

# TAXUS<sup>®</sup> Express<sup>2®</sup> and TAXUS<sup>®</sup> Express<sup>2®</sup> Atom<sup>™</sup>

Paclitaxel-Eluting Coronary Stent System  
Monorail<sup>®</sup> and Over-the-Wire Coronary Stent Delivery System

**CAUTION: U.S. Federal law restricts this product to sale by or on the order of a physician.**

## **Warning**

Contents supplied STERILE using an ethylene oxide (EO) process. Do not use if sterile barrier is damaged. If damage is found, call your Boston Scientific representative.

For single patient use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing or re-sterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or re-sterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the stent and/or the delivery catheter may lead to injury, illness or death of the patient.

After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

DIRECTIONS FOR USE

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# 1 TAXUS<sup>®</sup> Express<sup>2®</sup> and TAXUS<sup>®</sup> Express<sup>2®</sup> Atom<sup>™</sup> Paclitaxel-Eluting Coronary Stent System

The TAXUS Express<sup>2</sup> (2.50 mm - 4.0 mm) and TAXUS Express<sup>2</sup> Atom (2.25 mm) Paclitaxel-Eluting Coronary Stent Systems (hereinafter referred to as TAXUS Express<sup>2</sup> Stent System) is a device / drug combination product comprised of two regulated components: a device (Express<sup>2</sup> Coronary Stent System) and a drug product (a formulation of paclitaxel contained in a Polymer Coating). The characteristics of the TAXUS Express<sup>2</sup> Stent System are described in Table 1-1.

**Table 1-1. TAXUS Express<sup>2</sup> Stent System Product Description**

	TAXUS Express <sup>2</sup> Monorail <sup>®</sup> Stent Delivery System	TAXUS Express <sup>2</sup> Over-the-Wire Stent Delivery System
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32	
Available Stent Diameters (mm)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	
Stent Material	A 316L surgical grade stainless steel Express <sup>®</sup> stent	
Drug Product	A conformal coating of a polymer carrier loaded with 1µg/mm <sup>2</sup> paclitaxel in a slow release (SR)* formulation applied to the stent with a maximum nominal drug content of 282 µg on the largest stent (4.00 x 32 mm).	
<b>Delivery System</b>		
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 in (0.36mm)	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤ 0.014 in (0.36mm)
Stent Delivery	A compliant balloon, nominally 0.3 mm longer than the stent, with two radiopaque markers.	
<b>Balloon</b>		
Balloon Inflation	Nominal Inflation Pressure: 9 ATM (912 kPa); Rated Burst Inflation Pressure: 18 ATM (1824 kPa)	
<b>Pressure</b>		
Guide Catheter Inner Diameter	≥ 0.058in (1.47mm)	≥ 0.066in (1.68mm)
Catheter Shaft Outer Diameter	1.8F (0.61mm) proximally, 2.7F (0.91mm) distally (Ø up to 3.0mm, and 8-20mm long stents with Ø > 3.0mm) 2.0F (0.67mm) proximally, 2.7F (0.91mm) distally (24-32mm long stents with Ø > 3.0mm)	3.2F (1.08mm) proximally, 2.7F (0.91mm) 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

## 1.1 Device Component Description

The device component consists of the Express Stent mounted onto the Express<sup>2</sup> Stent Delivery System (SDS). The 2.25 – 4.00 mm diameter 316L stainless steel stents use two designs. The same

stents are crimped on various delivery catheter balloons, which are sized from 2.25 to 4.00 mm. The total drug per stent is a function of stent length (see Table 1-2).

## 1.2 Drug Component Description

The stent component of the TAXUS Express<sup>2</sup> Stent System (referred to as the TAXUS Express Stent) is a stent with a drug / Polymer Coating formulation consisting of paclitaxel (the active ingredient) and Translute™ Polymer Carrier (the inactive ingredient).

### 1.2.1 Paclitaxel

The active pharmaceutical ingredient in the TAXUS<sup>®</sup> Express<sup>®</sup> 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,

$\beta$ -(benzoylamino)- $\alpha$ -hydroxy-,6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1

H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2aR- [2a $\alpha$ ,4 $\beta$ ,4a $\beta$ ,6 $\beta$ ,9 $\alpha$  ( $\alpha$ R\*, $\beta$ S\*),11 $\alpha$ ,12 $\alpha$ ,12a $\alpha$ ,12ba]]-

The chemical structure of paclitaxel is shown below.

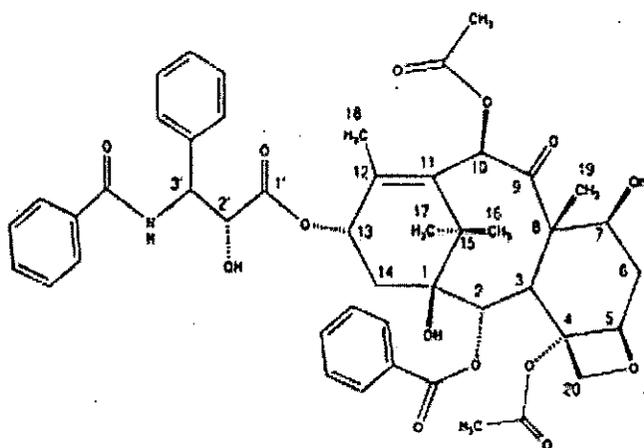


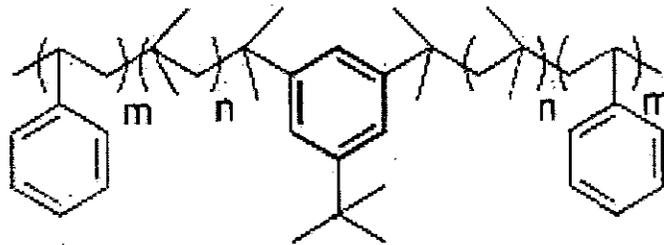
Figure 1.1. The Chemical Structure of Paclitaxel

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.

### 1.2.2 Translute™ Polymer Carrier

The only inactive ingredient in the TAXUS Express 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 ( $M_n$ -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 below.



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

Figure 1.2. The Chemical Structure of Translute™ Polymer Carrier

### 1.2.3 Product Matrix and Paclitaxel Content

Table 1-2. TAXUS® Express<sup>2</sup>® Stent System  
Product Matrix and Paclitaxel Content

Product Code MR	Product Code OTW	Nominal Expanded Stent Inner Diameter (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Paclitaxel Content (µg)
H7493897008220	H7493896808220	2.25	8	50
H7493897008250	H7493896808250	2.50	8	50
H7493897008270	H7493896808270	2.75	8	50
H7493897008300	H7493896808300	3.00	8	50
H7493897008350	H7493896808350	3.50	8	50
H7493897008400	H7493896808400	4.00	8	68
H7493897012220	H7493896812220	2.25	12	79
H7493897012250	H7493896812250	2.50	12	79
H7493897012270	H7493896812270	2.75	12	79
H7493897012300	H7493896812300	3.00	12	79
H7493897012350	H7493896812350	3.50	12	79
H7493897012400	H7493896812400	4.00	12	107
H7493897016220	H7493896816220	2.25	16	108
H7493897016250	H7493896816250	2.50	16	108
H7493897016270	H7493896816270	2.75	16	108
H7493897016300	H7493896816300	3.00	16	108
H7493897016350	H7493896816350	3.50	16	108
H7493897016400	H7493896816400	4.00	16	146
H7493897020220	H7493896820220	2.25	20	137
H7493897020250	H7493896820250	2.50	20	137
H7493897020270	H7493896820270	2.75	20	137
H7493897020300	H7493896820300	3.00	20	137
H7493897020350	H7493896820350	3.50	20	137
H7493897020400	H7493896820400	4.00	20	185
H7493897024220	H7493896824220	2.25	24	151
H7493897024250	H7493896824250	2.50	24	151
H7493897024270	H7493896824270	2.75	24	151
H7493897024300	H7493896824300	3.00	24	151
H7493897024350	H7493896824350	3.50	24	151
H7493897024400	H7493896824400	4.00	24	204
H7493897028270	H7493896828270	2.75	28	180
H7493897028300	H7493896828300	3.00	28	180

**Table 1-2. TAXUS<sup>®</sup> Express<sup>2®</sup> Stent System  
Product Matrix and Paclitaxel Content**

Product Code MR	Product Code OTW	Nominal Expanded Stent Inner Diameter (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Paclitaxel Content (µg)
H7493897028350	H7493896828350	3.50	28	180
H7493897028400	H7493896828400	4.00	28	243
H7493897032270	H7493896832270	2.75	32	209
H7493897032300	H7493896832300	3.00	32	209
H7493897032350	H7493896832350	3.50	32	209
H7493897032400	H7493896832400	4.00	32	282

## 2 Indications

The TAXUS Express<sup>2</sup> Paclitaxel-Eluting Coronary Stent System is indicated for improving luminal diameter:

- for the treatment of de novo lesions in native coronary arteries 2.25 mm to 2.50 mm in diameter in lesions ≤ 20 mm in length;
- for the treatment of de novo lesions in native coronary arteries 2.75 mm to 4.00 mm in diameter in lesions ≤ 28 mm in length;
- in patients undergoing primary angioplasty to treat acute ST-segment elevation myocardial infarction, true posterior myocardial infarction, or presumed new left bundle branch block with symptoms of acute myocardial infarction lasting > 20 minutes and < 12 hours in duration; or
- within bare metal stent restenotic lesions 2.50 mm to 3.75 mm in diameter and ≤ 28 mm in length.

## 3 Contraindications

Use of the TAXUS Express<sup>2</sup> 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 2).

Coronary Artery Stenting is contraindicated for use in:

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

## 4 Warnings

- To maintain sterility, the inner package should not be opened or damaged prior to use.
- The use of this product carries the risks associated with coronary artery stenting, including subacute thrombosis, vascular complications, and/or bleeding events.
- Patients with known hypersensitivity to 316L stainless steel may suffer an allergic reaction to this implant.
- This product should not be used in patients who are not likely to comply with recommended antiplatelet therapy.

## **5 Precautions**

### **5.1 General Precautions**

- Only physicians who have received adequate training should perform implantation of the stent.
- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Subsequent stent blockage may require repeat dilatation of the arterial segment containing the stent. The long-term outcome following repeat dilatation of endothelialized stents is not well characterized.
- Consideration should be given to the risks and benefits of use in patients with history of severe reaction to contrast agents.
- Do not expose the delivery system to organic solvents such as alcohol or detergents.
- Care should be taken to control the position of the guide catheter tip during stent delivery, deployment and balloon withdrawal.
- Before withdrawing the Stent Delivery System (SDS), visually confirm complete balloon deflation by fluoroscopy (See Table 5-1 for Deflation Time Specifications). Failure to do so may cause increased SDS withdrawal forces, and result in guide catheter movement into the vessel and subsequent arterial damage.
- Stent thrombosis is a low frequency event that current drug-eluting stent (DES) clinical trials are not adequately powered to fully characterize. Stent thrombosis is frequently associated with myocardial infarction (MI) or death. Data from TAXUS Stent randomized clinical trials have been prospectively evaluated and adjudicated using both the protocol definition of stent thrombosis and the definition developed by the Academic Research Consortium (ARC), and demonstrate specific patterns of stent thrombosis that vary depending on the definition used (See Section 9.6.1). In the TAXUS clinical trials analyzed to date, the differences in the incidence of stent thrombosis observed with the TAXUS Stent compared to bare metal stents have not been associated with an increased risk of cardiac death, MI, or all-cause mortality.
- When drug-eluting stents are used outside the specified Indications for Use, patient outcomes may differ from the results observed in the pivotal clinical trials.
- Compared to use within the specified Indications for Use, the use of drug-eluting stents in patients and lesions outside of the labeled Indications, including more tortuous anatomy, may have an increased risk of adverse events, including stent thrombosis, stent embolization, myocardial infarction, or death.
- At five years, the TAXUS V de novo study indicates that patients treated with TAXUS stents with lesion lengths > 26 mm by visual estimate and with  $\geq 2$  planned stents had a higher incidence of MI and the combined endpoint of MI or cardiac death, compared to bare metal stents. See Table 9.4.5.
- At five years, the TAXUS V de novo study indicates that patients treated with 2.25 mm stents had a higher incidence of the combined endpoint of cardiac death or MI compared to bare metal stents. See Table 9.4.4.

### **5.2 Pre-and Post-Procedure Antiplatelet Regimen**

In clinical trials of the TAXUS™ Express® Stent, clopidogrel or ticlopidine was administered pre-procedure and for a period of 6 months post-procedure. Aspirin was administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce the risk of thrombosis. See Section 9, Clinical Studies, for more specific information. In the HORIZONS AMI trial, clopidogrel or ticlopidine was to be administered pre-procedure and for a period of 6 months post-procedure, and recommended for 1 year or longer. Aspirin was to be administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely.

The optimal duration of antiplatelet therapy, specifically clopidogrel, is unknown after implantation of a DES and DES thrombosis may still occur despite continued therapy. Data from several studies suggest that a longer duration of antiplatelet therapy than was recommended post-procedurally in drug-eluting stent pivotal clinical trials (including TAXUS clinical trials) may be beneficial. Provided herein are recent recommendations from the "2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention (PCI)" for anti-thrombotic adjunctive therapies for Percutaneous Coronary Intervention (PCI), Section 5.2.1.

### 5.2.1 Oral Antiplatelet Therapy

#### For Elective PCI Procedures

Continuation of combination treatment with aspirin and a P2Y<sub>12</sub> inhibitor after PCI appears to reduce major adverse cardiac events. On the basis of randomized clinical trial protocols, secondary prevention measures, and expert consensus opinion, aspirin 81 mg daily should be given indefinitely after PCI. Likewise, a P2Y<sub>12</sub> inhibitor should be given daily for at least 12 months in patients who are not at high risk of bleeding. Full guidelines are provided at the following website:

<http://content.onlinejacc.org/cgi/content/short/58/24/2550>

#### For PCI in ST-Elevation MI (STEMI) Patients

There are ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction<sup>1</sup>, which recommend the following:

- 1) A loading dose of a P2Y<sub>12</sub> inhibitor is recommended for STEMI patients for whom PCI is planned. Regimens should be one of the following:
  - a) At least 300 to 600 mg of clopidogrel should be given as early as possible before or at the time of primary or nonprimary PCI.
  - b) Prasugrel 60 mg should be given as soon as possible for primary PCI.
  - c) For STEMI patients undergoing nonprimary PCI, the following regimens are recommended:
    - (i) If the patient has received fibrinolytic therapy and has been given clopidogrel, clopidogrel should be continued as the thienopyridine of choice;
    - (ii) If the patient has received fibrinolytic therapy without a thienopyridine, a loading dose of 300 to 600 mg of clopidogrel should be given as the thienopyridine of choice;
    - (iii) if the patient did not receive fibrinolytic therapy, either a loading dose of 300 to 600 mg of clopidogrel should be given or, once the coronary anatomy is known and PCI is planned, a loading dose of 60 mg of prasugrel should be given promptly and no later than 1 hour after PCI.
- 2) The duration of P2Y<sub>12</sub> inhibitor therapy should be as follows:
  - a) In patients receiving a stent (BMS or drug-eluting [DES]) during PCI for ACS, clopidogrel 75 mg, prasugrel 10 mg daily should be given for at least 12 months;
  - b) If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by P2Y<sub>12</sub> receptor inhibitor therapy, earlier discontinuation should be considered.

