per protocol population), which consists of all patients who received a study stent at baseline. Patients who did not receive a study stent were not followed beyond 9 months.

Numbers are % (Count/Sample Size).

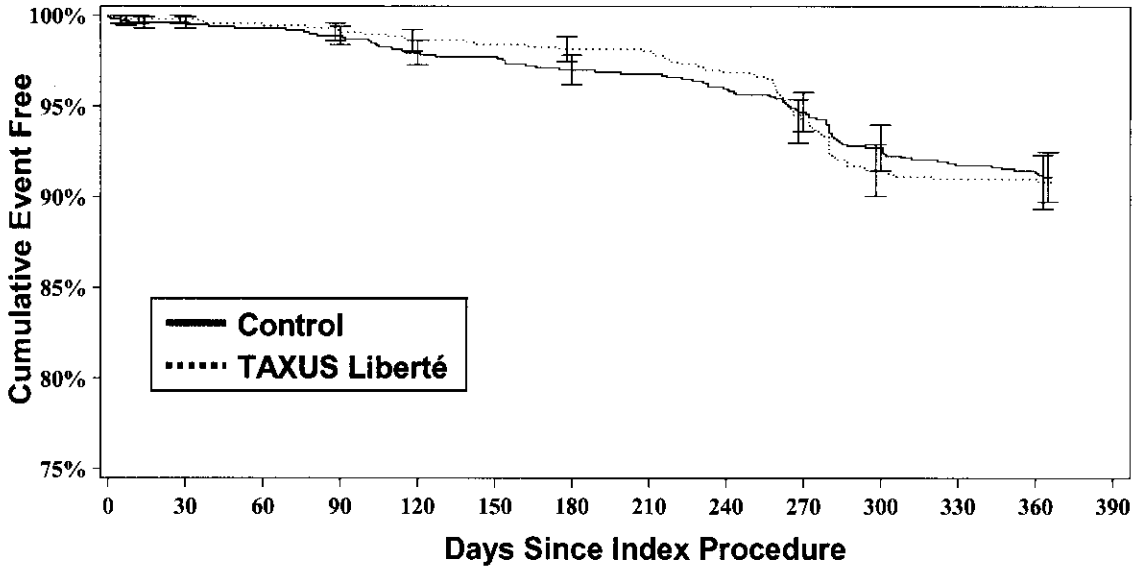
*P-values are two-sided from Fisher's exact test; p-values without * are two-sided from the Chi-square test.

P-values are not adjusted for multiple comparisons.

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

[4] Cutlip DE, Windecker S, Mehran R, et al. Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions. *Circulation.* 2007;115(17):2344-2351.

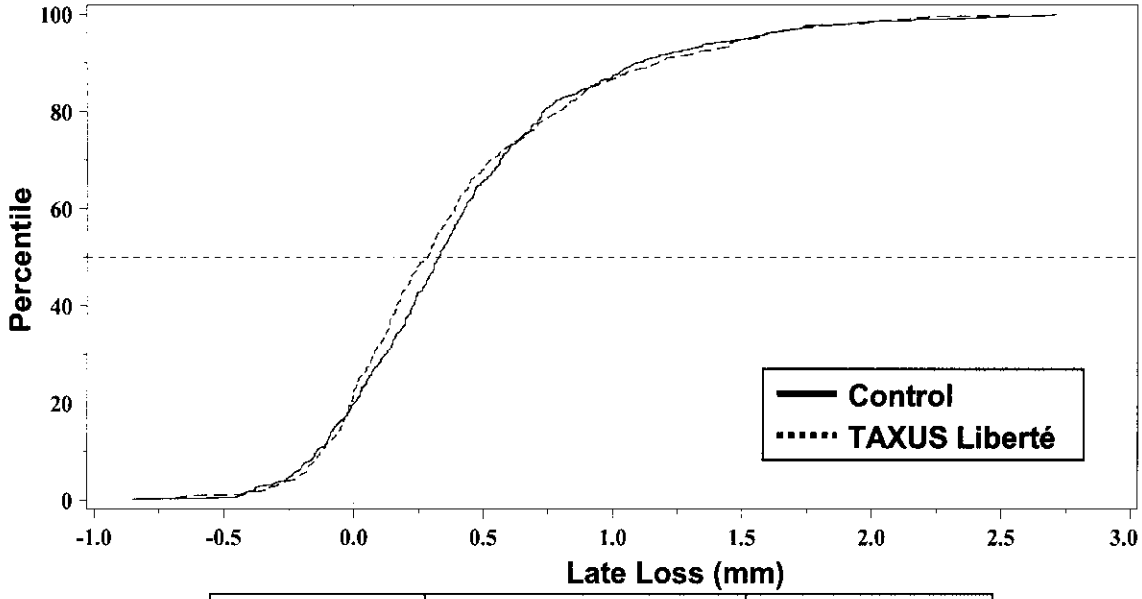
Figure 3: TAXUS ATLAS Freedom from TVR to 1 Year, Event-Free Survival ± 1.5 SE, Per Protocol Population, All Patients (N=1845)