<sup>1</sup> Kushner F, Hand M, Smith Jr S, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update)/ A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2009; 54 (23): 2205

It is very important that the patient is compliant with the post-procedural antiplatelet recommendations. Premature discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, myocardial infarction or death. Prior to PCI, if a surgical or dental procedure is anticipated that requires early discontinuation of antiplatelet therapy, the interventional cardiologist and patient should carefully consider whether a drug-eluting stent and its associated recommended antiplatelet therapy is the appropriate PCI choice. Following PCI, should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risk associated with premature discontinuation of antiplatelet therapy. Generally, it is recommended to postpone elective surgery for one year among those patients for whom surgery can be deferred. ASA should be considered during the perioperative period in high-risk DES patients.

Patients who require premature discontinuation of antiplatelet therapy secondary to significant active bleeding should be monitored carefully for cardiac events and, once stabilized, have their antiplatelet therapy restarted as soon as possible per the discretion of their treating physicians.

### **5.3 Use of Multiple Stents**

The use of multiple stents (bare metal or drug-eluting) and the resulting increase in stented length in the setting of extensive disease (e.g., long lesions > 26 mm) may increase the risk of patient complications. The use of multiple drug-eluting stents will expose the patient to larger amounts of drug and polymer.

In the TAXUS V de novo study, the use of  $\geq 2$  planned TAXUS Stents (including overlapping and non-overlapping placement) in patients with single lesions > 26 mm by visual estimate was associated with a numerically higher rate of peri-procedural ( $\leq 30$  days) non-Q-wave myocardial infarction (Non-Q wave MI: CK levels > 2.0 x ULN with positive CK-MB) relative to bare metal stent (BMS) controls (8.5% in TAXUS patients vs. 2.6% in BMS patients) with no cardiac deaths  $\leq 30$  days in either arm. Through 5-year follow-up in this subgroup, TAXUS patients had an overall MI rate of 15.6%, compared with 6.0% in the BMS group ( $P=0.0294$ ). The 5-year rate of the composite endpoint of Cardiac Death or MI was also higher in the TAXUS arm (22.9%) relative to the BMS arm (8.0%;  $P=0.0037$ ) for this subgroup. Furthermore, in TAXUS V patients treated with  $\geq 2$  planned study stents in lesions > 26 mm who were MI-free at 30 days, there were 15 total deaths, 8 cardiac deaths, and 4 MI (1 Q-wave and 3 non-Q wave) in TAXUS patients ( $N=106$ ) through 5 years follow-up compared with 10 total deaths, 2 cardiac deaths, and 3 MIs (0 Q-wave and 3 non-Q wave) in BMS patients ( $N=112$ ). In TAXUS V patients treated with  $\geq 2$  planned stents in lesions > 26 mm by visual estimate and who had MI within 30 days ( $N=11$  TAXUS;  $N=3$  BMS), there were 0 deaths to 5 years, with 0 new MI events from 31 days to 5 years in either treatment arm.

In TAXUS V patients treated with  $\geq 2$  planned study stents in lesions > 26 mm, TAXUS patients had a reduced target vessel revascularization (TVR) rate (27.1%) compared to BMS patients (42.0%) through 5-year follow-up. When considering placement of multiple TAXUS stents, the benefit of reduced target vessel revascularization should be weighed against the increased risk of MI or the composite of Cardiac Death or MI.

In the HORIZONS AMI trial, lesions > 26 mm in length were to be treated with 2 (or more as required) overlapping study stents. Table 5.1 provides clinical outcomes on patients from the HORIZONS AMI trial who were treated with multiple overlapping study stents (528 patients in the TAXUS Express arm and 124 patients in the bare metal Express arm).

**Table 5.1: Clinical Outcomes in HORIZONS AMI Patients with Multiple Overlapping Study Stents**

	1 Year		3 Year	
	TAXUS Express (N=528)	Bare Metal Express (N=124)	TAXUS Express (N=528)	Bare Metal Express (N=124)
Death	4.2% (22)	5.0% (6)	6.8% (35)	8.4% (10)
Cardiac Death	2.9% (15)	4.1% (5)	4.1% (21)	5.1% (6)
Noncardiac Death	1.4% (7)	0.9% (1)	2.8% (14)	3.6% (4)
Reinfarction	4.5% (23)	2.5% (3)	9.1% (45)	6.2% (7)
Q-Wave	1.9% (10)	1.7% (2)	3.4% (17)	2.6% (3)
Non-Q-Wave	2.6% (13)	0.8% (1)	5.7% (28)	3.7% (4)
Death or Reinfarction	8.6% (45)	6.6% (8)	15.1% (78)	13.6% (16)
Target Vessel Revascularization	6.4% (33)	11.8% (14)	15.7% (78)	28.5% (33)

When more than one stent is required, resulting in stent-to-stent contact, stent materials should be of similar composition to avoid the possibility of corrosion due to the presence of dissimilar metals in a conducting medium. Potential interactions of the TAXUS<sup>®</sup> Express<sup>®</sup> Stent with other drug-eluting or coated stents have not been evaluated and should be avoided whenever possible.

#### **5.4 Brachytherapy**

The safety and effectiveness of the TAXUS Express Stent in patients with prior brachytherapy of the target lesion have not been established. The safety and effectiveness of the use of brachytherapy to treat in-stent restenosis in a TAXUS Express Stent have not been established. Both vascular brachytherapy and the TAXUS Express Stent alter arterial remodeling. The synergy between these two treatments has not been determined.

#### **5.5 Use in Conjunction with Other Procedures**

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with TAXUS Express Stent implantation have not been established.

#### **5.6 Use in Special Populations**

##### **5.6.1 Pregnancy**

Pregnancy "Category C." See Drug Information – Section 6.5, Pregnancy. There are no adequate or well-controlled studies in pregnant women or men intending to father children. TAXUS Express Stents should be used in pregnant women only, if the potential benefit justifies the potential risk to the embryo or fetus. Because some paclitaxel remains on the stent indefinitely, use of the TAXUS Express Stent in women who are of childbearing potential or in men intending to father children should be given careful consideration.

##### **5.6.2 Lactation**

See Drug Information – Section 6.6, Lactation. A decision should be made whether to discontinue nursing prior to implanting the stent, taking into account the importance of the stent to the mother.

##### **5.6.3 Gender**

See Clinical Information - Section 9, Clinical Studies.

#### **5.6.4 Ethnicity**

In the TAXUS IV, TAXUS V *de novo*, TAXUS ATLAS Workhorse, TAXUS ATLAS Direct Stent, TAXUS ATLAS Small Vessel, and TAXUS ATLAS Long Lesion clinical trials and registries, there were 2,428 pooled patients, of which 127 (5.2%) were black. The clinical trials and registries conducted with paclitaxel-eluting stents were not designed or powered to analyze for differences in outcomes by race/ethnicity.

#### **5.6.5 Pediatric use**

The safety and effectiveness of the TAXUS Express Stent in pediatric patients have not been established.

#### **5.6.6 Geriatric Use**

In the pooled TAXUS IV and TAXUS V *de novo* studies, there were 564 patients in the TAXUS Express group who were age 65 or older. There were 86 TAXUS Express patients in these two TAXUS Express studies who were over 80 years of age. There were no significant differences in nine-month clinical outcomes (primary endpoint of ischemia-driven target vessel revascularization) in these studies between patients under 65 and over 65 years of age treated with TAXUS Express stents with the exception of the rate of myocardial infarction (5.6% in patients less than 65 years of age versus 2.9% in those 65 or older).

#### **5.7 Lesion/Vessel Characteristics**

The safety and effectiveness of the TAXUS<sup>®</sup> Express<sup>®</sup> Stent have not been established in the cerebral, carotid, or peripheral vasculature or the following coronary disease patient populations:

- Patients not being treated for STEMI, with vessel thrombus at the lesion site.
- Patients with coronary artery reference vessel diameters < 2.25 or > 4.00 mm.
- Patients with coronary artery lesions longer than 28 mm or requiring more than one TAXUS stent.
- Patients with lesions located in the saphenous vein grafts, in the unprotected left main coronary artery, ostial lesions, or lesions located at a bifurcation.
- Patients with in-stent thrombosis.
- Patients with diffuse disease or poor flow distal to the identified lesions.
- Patients with tortuous vessels (> 60 degrees) in the region of the obstruction or proximal to the lesion.
- Patients with moderate or severe calcification in the lesion or a chronic total occlusion.
- Patients with multi-vessel disease.

#### **5.8 Drug Interaction**

Because systemic levels of paclitaxel have not been detected post-stent placement in clinical trials, possible interactions of paclitaxel with concomitantly administered medications are unlikely to be detectable. The effect of potential drug interactions on the safety and efficacy of the TAXUS Express Stent has not been formally investigated. The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4.

See Drug Information – Section 6.3, Drug Interactions.

## **5.9 Magnetic Resonance Imaging (MRI)**

Non-clinical testing has demonstrated the TAXUS Express Stent, in single and in overlapped configurations up to 62 mm in length, is MR Conditional. It can be scanned safely under the following conditions:

- static magnetic field of 3 and 1.5 Tesla
- spatial gradient field of 700 Gauss/cm or less
- normal operating mode (maximum whole body averaged specific absorption rate (SAR) of 2 W/kg) for 15 minutes or less of scanning.

Patients with single TAXUS Express Stents or TAXUS Express Stents at overlapped lengths up to 62 mm may safely undergo MRI in normal operating mode of 1.5T and 3T MR systems for 15 minutes or less. Non-clinical testing at other field strengths has not been performed to evaluate stent migration or heating. MRI at 1.5 or 3 Tesla may be performed immediately following the implantation of the TAXUS Express Stent.

In non-clinical testing, the TAXUS Express Stent at overlapped lengths up to 62 mm produced a maximum temperature rise of 1.7°C at a maximum whole body averaged specific absorption rate (SAR) of 2.0 W/kg, as assessed by a validated calculation for 15 minutes of MR scanning in a 3.0 Tesla Magnetom Trio®, Siemens Medical Solutions, software version Numaris/4, Syngo® MR A30 MR scanner and in a 1.5 Tesla Intera® Philips Medical Systems, software version Release 10.6.2.0, 2006-03-10, MR scanner. Stent heating was derived in computer simulation using anatomically correct human models. These calculations do not take into consideration the cooling effects of blood flow.

The response of overlapped stents greater than 62 mm in length is unknown. 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. The image artifact extends approximately 9 mm from the device, both inside and outside the device lumen when scanned in nonclinical testing using the sequence: Spin Echo and Gradient Echo in a 3.0 Tesla Magnetom Trio, Siemens Medical Solutions, software version Numaris/4, Syngo MR A30 MR system with CP head coil.

## **5.10 Stent Handling (also see Section 13, Operator's Instructions)**

- For single use only. Do not resterilize or reuse this product. Note product "Use By" date. (See Warning, Page1.)
- The premounted TAXUS Express Stent and its delivery system are designed for use as a unit. The stent is not to be removed from its delivery balloon. The stent is not designed to be crimped onto another balloon. Removing the stent from its delivery balloon may damage the stent and coating and/or lead to stent embolization.
- Special care must be taken not to handle or in any way disrupt the stent position on the delivery balloon. This is most important during catheter removal from packaging, placement over guidewire, and advancement through hemostasis valve adapter and guide catheter hub.
- Excessive manipulation or handling may cause coating damage, contamination, or dislodgment of the stent from the delivery balloon.
- Use only the appropriate balloon inflation media (see Operator's Instructions - Section 13.3.3, Balloon Preparation). Do not use air or any gas medium to inflate the balloon.
- In the event the TAXUS® Express® stent is not deployed, follow product returns procedures.

## **5.11 Stent Placement Preparation**

- Do not prepare or pre-inflate balloon prior to stent deployment other than as directed. Use the balloon purging technique described in Operator's Instructions - Section 13.3.3, Balloon Preparation.
- If unusual resistance is felt at any time during lesion access before stent implantation, the stent system and the guide catheter should be removed as a single unit (See Precautions - Section 5.12, Stent System Removal).
- An unexpanded stent should be introduced into the coronary arteries one time only. An unexpanded stent should not be subsequently moved in and out through the distal end of the guide catheter, as stent or coating damage or stent dislodgment from the balloon may occur.

## Placement

The vessel should be pre-dilated with an appropriate sized balloon. Failure to do so may increase the risk of placement difficulty and procedural complications.

- Do not expand the stent if it is not properly positioned in the vessel (see Precautions - Section 5.12, Stent System Removal).
- Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on product label (see Table 13.1 Typical TAXUS<sup>®</sup> Express<sup>2®</sup> Stent System Compliance). Use of pressures higher than specified on product label may result in a ruptured balloon and potential intimal damage and dissection. The stent inner diameter should approximate 1.1 times the reference diameter of the vessel.
- Placement of the stent has the potential to compromise side branch patency.
- Implanting a stent may lead to dissection of the vessel distal and/or proximal to the stented portion, and may cause acute closure of the vessel requiring additional intervention (e.g., CABG, further dilation, placement of additional stents, or other).
- When treating multiple lesions, the distal lesion should be initially stented, followed by stenting of the more proximal lesion(s). Stenting in this order alleviates the need to cross the proximal stent in placement of the distal stent and reduces the chances of dislodging the proximal stent.
- When multiple stents are required for full coverage of a lesion, the distal stent should be placed first, followed by the more proximal stent. An approximate 4 mm stent-to-stent overlap is recommended to avoid the potential for gap restenosis.
- For ISR where details of the original stent are not known, the expanded inner diameter of the new stent should not exceed the RVD.

### 5.12 Stent System Removal

- If unusual resistance is felt at any time during lesion access before stent implantation, the Stent System and the guide catheter should be removed as a single unit.
- Do not attempt to pull an unexpanded stent back into the guide catheter, as stent or coating damage or stent dislodgment from the balloon may occur.
- Stent retrieval methods (use of additional wires, snares and/or forceps) may result in additional trauma to the vascular site. Complications can include bleeding, hematoma or pseudoaneurysm.

When removing the entire stent system and guide catheter as a single unit (NOTE: The following steps should be executed under direct visualization using fluoroscopy):

- Following stent placement, confirm complete balloon deflation (See Table 5-2 for Deflation Time Specifications). If greater than usual resistance is felt during delivery system balloon withdrawal, pay particular attention to guide catheter position. In some cases, it may be necessary to pull back slightly on the guide catheter in order to prevent deep seating (unplanned advancement) of the guide catheter and subsequent vessel damage. In cases where unplanned guide catheter

movement has occurred, angiographic assessment of the coronary tree should be undertaken to ensure that there is no damage to the coronary vasculature.

- Maintain guidewire placement across the lesion during the entire removal process. Carefully pull back the Stent System until the proximal balloon marker of the Stent System is just distal to the guide catheter distal tip.
- The Stent System and the guide catheter should be pulled back until the tip of the guide catheter is just distal to the arterial sheath, allowing the guide catheter to straighten. Carefully retract the Stent System into the guide catheter and remove the Stent System and the guide catheter from the patient as a single unit while leaving the guidewire across the lesion.

Failure to follow these steps, and/or applying excessive force to the Stent System, can potentially result in stent or coating damage, stent dislodgment from the balloon, and/or damage to the delivery System.

**Table 5-2 System Deflation Time Specifications**

Balloon Length/ Diameter	8 mm	12 mm	16 mm	20 mm	24 mm	28 mm	32 mm		
2.25 mm	≤ 16 seconds			≤ 16 seconds		Not offered			
2.50 mm				≤ 21 seconds		≤ 21 seconds		≤ 21 seconds	
2.75 mm								≤ 21 seconds	
3.00 mm				≤ 21 seconds					
3.50 mm				≤ 21 seconds					
4.00 mm				≤ 21 seconds					

\*All products tested during Design Verification met 95/95 confidence/conformance levels.

**5.13 Post-Procedure**

- Care must be exercised when crossing a newly deployed stent with an intravascular ultrasound (IVUS) catheter, a coronary guidewire, or a balloon catheter to avoid disrupting the stent placement, apposition, geometry, and/or coating.
- In clinical trials of the TAXUS<sup>®</sup> Express<sup>®</sup> Stent, clopidogrel or ticlopidine was administered pre-procedure and for a period of 6 months post-procedure. Aspirin was administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce the risk of thrombosis. See **Section 9 – Clinical Studies**, for more specific information.
- If the patient requires imaging, see **Precautions – Section 5.9, Magnetic Resonance Imaging (MRI)**.

**6 Drug Information**

**6.1 Mechanism of Action**

The mechanism (or mechanisms) by which a TAXUS Express 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.

**6.2 Pharmacokinetics**

In the clinical studies TAXUS I, II, and III, no paclitaxel levels were detected in blood or plasma after stent implantation using a bioanalytical method with a lower limit of quantitation (LLOQ) of 10 ng/ml. These findings were further 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 any systemically detectable systemic levels, standard pharmacokinetic parameters were not estimated.

**6.3 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 Express 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 Express 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 Express Stent.

#### **6.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicology**

No long-term studies in animals have been performed to evaluate the carcinogenic potential of paclitaxel. Paclitaxel interacts with microtubules; this is the major mechanism by which it inhibits cell growth. One consequence is the loss of whole chromosomes via interactions with spindle microtubules during cell division. As such, paclitaxel is defined as an aneugen (agent causing an alteration in chromosome number). This indirect action is consistent with positive responses in in vitro and in vivo micronucleus genotoxicity assays, which detect DNA fragments. Positive results have also been reported for chromosomal aberrations in primary human lymphocytes. It is not known whether paclitaxel has a separate direct action on DNA in the generation of DNA strand breaks or fragments. It is negative in assays for gene mutation, including salmonella and CHO/HPRT. Paclitaxel administered via IV prior to and during mating produced impairment of fertility in male and female rats at doses > 1 mg/kg (approximately 55 times the dose provided by the largest TAXUS<sup>®</sup> Express<sup>®</sup> Stent coated with 282 µg paclitaxel adjusted for body surface area)

#### **6.5 Pregnancy**

Pregnancy Category C: There are no adequate and well controlled studies in pregnant women of paclitaxel or TAXUS Express Stents. Studies performed in rats and rabbits receiving IV paclitaxel during organogenesis revealed evidence of maternal toxicity, embryotoxicity, and fetotoxicity at dosages of 1 and 3 mg/kg, respectively (approximately 40 and 220 times the dose provided by the largest TAXUS Express Stent coated with 282 µg paclitaxel adjusted for body surface area). The drug resulted in increased resorptions and increased fetal deaths. No teratogenicity was observed in gravid rats receiving daily IV paclitaxel doses of 1 mg/kg (approximately 40 times the dose provided by the largest TAXUS Express Stent coated with 282 µg paclitaxel adjusted for body surface area). TAXUS Express Stents should be used in pregnant women, only if the potential benefit justifies the potential risk. Because some paclitaxel remains on the stent indefinitely, use of the TAXUS Express Stent in women who are of childbearing potential should be given careful consideration.

#### **6.6 Lactation**

It is not known whether paclitaxel is distributed in human milk. However, in lactating rats given radio labeled paclitaxel, levels of radioactivity in plasma and milk were similar. Mothers should be advised of the potential for serious adverse reactions to paclitaxel in nursing infants. Prior to implantation of a TAXUS Express Stent, a decision should be made whether to discontinue nursing or to implant the stent, taking into account the importance of the stent to the mother.

### **7 Overview of Clinical Studies**

#### **7.1 TAXUS Clinical Trials**

The TAXUS clinical development program consists of a series of randomized, controlled trials designed to assess the risk/benefit profile of the polymer-controlled, paclitaxel-eluting TAXUS<sup>®</sup> stent. The specific goal of the TAXUS Clinical Trial program is to demonstrate that the TAXUS stent safely and significantly reduces the need for revascularization compared to bare metal stents within defined target lesions. The TAXUS Clinical Trial program was specifically designed to start with relatively focal lesions, and progress to increasingly more complex lesions, patient populations and procedures. It also includes trials to evaluate two dose formulations of paclitaxel: the slow release (SR) formulation

that was ultimately commercialized, and a moderate release (MR) formulation that was studied and has not been commercialized. This overview will focus on data generated with the approved and commercially available TAXUS Stent SR dose formulation.

TAXUS I<sup>2</sup> is a randomized, double-blind, controlled feasibility Phase I study comparing the 1 µg/mm<sup>2</sup> SR formulation of the paclitaxel-eluting TAXUS<sup>®</sup> NIRx<sup>™</sup> Stent with the NIR<sup>™</sup> Conformer uncoated control stent in de novo lesions. IVUS follow-up after the index procedure and at 6-month follow-up was included. Patients received aspirin indefinitely and clopidogrel or ticlopidine for 6 months. Sixty-one patients were randomized by 3 centers in Germany. Baseline demographic and lesion characteristics were similar between the 2 groups. The primary endpoint was 30-Day Major Adverse Cardiac Events (MACE). The 5-year planned follow-up is complete.

TAXUS II<sup>3</sup> is a randomized, double-blind, controlled Phase II optimization study of the safety and performance of the TAXUS NIRx Stent comparing the SR and MR formulations in two sequential cohorts of patients with low risk, de novo coronary artery lesions. The SR formulation was studied in Cohort I and the MR formulation in Cohort II. A total of 536 patients in 15 countries were enrolled. Patients in each cohort were randomized (1:1) to the TAXUS NIRx Stent or the NIR Conformer uncoated control stent. The primary endpoint for the study was mean percent in-stent net volume obstruction at 6 months as measured by intravascular ultrasound (IVUS). Secondary endpoints included 6-month clinical and angiographic parameters. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 6 months. The 5-year planned follow-up is complete. For TAXUS II, results are only presented for the SR treatment group (Cohort I) and corresponding control (see Section 9).

TAXUS IV<sup>4</sup> is a randomized, double-blind, controlled pivotal Phase III U.S. study of the safety and performance of the SR formulation TAXUS<sup>®</sup> Express<sup>®</sup> Paclitaxel-Eluting Coronary Stent System (hereafter referred to as the TAXUS stent) 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<sup>®</sup> Stent or the uncoated Express<sup>®</sup> control stent. 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 6 months. The 5-year planned follow-up is complete.

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- <sup>2</sup> Bullesfeld L, Gerckens U, Muller R, Grube E. Long-term evaluation of paclitaxel-coated stents for treatment of native coronary lesions. First results of both the clinical and angiographic 18 month follow-up of TAXUS I. *Z Kardiol.* 2003;92(10):825-832.  
Grube E, Silber S, Hauptmann KE, et al. Two-year-plus follow-up of a paclitaxel-eluting stent in de novo coronary narrowings (TAXUS I). *Am J Cardiol.* 2005;96(1):79-82.  
Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation.* 2003;107(1):38-42.
- <sup>3</sup> Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation.* 2003;108(7):788-794.  
Serruys PW, Degertekin M, Tanabe K, et al. Vascular responses at proximal and distal edges of paclitaxel-eluting stents: serial intravascular ultrasound analysis from the TAXUS II trial. *Circulation.* 2004;109(5):627-633.  
Tanabe K, Serruys PW, Degertekin M, et al. Chronic arterial responses to polymer-controlled paclitaxel-eluting-stents: comparison with bare metal stents by serial intravascular ultrasound analyses: data from the randomized TAXUS II trial. *Circulation.* 2004;109:196-200.  
Silber S, Hamburger J, Grube E, et al. Direct stenting with TAXUS stents seems to be as safe and effective as with predilatation: a post hoc analysis of TAXUS II. *Herz.* 2004;29:171-180.  
Tanabe K, Serruys PW, Degertekin M, et al. Incomplete stent apposition after implantation of paclitaxel-eluting stents or bare metal stents: insights from the randomized TAXUS II trial. *Circulation.* 2005;111:900-905.  
Aoki J, Colombo A, Dudek D, et al. Persistent remodeling and neointimal suppression 2 years after polymer-based paclitaxel-eluting stent implantation: insights from serial intravascular ultrasound analysis in the TAXUS II study. *Circulation.* 2005;112:3876-3883.  
Tsuchida K, Serruys PW, Bruining N et al. Two-year serial coronary angiographic and intravascular ultrasound analysis of in-stent angiographic late lumen loss and ultrasonic neointimal volume from the TAXUS II trial. *Am J Cardiol* 2007;99:607-615.
- <sup>4</sup> 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.

TAXUS V de novo<sup>5</sup> is a randomized, double-blind, controlled expansion study of the safety and performance of the SR formulation TAXUS<sup>®</sup> Express<sup>2®</sup> Paclitaxel-Eluting Coronary Stent System 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. The primary endpoint was the incidence rate of ischemia-driven target vessel revascularization (TVR) through 9 months post-index procedure. Secondary endpoints included the cumulative MACE rate at follow-up and detailed quantitative coronary angiography (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 6 months. The 5-year planned follow-up is complete.

TAXUS V – In-stent restenosis (ISR)<sup>5</sup> is a randomized, open-label, controlled study of the safety and performance of the 1 µg /mm<sup>2</sup> (loaded drug/stent surface area) slow rate-release formulation TAXUS Express Stent in patients with restenosis of 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). There were 37 US and Canadian study sites. The ITT population consisted of a total of 421 patients, of which 396 were randomized 1:1 to TAXUS (n=195) or brachytherapy (n=201). An additional 25 patients were enrolled in a single-arm TAXUS registry. 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. 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 through 4 years is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

HORIZONS AMI - The HORIZONS AMI trial<sup>6,7</sup> is a randomized, single-blind trial in patients with ST segment elevation MI designed to compare: (1) the outcomes of anticoagulation with either unfractionated heparin plus routine GP IIb/IIIa inhibition or bivalirudin and bail-out GP IIb/IIIa inhibition, and (2) primary angioplasty with stent implantation with either a slow rate-release paclitaxel-eluting stent (TAXUS Express) or an otherwise identical uncoated bare metal stent (Express). A total of 3602 patients were consented and randomized (primary randomization) in a 1:1 fashion in the emergency room to anticoagulation with unfractionated heparin plus routine GP IIb/IIIa inhibition or bivalirudin and bail-out GP IIb/IIIa inhibition. Emergent coronary angiography with left ventriculography was performed after primary randomization, followed by triage to either percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery or medical management at physician discretion. After coronary angiography, a total of 3006 patients were triaged to PCI and randomized (secondary randomization) in a 3:1 fashion to either a TAXUS Express stent or an uncoated bare metal Express stent. Patients were enrolled at 123 study centers in U.S., Argentina, Europe, and Israel. The primary effectiveness endpoint of the stent randomization was ischemic target lesion revascularization at 12

<sup>5</sup> 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.

<sup>5</sup> Stone GW, Ellis SG, O'Shaughnessy CD, et al. Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare metal stents: the TAXUS V ISR randomized trial. *JAMA*. 2006;295(11):1253-1263.

<sup>6</sup> Stone GW, Lansky AJ, Pocock SJ, et al. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. *N Engl J Med*. 2009 May 7;360(19):1946-59

<sup>7</sup> Mehran R, Brodie B, Cox DA, et al. The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial: study design and rationale. *Am Heart J*. 2008 Jul;156(1):44-56.

months and the primary safety endpoint was the composite rate of death, reinfarction, stent thrombosis or stroke (MACE) at 12 months. Secondary endpoints included the rate of analysis segment angiographic binary restenosis at 13 months in the 1,203 patient angiographic cohort, as well as ischemic target lesion revascularization, MACE and its components at clinical follow-up through 3 years. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 6 months (1 year or longer recommended). Follow-up through 3 years is complete.

**Table 7.1: TAXUS Slow Release Formulation Trials**

	TAXUS I (Feasibility)	TAXUS II SR (Supportive)	TAXUS IV (US Pivotal)	TAXUS V de novo (Expansion)	TAXUS V – ISR (Indication Expansion)	HORIZONS AMI (Indication Expansion)
Study Type	Prospective, multicenter, randomized, double-blind					
Number of Intent to Treat Patients	Total: 61 TAXUS: 31 Control: 30	Total: 267 TAXUS :131 Control: 136	Total: 1314 TAXUS: 662 Control: 652	Total: 1156 TAXUS: 577 Control: 579	Total: 421* TAXUS : 220 Brachytherapy: 201	Total: 3006 TAXUS: 2257 Control: 749
Dose Release Formulation	Slow Release (SR) (1 µg/mm2)					
Lesion Criteria: Vessel Diameter (by visual estimate)	≥ 3.0 mm to ≤ 3.5 mm in diameter	≥ 3.0 mm to ≤ 3.5 mm in diameter	≥ 2.5 mm to ≤ 3.75 mm in diameter	≥ 2.25 mm to ≤ 4.0 mm in diameter	≥ 2.5 mm to ≤ 3.75 mm in diameter	≥ 2.25 mm to ≤ 4.0 mm in diameter
Lesion Criteria: Lesion Length (by visual estimate)	≤ 12 mm	≤ 12 mm	≥ 10 mm and ≤ 28 mm	≥ 10 mm and ≤ 46 mm	≤ 46 mm in length	< 100 mm
Product Used	NIRx™ Stent hand-crimped on the Advance Monorail Stent Delivery Balloon Catheter	NIRx™ Stent pre-mounted on the Advance Monorail Stent Delivery Balloon Catheter	Express™ Stent on the Maverick™ Monorail Stent Delivery Balloon Catheter	Express™ Stent on the Maverick <sup>2</sup> ™ Monorail Stent Delivery Balloon Catheter	Express Stent on the Maverick <sup>2</sup> ™ 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 6 and 24 months: clinical, angiographic 1,3,4,5 years: clinical	30 days: clinical 6 months: clinical, angiographic, & IVUS substudy 2 years: clinical and angiographic/IVUS substudy 1,3,4,5 years: clinical	30 days: clinical 4 months: clinical 9 month: clinical, angiographic/IVUS substudy 1-5 years: clinical	30 days: clinical 4 months: clinical 9 months: clinical angiographic/IVUS substudy 1-5 years: clinical	30 days: clinical 4 months: clinical or telephone 9 months: clinical, angiographic, IVUS subgroup	30 days: clinical 6 months: clinical 12 month: clinical 13 month: angiographic/IVUS 2 and 3 years: clinical

	TAXUS I (Feasibility)	TAXUS II SR (Supportive)	TAXUS IV (US Pivotal)	TAXUS V de novo (Expansion)	TAXUS V – ISR (Indication Expansion)	HORIZONS AMI (Indication Expansion)
Multiple Stents	Bailout only	Bailout only	Bailout only	≥ 2 Planned and bailout	1 – 5 years: telephone 2 Planned and bailout	Allowed

\*ITT population consisted of a total of 421 patients of which 396 were randomized 1:1 to TAXUS (n=195) or brachytherapy (n=201) plus 25 additional TAXUS patients enrolled in a single arm registry.