	Event Rate	Event Free	P-value*
TAXUS Express Control	8.9%	91.1%	0.8092
TAXUS Liberté	9.2%	90.8%	

* Log-rank P-value. P-value is not adjusted for multiple comparisons.

Figure 4: TAXUS ATLAS Cumulative Frequency Distribution of In-Stent Late Loss by QCA, Intent-to-Treat, All Angiographic Subset Patients (N=1247)



	TAXUS Express Control (N=704)	TAXUS Liberté (N=543)
N	484	446
Median	0.33	0.29
Minimum	-0.85	-0.77
Maximum	2.71	2.55
Mean	0.42	0.41
SD	0.54	0.54
COV	126.64%	133.09%
Diff (95% CI)	-0.01 [-0.08, 0.06]	

COV = coefficient of variation.
MLD = Minimum Lumen Diameter
Late Loss = Final MLD – 9-Month MLD

Diabetic Patients in TAXUS ATLAS: Patients with diabetes mellitus represent a high-risk group for adverse events following percutaneous coronary intervention. The TAXUS ATLAS clinical trial did not stratify for diabetic status, and this trial was not adequately powered to study safety and effectiveness of TAXUS® Liberté™ versus TAXUS® Express® in patients with diabetes. Diabetics were further defined as medically treated (all patients treated with oral medication and/or insulin) for diabetes mellitus.

The TAXUS ATLAS clinical trial was not designed to specifically support an approval for use in diabetic patients. The following table includes patient level data from the TAXUS ATLAS clinical trial in diabetic patients.

Table 17: TAXUS ATLAS 1-year Clinical Results for Medically Treated Diabetic Patients

Per Protocol Population [a]	TAXUS Express Control (N=241)	TAXUS Liberté (N=220)	P-Value
EFFICACY			
TVR, Overall	12.9% (30/233)	13.5% (29/215)	0.8480
TLR, Overall	8.2% (19/233)	9.3% (20/215)	0.6668
TLR, PCI	7.7% (18/233)	8.8% (19/215)	0.6693
TLR, CABG	0.4% (1/233)	0.5% (1/215)	1.0000*
TVR Remote, Overall	5.2% (12/233)	6.0% (13/215)	0.6797
TVR Remote, PCI	3.0% (7/233)	4.7% (10/215)	0.3621
TVR Remote, CABG	2.1% (5/233)	1.4% (3/215)	0.7259*
SAFETY			
Total Death	3.0% (7/235)	2.3% (5/218)	0.6500
Cardiac Death or MI	4.3% (10/233)	5.1% (11/215)	0.6800
Cardiac Death	1.7% (4/233)	0.9% (2/215)	0.6869*
MI	3.0% (7/233)	5.1% (11/215)	0.2554
Q-Wave MI	0.0% (0/233)	0.9% (2/215)	0.2298*
Non-Q-Wave MI	3.0% (7/233)	4.2% (9/215)	0.5007
Stent Thrombosis [b]	0.4% (1/229)	1.4% (3/213)	0.3561*

[a] After 9 months, the TAXUS ATLAS study population was reduced to a pre-specified cohort (per protocol population), which consists of all patients who received a study stent at baseline. Patients who did not receive a study stent were not followed beyond 9 months.