## 7.2 ARRIVE Clinical Registry

The ARRIVE Program consists of 2 safety surveillance registries which enrolled 7,601 patients at 103 United States (US) based sites. ARRIVE 1 (2,585 enrolled patients) is a peri-approval registry established to satisfy FDA conditions of approval, and ARRIVE 2 (5,016 enrolled patients) is a BSC-initiated post-market registry. ARRIVE 1 and ARRIVE 2 are designed to study common, community-based, physician usage patterns and safety outcomes with the TAXUS Express Stent. Antiplatelet therapy at discharge included clopidogrel for 6 months and aspirin indefinitely. Clinical or telephone follow-up was conducted at 30 days, 6 months, and at 1 and 2 years to collect data on TAXUS Stent-related death, MI, stent thrombosis, re-intervention, and hypersensitivity events. The primary endpoint was the rate of protocol-defined TAXUS stent-related cardiac events (CE) at 1 year after the implant procedure as adjudicated by an independent Clinical Events Committee (CEC), with 100% of cardiac adverse event (AE) data verified against source documents. Clinical monitors assessed an additional 10-20% per site sampling of patients to encourage accuracy and completeness of data collection.

## 8 Adverse Events

### 8.1 Observed Adverse Events

Observed adverse event experience comes from six clinical studies: TAXUS V de novo and ISR, IV, II, and I, and HORIZONS AMI. Principal adverse events for these trials are shown in Tables 8.1 and 8.2. Additional information on all-cause death and expanded stent thrombosis endpoints is located in Section 9.

**Table 8.1 : TAXUS V (ISR and de novo), IV, II, and I Major Adverse Cardiac Events (MACE) From Post-Procedure to Latest Follow-Up**

	TAXUS V ISR to 4 Years*		TAXUS V de novo to 5 Years*		TAXUS IV To 5 Years <sup>§</sup>		TAXUS II SR to 5 Years		TAXUS I to 5 Years	
	TAXUS Express (N=220)	Brachy- therapy (N=201)	TAXUS Express (N=577)	Bare Metal Express (N=579)	TAXUS Express (N=662)	Bare Metal Express (N=652)	TAXUS NIRx (N=131)	Bare Metal NIRx (N=136)	TAXUS NIRx (N=31)	Bare Metal NIRx (N=30)
In-Hospital MACE	1.4% (3/220)	1.5% (3/201)	4.0% (23/577)	3.1% (18/579)	2.4% (16/662)	2.1% (14/652)	1.5% (2/131)	4.4% (6/136)	NA	NA
30-Day MACE, overall	2.3% (5/219)	2.5% (5/199)	5.1% (29/569)	3.6% (21/576)	2.9% (19/661)	2.5% (16/651)	2.3% (3/131)	4.4% (6/136)	0.0% (0/31)	0.0% (0/30)
6-Month MACE, overall	NA	NA	NA	NA	NA	NA	8.5% (11/130)	19.5% (26/133)	0.0% (0/31)	6.7% (2/30)
Cardiac Death	NA	NA	NA	NA	NA	NA	0.0% (0/130)	0.8% (1/133)	0.0% (0/31)	0.0% (0/30)
Q-Wave MI	NA	NA	NA	NA	NA	NA	0.0% (0/130)	1.5% (2/133)	NA	NA
Non-Q-Wave MI	NA	NA	NA	NA	NA	NA	1.5% (2/130)	3.8% (5/133)	NA	NA
TVR, Overall	NA	NA	NA	NA	NA	NA	7.7% (10/130)	14.3% (19/133)	0.0% (0/31)	6.7% (2/30)
TVR, Non-TLR	NA	NA	NA	NA	NA	NA	3.1% (4/130)	2.3% (3/133)	0.0% (0/31)	0.0% (0/30)
TVR, TLR	NA	NA	NA	NA	NA	NA	4.6% (6/130)	12.0% (16/133)	0.0% (0/31)	6.7% (2/30)
TVR, CABG	NA	NA	NA	NA	NA	NA	0.8% (1/130)	0.8% (1/133)	0.0% (0/31)	0.00% (0/30)
9-Month MACE,	11.1	20.1	14.9%	20.9%	8.5%	15.2%	NA	NA	3.2%	10.0%

**Table 8.1 : TAXUS V (ISR and de novo), IV, II, and I Major Adverse Cardiac Events (MACE)  
From Post-Procedure to Latest Follow-Up**

	TAXUS V ISR to 4 Years*		TAXUS V de novo to 5 Years*		TAXUS IV To 5 Years§		TAXUS II SR to 5 Years		TAXUS I to 5 Years	
	TAXUS Express (N=220)	Brachy- therapy (N=201)	TAXUS Express (N=577)	Bare Metal Express (N=579)	TAXUS Express (N=662)	Bare Metal Express (N=652)	TAXUS NIRx (N=131)	Bare Metal NIRx (N=136)	TAXUS NIRx (N=31)	Bare Metal NIRx (N=30)
overall	(24/216)	(39/194)	(84/562)	(119/569)	(56/655)	(98/646)			(1/31)	(3/30)
Cardiac Death	0.0% (0/216)	0.5% (1/194)	0.5% (3/562)	0.9% (5/569)	1.4% (9/655)	1.1% (7/646)	NA	NA	0.0% (0/31)	0.0% (0/30)
MI	3.7% (8/216)	4.6% (9/194)	5.3% (30/562)	4.6% (26/569)	3.5% (23/655)	3.7% (24/646)	NA	NA	0.0% (0/31)	0.0% (0/30)
Q-Wave MI	0.5% (1/216)	0.0% (0/194)	0.5% (3/562)	0.2% (1/569)	0.8% (5/655)	0.3% (2/646)	NA	NA	NA	NA
Non-Q-Wave MI	3.2% (7/216)	4.6% (9/194)	4.8% (27/562)	4.4% (25/569)	2.7% (18/655)	3.4% (22/646)	NA	NA	NA	NA
TVR, Overall	9.7% (21/216)	17.5% (34/194)	12.1% (68/562)	17.0% (97/569)	4.7% (31/655)	12.1% (78/646)	NA	NA	3.2% (1/31)	10.0% (3/30)
TLR, Overall	6.0% (13/216)	13.9% (27/194)	8.5% (48/562)	15.5% (88/569)	3.1% (20/655)	11.5% (74/646)	NA	NA	0.0% (0/31)	10.0% (3/30)
Non-TLR, Overall*	4.6% (10/216)	6.2% (12/194)	5.0% (27/562)	4.2% (24/569)	1.7% (11/655)	1.1% (7/646)	NA	NA	3.2% (1/31)	0.0% (0/30)
1-Year MACE	16.4% (35/214)	24.9% (47/189)	18.8% (105/558)	25.9% (146/564)	10.7% (70/654)	20.3% (131/646)	10.9% (14/129)	22.0% (29/132)	3.2% (1/31)	10.0% (3/30)
2-Year MACE	18.7% (39/209)	29.7% (55/185)	22.1% (120/542)	29.2% (159/545)	14.8% (96/647)	25.3% (161/637)	14.2% (18/127)	26.9% (36/134)	3.2% (1/31)	10.0% (3/30)
3-Year MACE	23.9% (49/205)	36.0% (64/178)	26.4% (140/531)	31.6% (168/532)	18.6% (116/622)	28.7% (178/620)	15.7% (20/127)	29.8% (39/131)	3.2% (1/31)	10.0% (3/30)
4-Year MACE	30.1% (59/196)	43.4% (76/175)	30.1% (156/518)	33.6% (176/524)	22.2% (135/609)	31.7% (192/606)	19.5% (24/123)	30.8% (41/133)	3.2% (1/31)	13.3% (4/30)
5-Year MACE	NA	NA	34.5% (166/481)	38.0% (186/490)	25.2% (151/599)	35.3% (208/589)	21.8% (26/119)	30.8% (41/133)	9.7% (3/31)	13.3% (4/30)
Cardiac Death	NA	NA	5.6% (27/481)	3.9% (19/490)	4.5% (27/599)	4.8% (28/589)	2.5% (3/119)	2.3% (3/133)	0.0% (0/31)	0.0% (0/30)
MI	NA	NA	10.8% (52/481)	6.3% (31/490)	7.5% (45/599)	8.0% (47/589)	5.0% (6/119)	7.5% (10/133)	0.0% (0/31)	0.0% (0/30)
Q-Wave MI	NA	NA	2.1% (10/481)	0.6% (3/490)	1.5% (9/599)	1.2% (7/589)	1.7% (2/119)	3.0% (4/133)	0.0% (0/31)	0.0% (0/30)
Non-Q-Wave MI	NA	NA	8.7% (42/481)	5.9% (29/490)	6.2% (37/599)	7.1% (42/589)	4.2% (5/119)	4.5% (6/133)	0.0% (0/31)	0.0% (0/30)
TVR, Overall	NA	NA	27.9% (134/481)	32.4% (159/490)	17.5% (105/599)	29.2% (172/589)	17.6% (21/119)	24.1% (32/133)	9.7% (3/31)	13.3% (4/30)
TLR, Overall	NA	NA	18.9% (91/481)	25.9% (127/490)	9.3% (56/599)	21.9% (129/589)	10.9% (13/119)	18.8% (25/133)	0.0% (0/31)	10.0% (3/30)
Non-TLR, Overall	NA	NA	14.1% (68/481)	14.3% (70/490)	9.3% (56/599)	10.9% (64/589)	7.6% (9/119)	12.0% (16/133)	9.7% (3/31)	3.3% (1/30)
Stent Thrombosis 4 Years	2.7% (5/184)	NA	2.1% (10/484)	0.8% (4/497)	1.5% (9/586)	1.0% (6/574)	2.5% (3/119)	0.0% (0/129)	0.0% (0/31)	0.0% (0/30)
Stent Thrombosis 5 Years	NA	NA	2.3% (10/432)	0.9% (4/446)	1.6% (9/564)	1.1% (6/548)	2.7% (3/113)	0.8% (1/127)	0.0% (0/31)	0.0% (0/30)

\* After 1 year the TAXUS V ISR and de novo study populations were reduced to pre-specified cohorts, which consist of all patients who received a study stent at baseline (Safety population).

§ 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 5 years, the safety population was comprised of 1294 (n=651 for TAXUS, n=643 for BMS).

Stent Thrombosis defined per protocol (See Section 9.7.1).

NA= Not Applicable; variable and/or time point not calculated.

**Table 8.2 : HORIZONS AMI Major Adverse Cardiac Events (MACE) From Post-Procedure to Latest Follow-Up**

	HORIZONS AMI	
	TAXUS Express (N=2257)	Bare Metal Express (N=749)
<b>30-Day</b>		
Net Adverse Clinical Events <sup>1</sup>	10.3% (232)	9.0% (67)
MACE 1 <sup>2</sup>	4.8% (109)	4.5% (34)
MACE 2 (Safety MACE) <sup>3</sup>	4.5% (102)	4.3% (32)
Death	2.1% (47)	1.9% (14)
- Cardiac	2.0% (44)	1.7% (13)
- Noncardiac	0.1% (3)	0.1% (1)
Reinfarction	1.7% (37)	2.2% (16)
- Q wave	1.2% (28)	1.6% (12)
- Non Q wave	0.4% (10)	0.5% (4)
Death or reinfarction	3.6% (80)	3.5% (26)
Ischemic TVR	2.3% (51)	2.6% (19)
Ischemic TLR	2.1% (46)	2.6% (19)
Stroke	0.5% (11)	0.5% (4)
Major bleeding (non-CABG)	7.1% (159)	5.6% (42)
TL stent thrombosis	2.3% (50)	2.7% (20)
<b>1-Year</b>		
Net Adverse Clinical Events <sup>1</sup>	15.8% (355)	16.3% (121)
MACE 1 <sup>2</sup>	10.6% (237)	12.4% (92)
MACE 2 (Safety MACE) <sup>3</sup>	8.1% (181)	8.0% (59)
<b>2-Year</b>		
Net Adverse Clinical Events <sup>1</sup>	21.5% (480)	26.0% (191)
MACE 1 <sup>2</sup>	16.8% (373)	22.2% (162)
MACE 2 (Safety MACE) <sup>3</sup>	11.0% (245)	11.2% (82)
<b>3-Year</b>		
Net Adverse Clinical Events <sup>1</sup>	24.5% (544)	28.0% (205)
MACE 1 <sup>2</sup>	20.0% (441)	24.0% (175)
MACE 2 (Safety MACE) <sup>3</sup>	13.6% (300)	12.9% (94)
Death	5.6% (123)	6.6% (48)
- Cardiac	3.2% (71)	3.8% (28)
- Noncardiac	2.4% (52)	2.9% (20)
Reinfarction	7.0% (150)	6.6% (47)
- Q wave	3.5% (75)	2.8% (20)
- Non Q wave	4.0% (84)	3.8% (27)
Death or reinfarction	11.8% (260)	11.5% (84)
Ischemic TVR	12.4% (265)	17.6% (125)
Ischemic TLR	9.4% (202)	15.1% (107)
Stroke	1.6% (35)	1.4% (10)
Major bleeding (non-CABG)	8.4% (188)	7.3% (54)
TL stent thrombosis	4.8% (103)	4.3% (31)

<sup>1</sup> Net Adverse Clinical Events includes MACE1 and non-CABG related major bleeding.

<sup>2</sup> MACE1 includes death, reinfarction, stroke, or ischemic target vessel revascularization.

<sup>3</sup> MACE2 includes death, reinfarction, stent thrombosis, or stroke.

## 8.2 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 but are not limited to:

- Abrupt stent closure
- Acute myocardial infarction
- Allergic reaction to anticoagulants or antithrombotic therapy or contrast medium or stent materials
- Angina
- Arrhythmias, including ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Arteriovenous fistula
- Cardiac tamponade
- Cardiogenic shock/ pulmonary edema
- Death
- Dissection
- Emboli, distal (air, tissue, or thrombotic material, or material from device(s) used in the procedure)
- Heart failure
- Hematoma
- Hemorrhage, requiring transfusion
- Hypotension/hypertension
- Infection, local and/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
- Shock
- Stent embolization
- Stent 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.

## 9 Clinical Studies

### 9.1. Results of the TAXUS IV Pivotal Clinical Trial

**Primary Objective:** To demonstrate superiority of the TAXUS<sup>®</sup> Express<sup>®</sup> Stent compared to a matched uncoated control stent for reduction of the target vessel revascularization rate (TVR) 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 of a single native coronary artery (reference vessel diameter [RVD] 2.5 to 3.75 mm) with a target lesion 10 to 28 mm in length and stenosis  $\geq 50\%$  in diameter using visual estimates, and who were candidates for percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) with 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<sup>®</sup> Coronary Stent (bare metal control). Study randomization was sub-stratified for medically treated diabetes, RVD, 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. 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 5 years, the safety population is comprised of 1294 patients (n=651 for TAXUS, n=643 for Control) and follow-up is available for 1230 patients (95.1%).

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).

**Results:** The 5-year planned follow-up is complete. The primary endpoint data (9-months) and 5-year follow-up results are presented below (Table 9.1.1, Table 9.1.2, and Figure 9.1.1), as well as stent thrombosis data through 5-years (Table 9.1.3).

**Table 9.1.1: TAXUS IV Clinical Results**

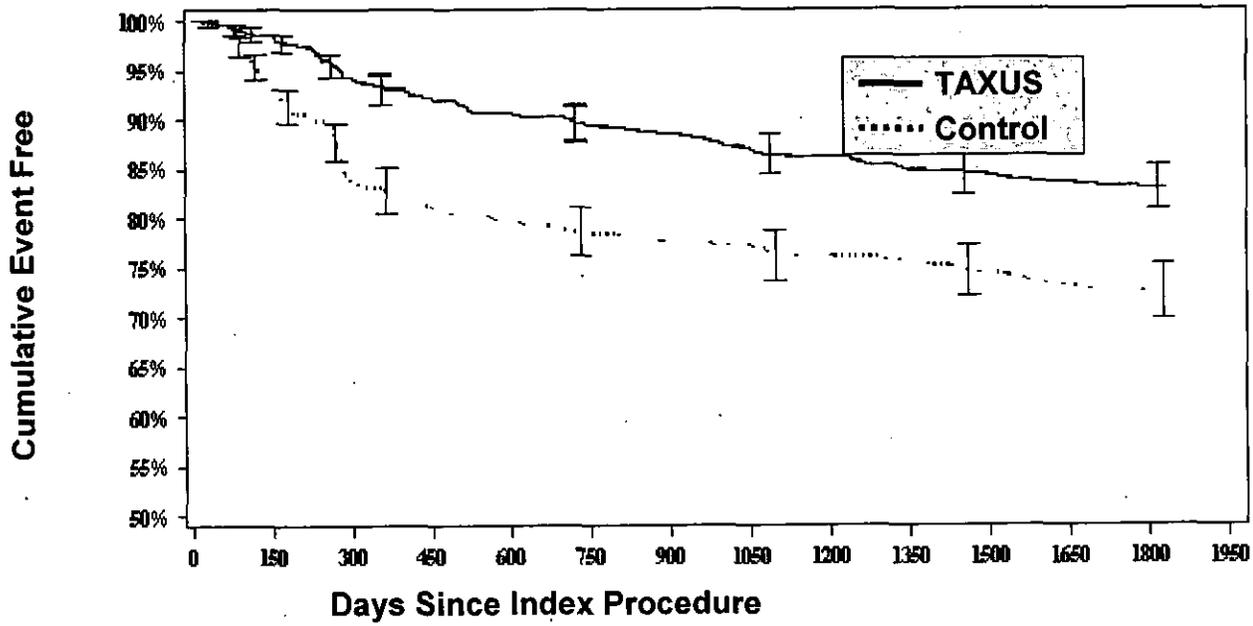
	9 months			5 years (final planned follow-up)		
	TAXUS Express (N=662)	Bare Metal Express (N=652)	P-Value	TAXUS Express (N=651)	Bare Metal Express (N=643)	P-Value
<b>EFFICACY</b>						
TVR, Overall <sup>§</sup>	4.7% (31/662)	12.0% (78/652)	<0.0001	17.5% (105/599)	29.2% (172/589)	< 0.0001
TLR, Overall	3.0% (20/662)	11.3% (74/652)	<0.0001	9.3% (56/599)	21.9% (129/589)	< 0.0001
TLR, PCI	2.4% (16/662)	8.7% (57/652)	<0.0001	8.3% (50/599)	17.5% (103/589)	< 0.0001
TLR, CABG	0.6% (4/662)	3.1% (20/652)	0.0008	1.0% (6/599)	5.6% (33/589)	< 0.0001
Non-TLR, Overall	1.7% (11/662)	1.1% (7/652)	0.4778	9.3% (56/599)	10.9% (64/589)	0.3857
Non-TLR, PCI	1.2% (8/662)	0.8% (5/652)	0.5793	6.7% (40/599)	9.5% (56/589)	0.0736
Non-TLR, CABG	0.5% (3/662)	0.3% (2/652)	1.0000	3.2% (19/599)	2.2% (13/589)	0.3044
<b>SAFETY</b>						
Total Death	2.1% (14/662)	1.5% (10/652)	0.5378	10.2% (63/619)	11.4% (70/614)	0.4888
Cardiac Death or MI	4.7% (31/662)	4.3% (28/652)	0.7905	11.0% (66/599)	11.4% (67/589)	0.8454
Cardiac Death	1.4% (9/662)	1.1% (7/652)	0.8025	4.5% (27/599)	4.8% (28/589)	0.8399
MI	3.5% (23/662)	3.7% (24/652)	0.8826	7.5% (45/599)	8.0% (47/589)	0.7633
Q-wave MI	0.8% (5/662)	0.3% (2/652)	0.4520	1.5% (9/599)	1.2% (7/589)	0.6387
Non-Q-wave MI	2.7% (18/662)	3.4% (22/652)	0.5237	6.2% (37/599)	7.1% (42/589)	0.5094
Per Protocol Stent Thrombosis	0.6% (4/662)	0.8% (5/652)	0.7513	1.6% (9/564)	1.1% (6/548)	0.4692

<sup>§</sup> 9-month primary endpoint.

Patients who did not receive a study stent were not followed beyond 2 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 9.1.1: TAXUS IV Freedom from TVR to 5 Years, Event-Free Survival  $\pm$  1.5 SE, Safety Population, All Patients (N=1294)**

	Event Rate	Event Free	P-Value*
Control	27.4%	72.6%	<0.0001
TAXUS	16.9%	83.1%	

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

**Table 9.1.2: TAXUS IV 9-Month Angiographic and IVUS Results**

	TAXUS Express (N=662)	Bare Metal Express (N=652)	P-Value
MLD (mm), In-stent			
Post-Procedure	2.65 ± 0.42 (373)	2.67 ± 0.41 (351)	0.6577
9-Month	2.26 ± 0.58 (291)	1.75 ± 0.65 (266)	< 0.0001
MLD (mm), Analysis Segment			
Post-Procedure	2.26 ± 0.48 (374)	2.29 ± 0.50 (356)	0.4562
9-Month	2.03 ± 0.55 (291)	1.68 ± 0.61 (267)	< 0.0001
% DS, In-stent			
Post-Procedure	4.21 ± 10.84 (373)	5.16 ± 11.41 (351)	0.2497
9-Month	17.43 ± 17.71 (291)	37.24 ± 19.76 (266)	< 0.0001
% DS, Analysis Segment			
Post-Procedure	19.16 ± 9.67 (374)	19.33 ± 10.45 (356)	0.8219
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 <sup>3</sup> ]	17.35 ± 18.20 (82)	41.48 ± 23.02 (80)	< 0.0001
% Net Volume Obstruction	12.05 ± 12.43 (82)	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.

The QCA subgroup included 375 TAXUS and 357 Control patients; the paired lesion analysis included 292 TAXUS and 267 Control patients.

The IVUS subgroup included 133 TAXUS and 135 Control patients.

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 9.1.3. TAXUS IV Protocol Defined Stent Thrombosis\* through 5 Years  
Safety Population (N=1294)**

	<b>TAXUS Express (N=662)</b>	<b>Bare Metal Express (N=652)</b>	<b>P-Value</b>
Cumulative Stent Thrombosis through 5 years	1.6% (9/564)	1.1% (6/548)	0.4692
Acute Stent Thrombosis (≤ 24 hrs)	0.0% (0/651)	0.3% (2/643)	0.2467
Subacute Stent Thrombosis (> 24 hrs and ≤ 30 days)	0.3% (2/650)	0.5% (3/641)	0.6849
Late Stent Thrombosis (> 30 days and ≤ 12 months)	0.3% (2/648)	0.2% (1/639)	1.0000
Very Late Stent Thrombosis (> 12 months to 5 years)	0.8% (5/632)	0.2% (1/625)	0.2177

To be included in the calculation of the 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).

\*Refer to Section 9.7.1 for ST protocol definition.

Numbers are % (Count/Sample Size).

Patients who did not receive a study stent were not followed beyond 2 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.

## **9.2 Results of the TAXUS II SR Supporting Clinical Trial**

**Primary Objective:** The primary objective of this study was to evaluate the safety and effectiveness of the TAXUS<sup>®</sup> NIRx<sup>™</sup> Paclitaxel-Eluting Coronary Stent System (1 µg/mm<sup>2</sup> SR formulation) compared to a matched, uncoated control stent.

**Design:** This was a prospective, double-blind trial conducted at 28 sites in 12 countries. Eligible patients had documented angina pectoris and a single de novo lesion in a native coronary artery measuring < 12 mm in length with a visual RVD > 3.0 mm and < 3.5 mm. A total of 267 patients were enrolled and evaluable in this study: 131 in the TAXUS Stent group and 136 in the Control group. Patients were randomized to receive either a TAXUS<sup>®</sup> NIRx<sup>™</sup> (SR) Stent or an uncoated NIR<sup>™</sup> Stent (bare metal control). After the procedure, patients were treated with aspirin indefinitely and clopidogrel or ticlopidine for 6 months.

Follow-up included 1, 6, and 12-month clinical assessments. In addition, patients agreed to annual clinical follow-up for MACE clinical parameters through 5 years post-procedure.

All patients were required to have angiographic and IVUS follow-up at 6 months. As an amendment to the original protocol, angiographic and IVUS follow-up at 2 years for a subset of patients were added. Angiographic assessments were performed for the area of the vessel within the stent margins (in-stent) plus the area immediately 5 mm proximal and 5 mm distal from the stent margins (analysis segment).

**Results:** The 5-year planned follow-up is complete. The primary endpoint (6 months) data and 5-year follow-up results are presented below (Table 9.2.1 and Figure 9.2.1):

**Table 9.2.1: TAXUS II Clinical Results**

	6 months			5 years (final planned follow-up)		
	TAXUS NIRx (N=131)	Bare Metal NIRx (N=136)	P-Value	TAXUS NIRx (N=131)	Bare Metal NIRx (N=136)	P-Value
<b>EFFICACY</b>						
TVR, Overall	7.7% (10/130)	14.3% (19/133)	0.1148*	17.6% (21/119)	24.1% (32/133)	0.2124
TVR, TLR (PCI)	4.6% (6/130)	12.0% (16/133)	0.0432*	8.4% (10/119)	16.5% (22/133)	0.0527
TVR, CABG	0.8% (1/130)	0.8% (1/133)	1.0000*	4.2% (5/119)	4.5% (6/133)	0.9044
TVR, Non-TLR (PCI)	3.1% (4/130)	2.3% (3/133)	0.7203*	5.9% (7/119)	10.5% (14/133)	0.1830
Non-TLR, CABG	NA	NA	NA	1.7% (2/119)	1.5% (2/133)	1.0000*
<b>SAFETY</b>						
Total Death	0.0% (0/131)	0.7% (1/136)	1.0000*	7.4% (9/122)	4.5% (6/133)	0.3313
Cardiac Death or MI	1.5% (2/130)	6.0% (8/133)	0.1029*	7.6% (9/119)	9.8% (13/133)	0.5347
Cardiac Death	0.0% (0/130)	0.8% (1/133)	1.0000*	2.5% (3/119)	2.3% (3/133)	1.0000*
MI	1.5% (2/130)	5.3% (7/133)	0.1724*	5.0% (6/119)	7.5% (10/133)	0.4208
Q-wave MI	0.0% (0/130)	1.5% (2/133)	0.4982*	1.7% (2/119)	3.0% (4/133)	0.6867*
Non-Q-wave MI	1.5% (2/130)	3.8% (5/133)	0.4470*	4.2% (5/119)	4.5% (6/133)	0.9044
Per Protocol Stent Thrombosis	0.8% (1/131)	0.0% (0/136)	0.4906*	2.7% (3/113)	0.8% (1/127)	0.3450*
<b>PRIMARY ENDPOINT</b>						
Change in Neointimal Volume (IVUS) (%) <sup>†</sup>	7.85±10.0 2 (111)	23.56±1 8.57 (117)	<0.0001 <sup>§</sup>	NA	NA	NA

\*Fisher's Exact test was used. The Chi-Square test was used for all other P-Values unless noted otherwise.

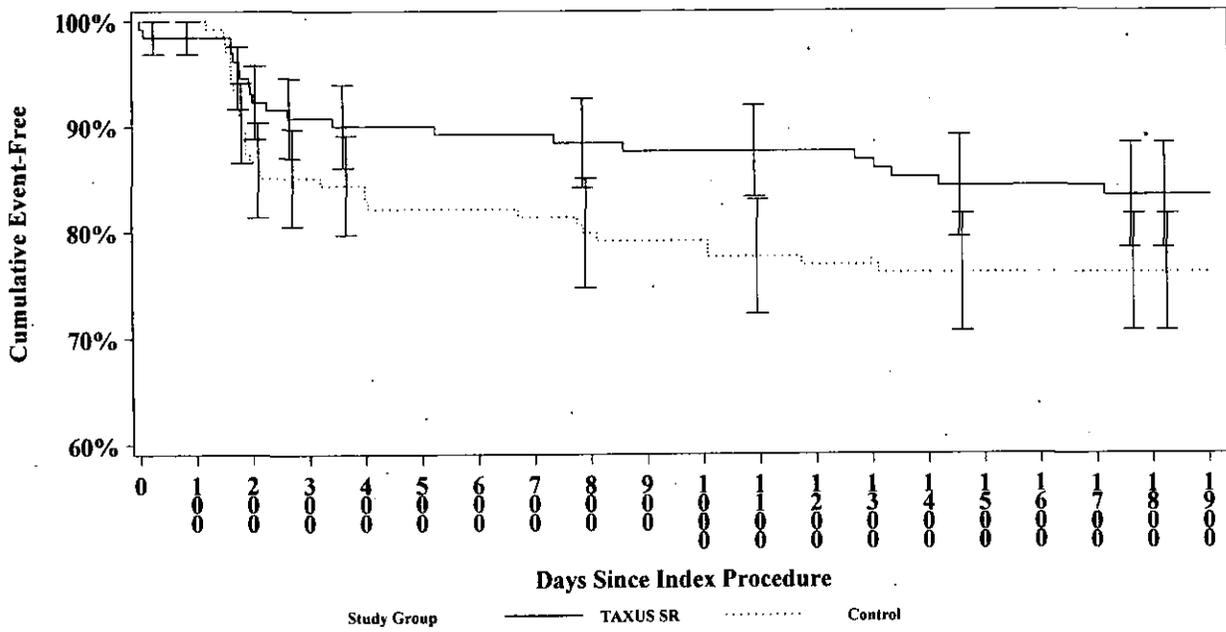
<sup>§</sup> Student's t-test was used.

<sup>†</sup> Primary endpoint data are mean± standard deviation (count).

NA= Not Applicable; variable not calculated.

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 9.2.1: TAXUS II Freedom from TVR to 5 Years, Event-Free Survival  $\pm$  1.5 SE, Intent-to-Treat Population, All Patients (N=267)**

	Event Rate	Event Free	P-Value*
Control	23.9%	76.1%	0.1149
TAXUS	16.6%	83.4%	

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

### **9.3 Results of the TAXUS I Feasibility Clinical Trial**

**Primary Objective:** The primary objective of this study was to evaluate the performance and safety at 30 days (MACE) of the TAXUS™ NIRx™ Paclitaxel-Eluting Coronary Stent System (1 µg /mm<sup>2</sup> SR formulation), as compared to a matched uncoated control stent. Secondary objectives included QCA and IVUS evaluation at 6 months.