[b] Per protocol stent thrombosis.

Numbers are % (Count/Sample Size).

*P-values are two-sided from Fisher exact test; p-values without * are two-sided 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 a control group, nor was it sized to determine the rate of low frequency events with a pre-specified precision.

B. Results of the TAXUS IV Pivotal Clinical Trial

Primary Objective: To demonstrate superiority of the TAXUS® Express™ Stent compared to a matched, uncoated control stent for reduction of the TVR rate at 9 months post-index procedure.

Design: This was a multi-center, prospective, randomized, double-blind study in patients at 73 U.S. sites. Eligible patients were those presenting for stenting of de novo lesions in a single native coronary artery (RVD 2.5 to 3.75 mm) with a target lesion 10 to 28 mm in length and stenosis ≥ 50% in diameter using visual estimates, and who were candidates for PCI or CABG, and had documented angina pectoris or functional ischemia.

A total of 1314 patients were enrolled and evaluable in this study: 662 in the TAXUS group and 652 in the Control group. Patients were randomized to receive either a TAXUS Express Stent or an uncoated Express™ coronary stent (bare metal control). Study randomization was sub-stratified for medically-treated diabetes, reference vessel diameter, and lesion length. Multiple stenting was allowed for bailout only. After the procedure, patients were treated with aspirin indefinitely and clopidogrel or ticlopidine for 6 months.

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. Follow-up through 2 years is available in 1238/1314 (94.2%) of patients. After the 2-year follow-up, the TAXUS IV study population was reduced to a pre-specified cohort, which consists of all patients who received a study stent at baseline (Safety Population). At 4 years, the safety population is comprised of 1290 (N=649 for TAXUS, N=641 for Control) and follow-up is available for 1230 patients (95.4%).

A subset of patients was pre-assigned to have angiographic (N=732) and IVUS (N=268) follow-up at 9 months. Angiographic assessments were performed for the area of the vessel within the stent margins (in-stent) and for the area within the stent margins, plus the area immediately 5 mm proximal and distal from the stent margins (analysis segment).

The primary endpoint data (9 months) and latest available follow-up (48 months) results are presented below (**Table 18**, **Table 19**, and **Figure 5**), as well as stent thrombosis data through 48 months (**Table 20**).

Table 18: TAXUS IV Clinical Results

	9 months (ITT population)			4 years (safety population*)		
	TAXUS (N=662)	**Control (N=652)**	**P-Value**	**TAXUS (N=649)**	**Control (N=641)**	**P-Value**
EFFICACY						
TVR, Overall[§]	4.7% (31/ 662)	12.0% (78/ 652)	< 0.0001	16.0% (96/601)	26.0% (157/604)	< 0.0001
TLR, Overall	3.0% (20/662)	11.3% (74/652)	< 0.0001	7.8% (47/601)	20.2% (122/604)	< 0.0001
TLR, PCI	2.4% (16/662)	8.7% (57/652)	< 0.0001	7.0% (42/601)	15.9% (96/604)	< 0.0001
TLR, CABG	0.6% (4/662)	3.1% (20/652)	0.0008	0.8% (5/601)	5.5% (33/604)	< 0.0001
Non-TLR, Overall	1.7% (11/662)	1.1% (7/652)	0.4778	9.0% (54/601)	9.3% (56/604)	0.8629
Non-TLR, PCI	1.2% (8/662)	0.8% (5/652)	0.5793	6.5% (39/601)	7.8% (47/604)	0.3836
Non-TLR, CABG	0.5% (3/662)	0.3% (2/652)	1.0000	2.7% (16/601)	2.2% (13/604)	0.5636
SAFETY						
Total Death	2.1% (14/662)	1.5% (10/652)	0.5378	7.3% (45/618)	8.4% (52/617)	0.4540
Cardiac Death or MI	4.7% (31/662)	4.3% (28/652)	0.7905	9.3% (56/601)	9.9% (60/604)	0.7170
Cardiac Death	1.4% (9/662)	1.1% (7/652)	0.8025	3.0% (18/601)	4.0% (24/604)	0.3545
MI	3.5% (23/662)	3.7% (24/652)	0.8826	7.2% (43/601)	7.1% (43/604)	0.9809
Q-wave MI	0.8% (5/662)	0.3% (2/652)	0.4520	1.3% (8/601)	1.0% (6/604)	0.5844
Non-Q-wave MI	2.7% (18/662)	3.4% (22/652)	0.5237	6.0% (36/601)	6.5% (39/604)	0.7373
Stent Thrombosis	0.6% (4/662)	0.8% (5/652)	0.7513	1.6% (9/579)	1.1% (6/569)	0.4558