**Design:** This was a multi-center, prospective, randomized, double-blind study. Eligible patients were those presenting for stenting of de novo or restenotic lesions of a native coronary artery (RVD 3.0 to 3.5 mm) with a target lesion ≤ 12 mm in length and stenosis between 50% and 99% in diameter using visual estimates, who were candidates for PCI and CABG, and had documented angina pectoris or functional ischemia. A total of 61 patients were enrolled and evaluable in this study: 31 in the TAXUS Stent group and 30 in the Control group. Patients were randomized to receive either a paclitaxel-eluting TAXUS NIRx (SR) Stent or an uncoated NIR® Coronary Stent (bare metal control). After the procedure, patients were treated with aspirin indefinitely and clopidogrel or ticlopidine for 6 months.

Follow-up included 1, 6, 9, 12 months, and 2-year clinical assessments. In addition, patients agreed to annual telephone follow-up for clinical parameters through 5 years post-procedure. Angiography and IVUS were performed at the 6-month follow-up visit for all patients.

**Results:** The 5-year planned follow-up is complete. The primary endpoint (30 days) data and the final 5-year follow-up results are presented below (Table 9.3.1 and Figure 9.3.1).

**Table 9.3.1: TAXUS I Clinical Results**

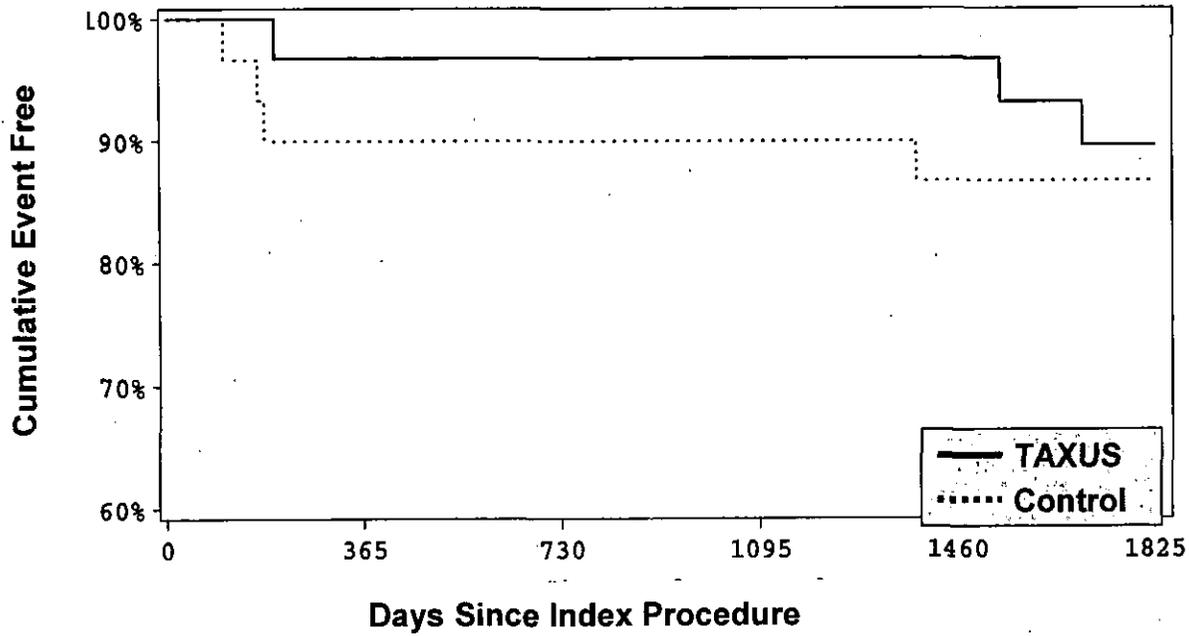
	30 Days			5 years (final planned follow-up)		
	TAXUS NIRx (N=31)	Bare Metal NIRx (N=30)	P-Value	TAXUS NIRx (N=31)	Bare Metal NIRx (N=30)	P-Value
<b>PRIMARY ENDPOINT</b>						
MACE	0.0% (0/31)	0.0% (0/30)	Undef	9.7% (3/31)	13.3% (4/30)	0.7072*
<b>EFFICACY</b>						
TVR, Overall	0.00% (0/31)	0.00% (0/30)	Undef	9.7% (3/31)	13.3% (4/30)	0.7072*
TLR, Overall	0.00% (0/31)	0.00% (0/30)	Undef	0.0% (0/31)	10.0% (3/30)	0.1128*
TLR, PCI	0.00% (0/31)	0.00% (0/30)	Undef	0.0% (0/31)	10.0% (3/30)	0.1128*
TLR, CABG	0.00% (0/31)	0.00% (0/30)	Undef	0.0% (0/31)	3.3% (1/30)	0.4918*
Non-TLR, Overall	0.00% (0/31)	0.00% (0/30)	Undef	9.7% (3/31)	3.3% (1/30)	0.6124*
Non-TLR, PCI	0.00% (0/31)	0.00% (0/30)	Undef	9.68% (3/31)	3.3% (1/30)	0.6124*
Non-TLR, CABG	0.00% (0/31)	0.00% (0/30)	Undef	0.0% (0/31)	3.3% (1/30)	0.4918*
<b>SAFETY</b>						
Total Death	0.00% (0/31)	0.00% (0/30)	Undef	9.7% (3/31)	0.0% (0/30)	0.2377*
Cardiac Death	0.00% (0/31)	0.00% (0/30)	Undef	0.0% (0/31)	0.0% (0/30)	Undef
MI	0.00% (0/31)	0.00% (0/30)	Undef	0.0% (0/31)	0.0% (0/30)	Undef
Per Protocol Stent Thrombosis	0.00% (0/31)	0.00% (0/30)	Undef	0.00% (0/31)	0.00% (0/30)	Undef

\*Fisher's Exact test was used.

Undef = Undefined

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 9.3.1: TAXUS I Freedom from TVR to 5 Years, Event-Free Survival  $\pm$  1.5 SE, Safety Population (N=61)**

	Event Rate	Event Free	P-Value*
Control	13.3%	86.7%	0.6531
TAXUS	10.4%	89.6%	

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

#### 9.4 TAXUS V – De Novo Expansion Clinical Trial

**Objective:** The primary objective of this study was to demonstrate a superior 9-month ischemia-driven target vessel revascularization (TVR) rate for the TAXUS<sup>®</sup> Express<sup>®</sup> Stent compared to the uncoated Express<sup>®</sup> 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  $\geq 2.25$  and  $\leq 4.00$  mm) with a target lesion 10 to 46 mm in length, stenosis  $\geq 50\%$  (visual estimate), candidates for PCI or CABG, and had documented angina pectoris or functional ischemia.

A total of 1156 intent-to-treat (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 ( $< 18$  mm vs.  $\geq 18$  mm), the presence or absence of medically treated diabetes, and clinical site. Enrollment targeted high-risk sub-populations including patients with small diameter vessels (RVD of  $\leq 2.5$  mm), large diameter vessels, and long lesions. The small diameter group included a minimum of 350 patients with at least 200 of those patients receiving a 2.25 mm stent. The large diameter group included a minimum of 200 patients receiving a 4.0 mm stent. The long lesion group included a minimum of 400 patients with  $\geq 18$  mm lesion length with at least 300 patients with lesion lengths  $> 26$  mm (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 5 years is currently available in 871/1048 (83.1%) of patients eligible for 5-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).

**Results:** Patient subgroup characteristics are presented in Table 9.4.1. The primary endpoint data (9 months) and final follow-up (5 years) results are presented below for the overall population in Table 9.4.2 and Figure 9.4.1. The workhorse (2.5, 3.0, or 3.5 mm stent diameter), high-risk small vessel (2.25 mm stent diameter), planned multiple stent, and large vessel (4.0 mm stent diameter) subgroups are presented in Tables 9.4.3, 9.4.4, 9.4.5 and 9.4.6, respectively.

**Table 9.4.1: TAXUS V de novo Baseline Characteristics**

	TAXUS Express	Bare Metal Express	P-Value*
<b>Intent-to-Treat, All Patients (N=1156)</b>			
Patients with Medically Treated Diabetes	31.7% (183/577)	29.9% (173/579)	0.4988
Lesion Length (mm)	17.32±9.05 (565)	17.15±9.41 (573)	0.7488
Baseline RVD (mm)	2.68±0.58 (570)	2.69±0.56 (574)	0.8522
Multiple Stents Implanted	33.8% (195/577)	31.8% (184/579)	0.4908
<b>Patients with Implanted Stent Diameter of 2.25 mm, Intent-to-Treat (N=203)</b>			
Patients with Medically Treated Diabetes	47.2% (51/108)	31.6% (30/95)	0.0310
Lesion Length (mm)	16.60±9.65 (105)	16.44±9.21 (95)	0.9087
Baseline RVD (mm)	2.07±0.31 (107)	2.10±0.33 (95)	0.4590
Multiple Stents Implanted	34.3% (37/108)	35.8% (34/95)	0.8831
<b>Patients with Implanted Stent Diameter of 4.0 mm (Large Vessel Subgroup) Intent-to-Treat (N=202)</b>			
Patients with Medically Treated Diabetes	29.3% (29/99)	22.3% (23/103)	0.2655
Lesion Length (mm)	16.45±8.45 (99)	15.97±8.00 (102)	0.6765
Baseline RVD (mm)	3.41±0.45 (99)	3.33±0.44 (102)	0.1915
Multiple Stents Implanted	23.2% (23/99)	25.2% (26/103)	0.7460
<b>Patients with Lesion Length &gt; 26 mm by Visual Estimate and ≥ 2 Planned Stents Intent-to-Treat (N=233)</b>			
Patients with Medically Treated Diabetes	37.3% (44/118)	30.4% (35/115)	0.3327
Lesion Length (mm)	28.52±8.78 (116)	28.79±10.33 (114)	0.8301
Baseline RVD (mm)	2.68±0.50 (118)	2.69±0.53 (114)	0.8335
Multiple Stents Implanted	100.0% (118/118)	100.0% (115/115)	Undef

\* P-Values are two-sided from Fisher's exact test (binary variables) or two-sided from a t-test (continuous variables).  
Undef=Undefined

**Table 9.4.2: TAXUS V de novo Clinical Results**

	9 months (ITT Population)			5 years (final planned follow-up) (Safety Population)		
	TAXUS Express (N=577)	Bare Metal Express (N=579)	P-Value	TAXUS Express (N=575)	Bare Metal Express (N=571)	P-Value
<b>EFFICACY</b>						
TVR, Overall <sup>§</sup>	12.1% (68/562)	17.0% (97/569)	0.0184	27.9% (134/481)	32.4% (159/490)	0.1192
TLR, Overall	8.5% (48/562)	15.5% (88/569)	0.0003	18.9% (91/481)	25.9% (127/490)	0.0090
TLR, PCI	7.8% (44/562)	13.7% (78/569)	0.0014	17.5% (84/481)	23.3% (114/490)	0.0249
TLR, CABG	0.7% (4/562)	1.8% (10/569)	0.1118	2.1% (10/481)	4.3% (21/490)	0.0505
Non-TLR, Overall	5.0% (28/562)	4.2% (24/569)	0.5395	14.1% (68/481)	14.3% (70/490)	0.9472
Non-TLR, PCI	4.6% (26/562)	3.2% (18/569)	0.2033	11.6% (56/481)	11.4% (56/490)	0.9169
Non-TLR, CABG	0.4% (2/562)	1.1% (6/569)	0.2874*	2.9% (14/481)	3.1% (15/490)	0.8903

**Table 9.4.2: TAXUS V de novo Clinical Results**

	<b>TAXUS Express (N=577)</b>	<b>Bare Metal Express (N=579)</b>	<b>P-Value</b>		<b>TAXUS Express (N=575)</b>	<b>Bare Metal Express (N=571)</b>	<b>P-Value</b>
<b>SAFETY</b>							
Total Death	1.2% (7/562)	1.4% (8/569)	0.8136		11.1% (53/479)	9.3% (45/486)	0.3532
Cardiac Death or MI	5.7% (32/562)	5.4% (31/569)	0.8570		15.4% (74/481)	9.6% (47/490)	0.0063
Cardiac Death	0.5% (3/562)	0.9% (5/569)	0.7256*		5.6% (27/481)	3.9% (19/490)	0.2030
MI	5.3% (30/562)	4.6% (26/569)	0.5513		10.8% (52/481)	6.3% (31/490)	0.0125
Q-wave MI	0.5% (3/562)	0.2% (1/569)	0.3713*		2.1% (10/481)	0.6% (3/490)	0.0468
Non-Q-wave MI	4.8% (27/562)	4.4% (25/569)	0.7417		8.7% (42/481)	5.9% (29/490)	0.0922
Per Protocol Stent Thrombosis	0.7% (4/560)	0.7% (4/565)	1.0000*		2.3% (10/432)	0.9% (4/446)	0.0936

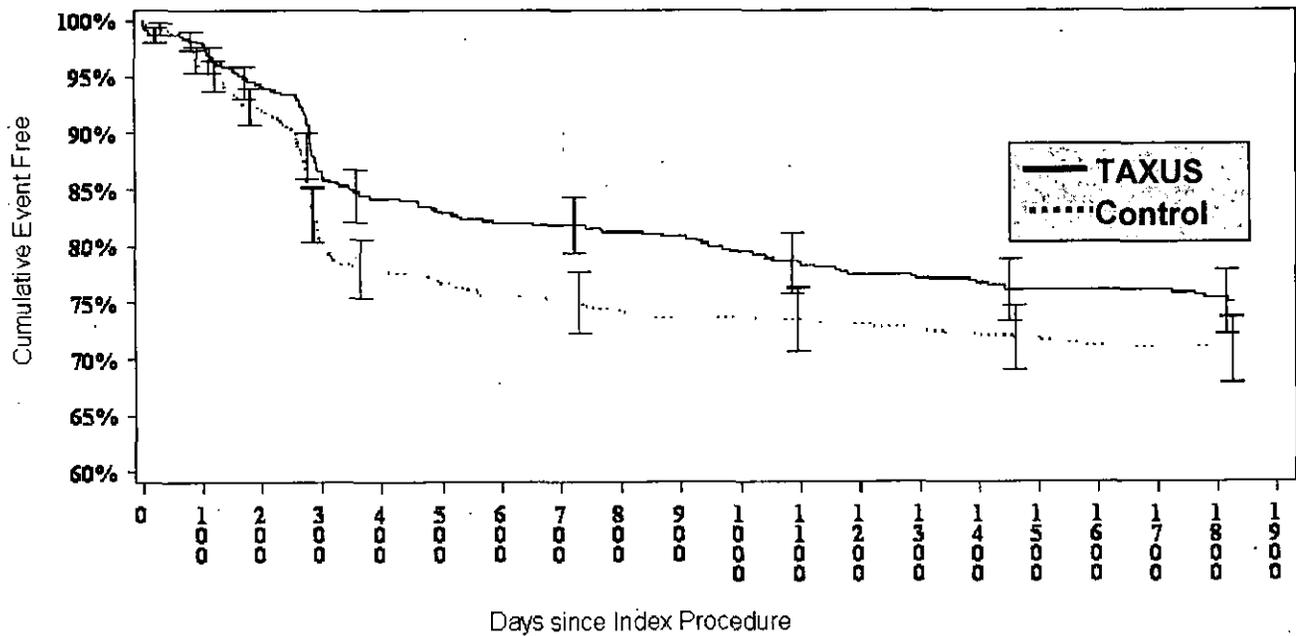
Patients who did not receive a study stent were not followed beyond 1 year.

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

§ Primary Endpoint at 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.



**Figure 9.4.1: TAXUS V Freedom from TVR to 5 Years, Event-Free Survival  $\pm$  1.5 SE, Safety Population, All Patients (N=1146)**

	Event Rate at 5 years	Event-Free Rate at 5 years	P-Value*
Control	29.2%	70.8%	0.0534
TAXUS	24.9%	75.1%	

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

**Table 9.4.3: TAXUS V de novo Workhorse Subgroup (one implanted 2.5 mm, 3.0 mm, or 3.5 mm diameter study stent) Clinical Results**

	9 months (ITT Population)			5 years (final planned follow-up) (Safety Population)		
	TAXUS Express (N=233)	Bare Metal Express (N=250)	P-Value	TAXUS Express (N=233)	Bare Metal Express (N=250)	P-Value
<b>EFFICACY</b>						
TVR, Overall	9.3% (21/226)	11.8% (29/245)	0.3704	26.5% (53/200)	25.6% (55/215)	0.8312
TLR, Overall	6.2% (14/226)	11.0% (27/245)	0.0635	17.0% (34/200)	21.4% (46/215)	0.2567
TLR, PCI	6.2% (14/226)	9.4% (23/245)	0.1982	16.5% (33/200)	18.6% (40/215)	0.5737
TLR, CABG	0.0% (0/226)	1.6% (4/245)	0.1246*	1.0% (2/200)	4.7% (10/215)	0.0266
Non-TLR, Overall	4.0% (9/226)	2.4% (6/245)	0.3437	14.0% (28/200)	10.2% (22/215)	0.2388
Non-TLR, PCI	3.1% (7/226)	2.0% (5/245)	0.4672	10.5% (21/200)	8.4% (18/215)	0.4579
Non-TLR, CABG	0.9% (2/226)	0.4% (1/245)	0.6096*	3.5% (7/200)	2.3% (5/215)	0.4756
<b>SAFETY</b>						
Total Death	0.9% (2/225)	1.2% (3/244)	1.0000*	8.1% (16/197)	7.2% (15/209)	0.7201
Cardiac Death or MI	4.4% (10/226)	4.9% (12/245)	0.8079	13.5% (27/200)	8.4% (18/215)	0.0932
Cardiac Death	0.0% (0/226)	1.2% (3/245)	0.2496*	4.0% (8/200)	3.7% (8/215)	0.8827
MI	4.4% (10/226)	3.7% (9/245)	0.6789	10.5% (21/200)	5.1% (11/215)	0.0399
Q-wave MI	0.0% (0/226)	0.4% (1/245)	1.0000*	2.0% (4/200)	0.9% (2/215)	0.4347*
Non-Q-wave MI	4.4% (10/226)	3.3% (8/245)	0.5120	8.5% (17/200)	4.2% (9/215)	0.0700
Per Protocol Stent Thrombosis	0.4% (1/225)	0.8% (2/243)	1.0000*	2.7% (5/182)	1.0% (2/197)	0.2678*

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 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.

**Table 9.4.4: TAXUS V de novo 2.25 mm Diameter Stent Clinical Results**

	9 months (ITT Population)			5 years (final planned follow-up) (Safety Population)		
	TAXUS Express (N=108)	Bare Metal Express (N=95)	P-Value	TAXUS Express (N=108)	Bare Metal Express (N=95)	P-Value
<b>EFFICACY</b>						
TVR, Overall	16.0% (17/106)	24.7% (23/93)	0.1268	31.6% (30/95)	41.0% (34/83)	0.1930
TLR, Overall	10.4% (11/106)	21.5% (20/93)	0.0308	21.1% (20/95)	33.7% (28/83)	0.0572
TLR, PCI	9.4% (10/106)	19.4% (18/93)	0.0446	18.9% (18/95)	30.1% (25/83)	0.0823
TLR, CABG	0.9% (1/106)	2.2% (2/93)	0.5999*	2.1% (2/95)	6.0% (5/83)	0.2536*
Non-TLR, Overall	8.5% (9/106)	8.6% (8/93)	0.9776	17.9% (17/95)	19.3% (16/83)	0.8128
Non-TLR, PCI	8.5% (9/106)	6.5% (6/93)	0.5867	16.8% (16/95)	15.7% (13/83)	0.8317
Non-TLR, CABG	0.0% (0/106)	2.2% (2/93)	0.2171*	2.1% (2/95)	3.6% (3/83)	0.6652*
<b>SAFETY</b>						
Total Death	1.9% (2/106)	2.1% (2/94)	1.0000*	15.5% (15/97)	7.4% (6/81)	0.0971
Cardiac Death or MI	6.6% (7/106)	3.2% (3/93)	0.3420*	15.8% (15/95)	6.0% (5/83)	0.0396
Cardiac Death	1.9% (2/106)	1.1% (1/93)	1.0000*	6.3% (6/95)	2.4% (2/83)	0.2870*
MI	5.7% (6/106)	2.2% (2/93)	0.2876*	10.5% (10/95)	3.6% (3/83)	0.0771
Q-wave MI	0.9% (1/106)	0.0% (0/93)	1.0000*	2.1% (2/95)	0.0% (0/83)	0.4995*
Non-Q-wave MI	4.7% (5/106)	2.2% (2/93)	0.4519*	8.4% (8/95)	3.6% (3/83)	0.1840
Per protocol Stent Thrombosis	1.0% (1/105)	1.1% (1/92)	1.0000*	2.4% (2/84)	1.3% (1/75)	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 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.

**Table 9.4.5: Patients with Lesion Length > 26 mm by Visual Estimate and ≥ 2 Planned Stents Clinical Results**

	TAXUS Express (N=118)	Bare Metal Express (N=115)	P value
<b>30 Days (ITT Population)</b>			
<b>EFFICACY</b>			
TVR, Overall	0.9% (1/117)	0.0% (0/115)	1.0000*
TLR, Overall	0.9% (1/117)	0.0% (0/115)	1.0000*
TLR, PCI	0.0% (0/117)	0.0% (0/115)	Undef
TLR, CABG	0.9% (1/117)	0.0% (0/115)	1.0000*
Non-TLR, Overall	0.0% (0/117)	0.0% (0/115)	Undef
Non-TLR, PCI	0.0% (0/117)	0.0% (0/115)	Undef
Non-TLR, CABG	0.0% (0/117)	0.0% (0/115)	Undef
<b>SAFETY</b>			
Total Death	0.0% (0/117)	0.0% (0/115)	Undef
Cardiac Death or MI	9.4% (11/117)	2.6% (3/115)	0.0298
Cardiac Death	0.0% (0/117)	0.0% (0/115)	Undef
MI	9.4% (11/117)	2.6% (3/115)	0.0298
Q-wave MI	0.9% (1/117)	0.0% (0/115)	1.0000*
Non-Q-wave MI	8.5% (10/117)	2.6% (3/115)	0.0493
Per Protocol Stent Thrombosis	0.0% (0/117)	0.0% (0/115)	Undef
Stent Thrombosis (ARC <sup>8</sup> definite/probable)	0.0% (0/117)	0.0% (0/115)	Undef
<b>9 Months (ITT Population)</b>			
<b>EFFICACY</b>			
TVR, Overall	12.8% (15/117)	24.8% (28/113)	0.0200
TLR, Overall	11.1% (13/117)	23.9% (27/113)	0.0106
TLR, PCI	9.4% (11/117)	21.2% (24/113)	0.0125
TLR, CABG	1.7% (2/117)	2.7% (3/113)	0.6794*
Non-TLR, Overall	4.3% (5/117)	3.5% (4/113)	1.0000*
Non-TLR, PCI	4.3% (5/117)	1.8% (2/113)	0.4464*
Non-TLR, CABG	0.0% (0/117)	1.8% (2/113)	0.2403*
<b>SAFETY</b>			
Total Death	0.9% (1/117)	2.6% (3/115)	0.3674*
Cardiac Death or MI	10.3% (12/117)	4.4% (5/113)	0.0910
Cardiac Death	0.9% (1/117)	0.9% (1/113)	1.0000*
MI	9.4% (11/117)	3.5% (4/113)	0.0719
Q-wave MI	0.9% (1/117)	0.0% (0/113)	1.0000*
Non-Q-wave MI	8.5% (10/117)	3.5% (4/113)	0.1123
Per Protocol Stent Thrombosis	0.0% (0/117)	0.0% (0/112)	Undef
Stent Thrombosis (ARC definite/probable)	0.9% (1/115)	0.9% (1/112)	1.0000*

<sup>8</sup> "Academic Research Consortium (Circulation. 2007;115[17]:2344-2351)".

**Table 9.4.5: Patients with Lesion Length > 26 mm by Visual Estimate and ≥ 2 Planned Stents Clinical Results**

	<b>TAXUS Express (N=118)</b>	<b>Bare Metal Express (N=115)</b>	<b>P value</b>
<b>5-Years (final planned follow-up) (Safety Population)</b>			
<b>EFFICACY</b>			
TVR, Overall	27.1% (26/96)	42.0% (42/100)	0.0283
TLR, Overall	18.8% (18/96)	36.0% (36/100)	0.0069
TLR, PCI	15.6% (15/96)	33.0% (33/100)	0.0047
TLR, CABG	4.2% (4/96)	4.0% (4/100)	1.0000*
Non-TLR, Overall	14.6% (14/96)	13.0% (13/100)	0.7478
Non-TLR, PCI	12.5% (12/96)	9.0% (9/100)	0.4284
Non-TLR, CABG	3.1% (3/96)	4.0% (4/100)	1.0000*
<b>SAFETY</b>			
Total Death	15.0% (15/100)	9.7% (10/103)	0.2514
Cardiac Death or MI	22.9% (22/96)	8.0% (8/100)	0.0037
Cardiac Death	8.3% (8/96)	2.0% (2/100)	0.0546*
MI	15.6% (15/96)	6.0% (6/100)	0.0294
Q-wave MI	2.1% (2/96)	0.0% (0/100)	0.2386*
Non-Q-wave MI	13.5% (13/96)	6.0% (6/100)	0.0744
Per Protocol Stent Thrombosis	0.0% (0/85)	0.0% (0/93)	Undef
Stent Thrombosis (ARC definite/probable)	1.2% (1/86)	1.1% (1/94)	1.0000*

All patients with ≥2 planned stents implanted (all implanted stents were planned) are included in this analysis.

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

\* 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

Undef = Undefined

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 9.4.6: TAXUS V de novo Large Vessel Subgroup (4.0 mm diameter stent)  
Clinical Results**

	9 months (ITT Population)			5 years (latest available follow-up) (Safety Population)		
	TAXUS Express (N=99)	Bare Metal Express (N=103)	P-Value	TAXUS Express (N=99)	Bare Metal Express (N=103)	P-Value
<b>EFFICACY</b>						
TVR, Overall	4.3% (4/94)	7.8% (8/102)	0.2952	15.1% (11/73)	21.7% (18/83)	0.2890
TLR, Overall	0.0% (0/94)	4.9% (5/102)	0.0604*	8.2% (6/73)	9.6% (8/83)	0.7569
TLR, PCI	0.0% (0/94)	4.9% (5/102)	0.0604*	6.8% (5/73)	8.4% (7/83)	0.7110
TLR, CABG	0.0% (0/94)	0.0% (0/102)	Undef	1.4% (1/73)	1.2% (1/83)	1.0000*
Non-TLR, Overall	4.3% (4/94)	3.9% (4/102)	1.0000*	8.2% (6/73)	16.9% (14/83)	0.1069
Non-TLR, PCI	4.3% (4/94)	3.9% (4/102)	1.0000*	6.8% (5/73)	16.9% (14/83)	0.0563
Non-TLR, CABG	0.0% (0/94)	0.0% (0/102)	Undef	1.4% (1/73)	0.0% (0/83)	0.4679*
<b>SAFETY</b>						
Total Death	1.1% (1/95)	2.0% (2/102)	1.0000*	11.0% (8/73)	16.1% (14/87)	0.3477
Cardiac Death or MI	3.2% (3/94)	6.9% (7/102)	0.3352*	11.0% (8/73)	14.5% (12/83)	0.5142
Cardiac Death	0.0% (0/94)	1.0% (1/102)	1.000*	5.5% (4/73)	7.2% (6/83)	0.7511*
MI	3.2% (3/94)	5.9% (6/102)	0.5009*	6.8% (5/73)	8.4% (7/83)	0.7110
Q-wave MI	0.0% (0/94)	0.0 (0/102)	Undef	0.0% (0/73)	1.2% (1/83)	1.0000*
Non-Q-wave MI	3.2% (3/94)	5.9% (6/102)	0.5009*	6.8% (5/73)	8.4% (7/83)	0.7110
Per Protocol Stent Thrombosis	0.0% (0/94)	0.0% (0/101)	Undef	0.0% (0/65)	0.0% (0/73)	Undef

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 from the Chi-square test.

P-Values are not adjusted for multiple comparisons

Undef = Undefined

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.

## 9.5 TAXUS V – In-stent Restenosis Indication Expansion Clinical Trial

**Objective:** To demonstrate a non-inferior or superior 9-month target vessel revascularization (TVR) rate for 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.

**Design:** This was a prospective, randomized, controlled, multicenter trial conducted in the U.S. and Canada. Treatment was necessarily open-label. Eligible patients were those presenting for restenosis of a previously implanted bare metal stent in a single, native coronary artery (RVD  $\geq$  2.5 and  $\leq$  3.75 mm) with a target lesion  $\leq$  46 mm in length, stenosis  $\geq$  50% (visual estimate), candidates for PCI or CABG, and documented angina pectoris or functional ischemia.

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, BSC received permission from the FDA 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) 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.

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, which consists of all patients who received a study treatment (TAXUS Stent implanted or delivery of brachytherapy at index procedure (Safety Population)).

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. 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.

**Results:** The primary endpoint data (9 months) and latest available follow-up (4 years) results are presented below (Tables 9.5.1 and 9.5.2 and Figure 9.5.1).