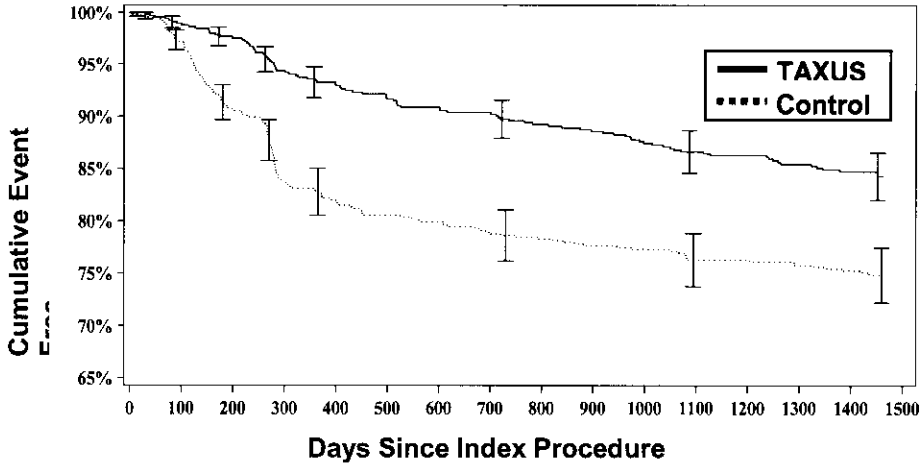
[§] 9-month primary endpoint.

* Patients who did not receive a study stent were not followed beyond two years.

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.

Figure 5: TAXUS IV Freedom from TVR to 4 Years, Event-Free Survival ± 1.5 SE, Safety Population, All Patients (N=1290)



	Event Rate	Event Free	P-value*
Uncoated Control	25.2%	74.8%	< 0.0001
TAXUS Express	15.7%	84.3%	

* Log-rank P-value. P-value is not adjusted for multiple comparisons.

Table 19: TAXUS IV 9- Month Angiographic and IVUS Results

	TAXUS Express (N=662)	Uncoated Control (N=652)	P-Value
MLD (mm), In-stent			
Post-Procedure	2.65 +/- 0.42 (372)	2.67 +/- 0.41 (350)	0.6338
9-Month	2.26 +/- 0.58 (291)	1.75 +/- 0.65 (266)	< 0.0001
MLD (mm), Analysis Segment			
Post-Procedure	2.26 +/- 0.48 (373)	2.29 +/- 0.50 (355)	0.4617
9-Month	2.03 +/- 0.55 (291)	1.68 +/- 0.61 (267)	< 0.0001
% DS, In-stent			
Post-Procedure	4.22 +/- 10.85 (372)	5.14 +/- 11.42 (350)	0.2695
9-Month	17.43 +/-17.71 (291)	37.24 +/- 19.76 (266)	< 0.0001
% DS, Analysis Segment			
Post-Procedure	19.14 +/- 9.67 (373)	19.31 +/- 10.47 (355)	0.8136
9-Month	26.29 +/- 15.45 (291)	39.79 +/- 18.45 (267)	< 0.0001
Late Loss, In-stent (mm)	0.39 +/- 0.50 (291)	0.92 +/- 0.58 (266)	< 0.0001
Late Loss, Analysis Segment (mm)	0.23 +/- 0.44 (291)	0.61 +/- 0.57 (267)	< 0.0001
Binary Restenosis			
In-stent restenosis	5.5% (16/ 291)	24.4% (65/ 266)	< 0.0001
Analysis segment restenosis	7.9% (23/ 291)	26.6% (71/ 267)	< 0.0001
IVUS			
Neointimal Volume (mm^3)	17.56 +/- 18.21 (81)	41.48 +/- 23.02 (80)	< 0.0001
% Net Volume Obstruction	12.20 +/- 12.44 (81)	29.40 +/- 14.05 (80)	< 0.0001
Incomplete Apposition			
Late (9 months)	4.0% (4/99)	3.0% (3/100)	0.7209
Late Acquired	1.1% (1/94)	2.2% (2/93)	0.6210

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.

Table 20: TAXUS IV Protocol Defined Stent Thrombosis* through 4 Years Safety Population

	TAXUS	Control	P-Value
Cumulative ST through 4 years	1.6% (9/579)	1.1% (6/569)	0.4558[†]
Acute ST (≤24 hrs)	0.0% (0/660)	0.3% (2/650)	0.2467
Subacute ST (> 24 hrs and ≤30days)	0.3% (2/660)	0.5% (3/649)	0.6849
Late ST (> 30 days and ≤12 months)	0.3% (2/658)	0.2% (1/647)	1.0000
Very Late ST (> 12 months to 4 years)	0.8% (5/630)	0.2% (1/625)	0.2177

To be included in the calculation of stent thrombosis rate for a given interval, a patient either had to have a stent thrombosis during the interval (e.g. 31-365 days inclusive) or they had to be stent thrombosis-free during the interval with last follow-up on or after the first day of the given interval (e.g. 31 days).

*Per protocol, stent thrombosis is defined as the occurrence of any of the following:

1. Clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis:
   a) Angiographic documentation of a complete occlusion (TIMI flow 0 or 1) of a previously successfully treated artery (TIMI flow 2 to 3 immediately after stent placement and diameter stenosis ≤ 30%) and/or
   b) Angiographic documentation of a flow-limiting thrombus within or adjacent to a previously successfully treated lesion.
2. Acute MI of the distribution of the treated vessel.
3. Death within the first 30 days (without other obvious cause) is considered a surrogate for stent thrombosis when angiography is not available.

Numbers are % (Count/Sample Size).

Patients who did not receive a study stent were not followed beyond two years

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.

C. TAXUS V de novo Expansion Clinical Trial

Objective: The primary objective of this study was to demonstrate a superior 9-month ischemia-driven TVR rate for the TAXUS® Express$^{2™}$ Stent compared to the uncoated Express Stent in long lesion lengths, small and large vessel diameters and with multiple overlapping stents in the treatment of de novo coronary artery lesions.

Design: This was a multicenter, prospective, randomized, double-blind study in patients at 66 U.S. sites. Eligible patients were those presenting for stenting of de novo lesions of a single, native coronary artery (RVD ≥2.25 and ≤4.00mm) with a target lesion 10 to 46 mm in length, stenosis ≥ 50% (visual estimate), candidates for PCI or CABG, and had documented angina pectoris or functional ischemia.

A total of 1156 ITT patients were enrolled and evaluable in this study: 577 in the TAXUS group and 579 in the Control group. Patients were randomized to receive either a TAXUS Express Stent or uncoated Express Stent (bare metal control). Study randomization was sub-stratified for target lesion length (<18mm vs. ≥ 18mm), the presence or absence of medically treated diabetes, and clinical site. Enrollment targeted high-risk sub-populations including patients with small diameter vessels (RVD ≤ 2.5mm n≥50 with at least 200 2.25mm stent patients), large diameter vessels (4.00mm diameter stent; n ≥200), and long lesions (≥18mm lesion length n ≥400 with at least 300 patients with lesion lengths >26mm [overlapping stents]). Post-procedure patients were treated with aspirin (recommended indefinitely, mandatory for 9 months) and clopidogrel or ticlopidine for 6 months.

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 de novo study population was reduced to a pre-specified cohort, which consists of all patients who received an assigned study stent at baseline (Safety Population). Follow-up through 2 years is currently available in 1052/1108 (94.9%) of patients eligible for 2-year follow-up.

All patients were to have angiographic follow-up at 9 months and a subset of patients were to receive IVUS at 9 months (N=300). Angiographic assessments were performed for the area of the vessel within the stent margins (in-stent) and for the area within the stent margins, plus the area immediately 5 mm proximal and distal from the stent margins (analysis segment).

The TAXUS ATLAS trial utilized data from the TAXUS V *de novo* trial as part of the case-matched historical control. Specifically, control patients were identified based on lesion characteristics to match those of the TAXUS ATLAS clinical trial. From the 577 patients in the TAXUS group of TAXUS V *de novo*, 108 patients were excluded who has RVD less than 2.5 mm, 90 patients were excluded who had lesions greater than 28 mm in length, and 50 patients were excluded who had planned use of more than one study stent. This resulted in a total of 329 patients used from the TAXUS V *de novo* study as part of the case-matched historical control. These patients, along with all 662 patients from the TAXUS arm of the TAXUS IV trial constituted the entire TAXUS Express control population (N=991) for the TAXUS ATLAS trial.

The primary endpoint data (9 months) and latest available follow-up (2 years) results are presented below for the overall population (**Table 21** and **Figure 6**).

Table 21: TAXUS V de novo Clinical Results

	9 months (ITT Population)			2 years (Safety Population**)		
	TAXUS Express (N=577)	**Uncoated Control (N=579)**	**P-Value**	**TAXUS Express (N=575)**	**Uncoated Control (N=571)**	**P-Value**
EFFICACY						
TVR, Overall[§]	12.1% (68/560)	17.3% (98/567)	0.0184	18.6% (101/542)	25.4% (138/544)	0.0074
TLR, Overall	8.6% (48/560)	15.7% (89/567)	0.0003	13.3% (72/542)	21.5% (117/544)	0.0004
TLR, PCI	7.9% (44/560)	13.9% (79/567)	0.0011	12.5% (68/542)	19.5% (106/544)	0.0018
TLR, CABG	0.7% (4/560)	1.8% (10/567)	0.1770	0.7% (4/542)	2.4% (13/544)	0.0283
Non-TLR, Overall	4.8% (27/560)	4.2% (24/567)	0.6691	7.9% (43/542)	8.6% (47/544)	0.6730
Non-TLR, PCI	4.5% (25/560)	3.2% (18/567)	0.2793	7.2% (39/542)	6.8% (37/544)	0.7991
Non-TLR, CABG	0.4% (2/560)	1.1% (6/567)	0.2874	0.9% (5/542)	1.8% (10/544)	0.1961
SAFETY						
Total Death	1.3% (7/559)	1.4% (8/566)	1.0000	3.3% (18/541)	3.8% (21/548)	0.6539
Cardiac Death or MI	5.7% (32/560)	5.5% (32/567)	0.8973	7.2% (39/542))	6.1% (33/544)	0.4545
Cardiac Death	0.5% (3/560)	0.9% (5/567)	0.7256	1.7% (9/542)	1.55 (8/544)	0.8010
MI	5.4% (30/560)	4.6% (26/567)	0.5853	5.9% (32/542)	4.8% (26/544)	0.4098
Q-wave MI	0.5% (3/560)	0.2% (1/567)	0.3712	0.6% (3/542)	0.4% (2/544)	0.6863*
Non-Q-wave MI	4.8% (27/557)	4.4% (25/562)	0.7777	5.4% (29/542)	4.4% (24/544)	0.4728
Stent Thrombosis	0.7% (4/557)	0.7% (4/562)	1.0000	0.8% (4/529)	0.8% (4/530)	1.0000*

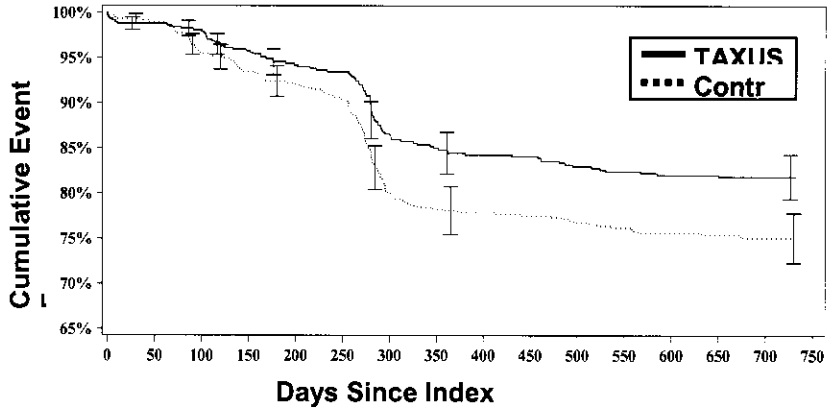
** Patients who did not receive a study stent were not followed beyond 1 year.

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

[§] Primary Endpoint at 9 months.

With the exception of the 9-month TVR p-value, 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.

Figure 6: TAXUS V de novo Freedom from TVR to 2 Years, Event-Free Survival ± 1.5 SE, Safety Population, All Patients (N=1146)



	Event Rate	Event Free	P-value*
Uncoated Control	24.9%	75.1%	0.0053
TAXUS Express	18.2%	81.8%	

* Log-rank P-value – not adjusted for multiple comparisons.

D. Gender Bias

The gender selection in this clinical study was completely random, and solely based upon exclusion and inclusion criteria. In the TAXUS ATLAS cohort of patients, women represented 30.5% of the population. According to the American Heart Association Heart Disease and Stroke Statistics (2008 Update), women represent approximately 40% of patients age 60-79 with coronary heart disease. Although the ratio of men to women in the TAXUS ATLAS study does not match the prevalence of coronary artery disease in the general U.S. population, it is reflective of the underlying distribution of the disease for the types of patients that would meet the study inclusion/exclusion criteria (i.e., younger, less complex disease). No selection bias on the basis of gender was identified during the review. In addition, gender was not identified as a multivariate predictor with respect to the primary study endpoint of TVR.

XII. CONCLUSIONS FROM CLINICAL AND NON-CLINICAL STUDIES

The safety and effectiveness of the TAXUS Liberté MR and OTW Coronary Stent Systems is based on the results obtained from: biocompatibility; *in vivo* pharmacokinetics; *in vitro* engineering testing; coating characterization; chemistry, manufacturing and controls information; *in vivo* animal testing; sterilization and stability testing; and clinical studies. These test results revealed the following:

The biocompatibility, *in vivo* pharmacokinetics, and *in vivo* animal testing that were conducted demonstrated that the acute and chronic *in vivo* performance characteristics of the product provide reasonable assurance of safety and are acceptable for clinical use.

The *in vitro* engineering testing conducted on the stent and delivery system(s) demonstrated that the performance characteristics met the product specifications and the coating characterization testing adequately described the important attributes of the paclitaxel/polymer coating. The chemistry, manufacturing, and controls information ensures that product meeting specifications will be released.

The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The stability testing demonstrated that the product can be labeled with a shelf life of 18 months.

The clinical testing conducted demonstrated that the product provides a reasonable assurance of safety and effectiveness when used as indicated in accordance with the instructions for use.

XIII. PANEL RECOMMENDATIONS

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 Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CDRH DECISION

The applicant's manufacturing and sterilization facilities were inspected and were found to be in compliance with the Quality System Regulation (21 CFR 820 and pharmaceutical current Good Manufacturing Practice (cGMP) regulations.

FDA issued an approval order on October 10, 2008.

XV. APPROVAL SPECIFICATIONS

Directions for Use: See product labeling.

Hazard to Health from Use of the Product: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Post Approval Requirements and Restrictions: See Approval Order.