**Table 9.5.1: TAXUS V ISR Clinical Results**

	9 months (ITT Population)			4 years (latest available follow-up) (Safety Population)		
	TAXUS Express (N=220)	Brachy- therapy (N=201)	P-Value	TAXUS Express (N=217)	Brachy- therapy (N=193)	P-Value
<b>EFFICACY</b>						
TVR, Overall <sup>§</sup>	9.7% (21/216)	17.5% (34/194)	0.0206 <sup>a</sup> -2.3% <sup>b</sup>	25.0% (49/196)	40.6% (71/175)	0.0014
TLR, Overall	6.0% (13/216)	13.9% (27/194)	0.0071	13.3% (26/196)	30.3% (53/175)	<.0001
TLR, PCI	4.2% (9/216)	12.4% (24/194)	0.0023	10.7% (21/196)	27.4% (48/175)	<.0001
TLR, CABG	2.3% (5/216)	2.6% (5/194)	1.0000*	3.6% (7/196)	5.7% (10/175)	0.3244
Non-TLR, Overall	4.6% (10/216)	6.2% (12/194)	0.4851	14.3% (28/196)	17.7% (31/175)	0.3673
Non-TLR, PCI	2.8% (6/216)	3.6% (7/194)	0.6318	10.2% (20/196)	12.0% (21/175)	0.5818
Non-TLR, CABG	1.9% (4/216)	2.6% (5/194)	0.7409*	4.1% (8/196)	5.7% (10/175)	0.4650
<b>SAFETY</b>						
Total Death	0.0% (0/216)	0.5% (1/193)	0.4719*	7.1% (14/198)	6.8% (12/177)	0.9118
Cardiac Death or MI	3.7% (8/216)	5.2% (10/194)	0.4740	9.7% (19/196)	12.6% (22/175)	0.3775
Cardiac Death	0.0% (0/216)	0.5% (1/194)	0.4732*	4.6% (9/196)	3.4% (6/175)	0.5701
MI	3.7% (8/216)	4.6% (9/194)	0.6352	5.6% (11/196)	9.7% (17/175)	0.1354
Q-wave MI	0.5% (1/216)	0.0% (0/194)	1.0000*	1.0% (2/196)	2.3% (4/175)	0.4269*
Non-Q-wave MI	3.2% (7/216)	4.6% (9/194)	0.4654	4.6% (9/196)	8.0% (14/175)	0.1742
Per Protocol Stent Thrombosis**	1.4% (3/216)	NA	NA	2.7% (5/184)	NA	NA
Stent Thrombosis (ARC definite/probable) <sup>†</sup>	1.4% (3/216)	NA	NA	2.7% (5/184)	NA	NA

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

<sup>§</sup> Primary Endpoint at 9 months.

<sup>a</sup> P-Value for two-sided Z test

<sup>b</sup> 95% upper one-sided confidence bound for TAXUS - Brachy

Decision rule:

- Non-inferiority shown if 95% upper 1-sided confidence bound < 10% and the two-sided P-Value > 0.05.
- Superiority shown if two-sided P-Value ≤ 0.05 and TAXUS < Brachy.
- 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:

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)

<sup>†</sup> Academic Research Consortium (Circulation. 2007;115[17]:2344-2351)

25

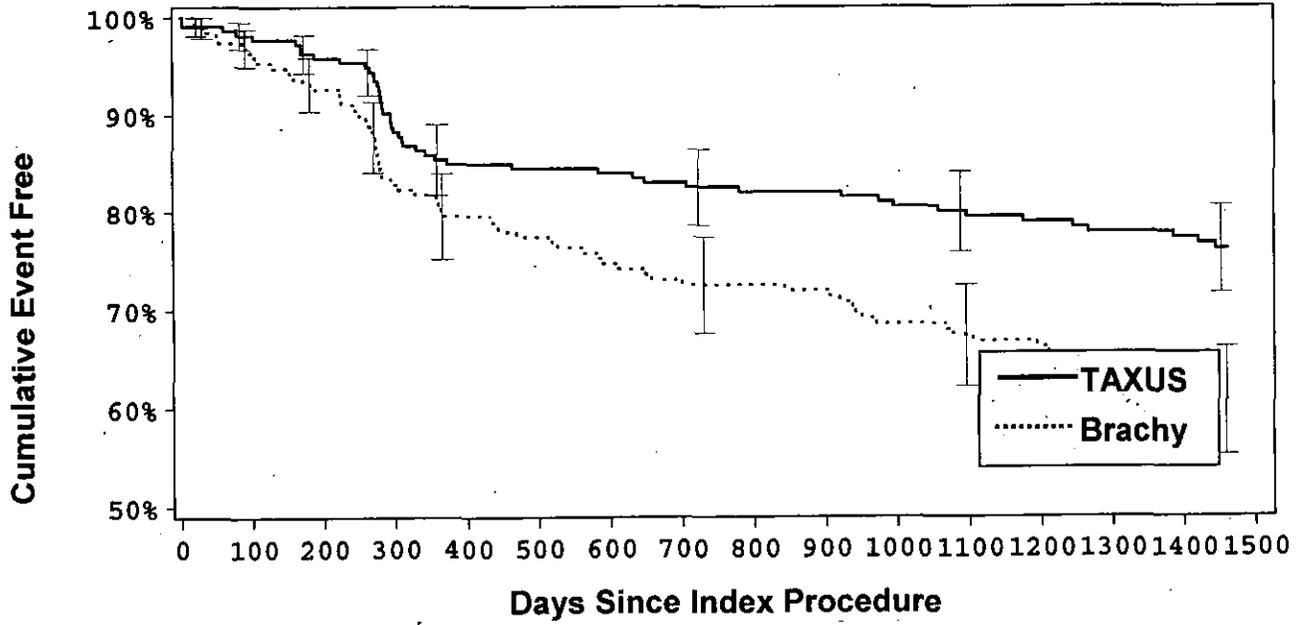


Figure 9.5.1: TAXUS V ISR Freedom from TVR to 4 Years, Event-Free Survival  $\pm$  1.5 SE, Safety Population, All Patients (N=410)

	Event Rate	Event Free	P-Value*
Brachy	39.3%	60.7%	0.0013
TAXUS	23.8%	76.2%	

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

**Table 9.5.2: TAXUS V ISR 9- Month Angiographic and IVUS Results**

	<b>TAXUS Express (N=220)</b>	<b>Brachy (N=201)</b>	<b>P-Value</b>
<b>QCA</b>			
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
<b>IVUS</b>			
Neointimal Volume (mm <sup>3</sup> )			
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			
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.

## 9.6 HORIZONS AMI Clinical Trial

**Objectives:** The trial had two primary objectives and was designed and powered to address both the primary and sub-study objectives.

**Primary objective for the pharmacology randomization:** To evaluate the use of bivalirudin in patients with ST segment elevation acute myocardial infarction (STEMI) undergoing a primary angioplasty strategy compared to unfractionated heparin plus routine use of GP IIb/IIIa inhibitors.

**Primary objective for the stent randomization:** To establish the safety and effectiveness of the paclitaxel-eluting TAXUS Express stent in STEMI patients by showing that compared to an otherwise identical Express BMS, the TAXUS Express results in: (1) reduced rates of ischemia-driven target lesion revascularization at 1 year; (2) a similar rate of the composite of death, reinfarction, stroke or stent thrombosis at 1 year; and (3) a lower rate of analysis segment binary angiographic restenosis at 13 months.

**Design:** The HORIZONS AMI trial was a prospective, dual-arm, single-blind, randomized multi-center trial that enrolled STEMI patients defined by clinical symptoms consistent with acute MI lasting greater than 20 minutes but less than 12 hours, and specific ECG criteria consisting of ST-segment elevation of  $\geq 1$ mm in  $\geq 2$  contiguous leads, presumed new LBBB, or true posterior MI with ST depression of  $\geq 1$ mm in  $\geq 2$  contiguous anterior leads. A total of 3602 patients were randomized (primary randomization) in a 1:1 fashion in the emergency room to anticoagulation with unfractionated heparin plus routine GP IIb/IIIa inhibition or bivalirudin and bail-out GP IIb/IIIa inhibition.

Emergent coronary angiography with left ventriculography was performed after the primary randomization, followed by triage to either percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery or medical management at physician discretion.

After coronary angiography, a total of 3006 patients were triaged to PCI and randomized (secondary randomization) in a 3:1 fashion to either a TAXUS Express stent or an Express stent. In order to be eligible for the second randomization, patients had to have at least one acute infarct-related artery with an expectation that study stents could be delivered to all culprit lesions. Exclusion criteria included true bifurcation lesions definitely requiring stenting of the side branch vessel, lesions requiring greater than 100 mm of stent length, unprotected left main culprit lesions, and stent thrombosis lesions. The secondary randomization was stratified by the following four factors: the result from the primary randomization (to ensure equal distribution of the two arms from the primary randomization in the secondary randomization); the presence or absence of medically treated diabetes; whether any of the lesions were greater than 26 mm in length, such that overlapping stents would be used; and whether the clinical study site was within or outside of the U.S.

Clinical follow-up was performed at 30 days ( $\pm 1$  week), 6 months ( $\pm 2$  weeks), 1 year ( $\pm 2$  weeks), 2 years ( $\pm 1$  month), and 3 years ( $\pm 1$  month). Angiographic follow-up was performed at 13 months ( $-2$  weeks,  $+ 52$  weeks) for a subset of patients (approximately the first 1500 randomized patients). Certain sites also participated in the HORIZONS IVUS substudy, where intravascular ultrasound was performed at baseline (post-procedure) and at 13 month follow-up (approximately the first 400 patients).

**Results:** The baseline demographics and medical history are reported in Table 9.6.1. The primary and secondary endpoints of the trial were met and are reported in Table 9.6.2 and Table 9.6.3. The clinical results of the trial are reported in Table 9.6.4. In Figure 9.6.1, the rates of ischemic TLR are illustrated

for all patients and those patients who were not in the protocol-required angiographic subset. Figures 9.6.2, 9.6.3, 9.6.4, 9.6.5, and 9.6.6 provide results of major clinical outcomes to 3 years. Angiographic and IVUS results are reported in Table 9.6.5.

**Table 9.6.1: HORIZONS AMI Patient Demographics and Medical History (ITT Population)**

	<b>TAXUS Express (N=2257)</b>	<b>Bare Metal Express (N=749)</b>
Age (median (IQR), yrs)	59.9 (52.4, 69.4)	59.3 (51.8, 69.2)
Male	77.0% (1738/2257)	76.0% (569/749)
Diabetes mellitus	16.1% (364/2256)	15.2% (114/749)
- Insulin requiring	4.3% (98/2256)	4.1% (31/749)
Hypertension	51.2% (115/2256)	51.9% (389/749)
Hyperlipidemia	42.2% (953/2256)	41.1% (308/749)
Current smoker	46.3% (1041/2246)	51.9% (388/748)
Prior myocardial infarction	9.1% (206/2256)	10.9% (82/749)
Prior percutaneous coronary intervention	9.5% (214/2255)	7.7% (58/749)
Prior coronary artery bypass graft	2.2% (50/2256)	1.9% (14/749)
Anemia <sup>1</sup>	11.0% (235/2130)	7.6% (54/715)
Killip class 2-4	8.8% (199/2254)	8.0% (60/748)
Renal insufficiency <sup>2</sup>	15.6% (328/2102)	15.4% (107/696)
LVEF <sup>3</sup> <40%	14.3% (279/1948)	14.0% (91/652)

IQR = interquartile range

<sup>1</sup> Defined using the World Health Organization (WHO) criteria as a hematocrit value at initial presentation of <39% for men and <36% for women;

<sup>2</sup> Baseline calculated creatinine clearance using the Cockcroft-Gault equation <60 mL/min;

<sup>3</sup> Left ventricular ejection fraction, visual assessment from the baseline contrast left ventriculogram.

**Table 9.6.2: HORIZONS AMI Primary Endpoints**

<b>Ischemic TLR</b>	<b>TAXUS Express (N=2257)</b>	<b>Bare Metal Express (N=749)</b>	<b>Difference (95% CI)</b>	<b>Hazard Ratio (95% CI)</b>	<b>P-value<sup>1</sup></b>
<b>1 Year</b>	4.5% (98)	7.5% (54)	-3.0% (-5.1, -0.9)	0.59 (0.43, 0.83)	0.0018
<b>Safety MACE<sup>2</sup></b>	<b>TAXUS Express (N=2257)</b>	<b>Bare Metal Express (N=749)</b>	<b>Difference (95% CI)</b>	<b>Hazard Ratio (95% CI)</b>	<b>P-value<sup>3</sup></b>
<b>1 Year</b>	8.1% (181)	8.0% (59)	0.1% (-2.1, 2.4)	1.02 (0.76, 1.36)	0.0075

<sup>1</sup> P-value for the test of superiority

<sup>2</sup> Safety MACE includes death, reinfarction, stroke or stent thrombosis.

<sup>3</sup> P-value for the test of non-inferiority

**Table 9.6.3: HORIZONS AMI Secondary Endpoint**

<b>Binary Restenosis (Per Lesion)</b>	<b>TAXUS Express (N=2257)</b>	<b>Bare Metal Express (N=749)</b>	<b>Difference (95% CI)</b>	<b>Hazard Ratio (95% CI)</b>	<b>P-value<sup>1</sup></b>
<b>13 Month</b>	10.0% (108/1081)	22.9% (76/322)	-12.9% (-18.0, -7.8)	0.44 (0.33, 0.57)	<0.0001

<sup>1</sup> P-value for the test of superiority

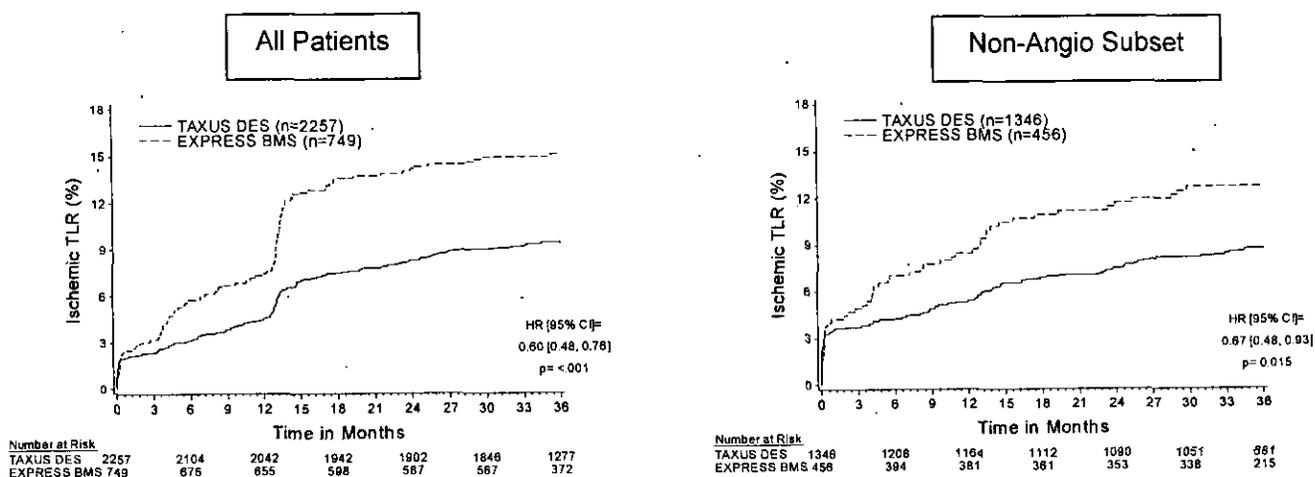
**Table 9.6.4: HORIZONS AMI Kaplan-Meier Estimates of Clinical Endpoints at 30 Day, 1, 2, and 3 Years (ITT Population)**

	<b>TAXUS Express (N=2257)</b>	<b>Bare Metal Express (N=749)</b>
<b>30 Day Clinical Endpoints</b>		
Net Adverse Clinical Events <sup>1</sup>	10.3% (232)	9.0% (67)
MACE 1 <sup>2</sup>	4.8% (109)	4.5% (34)
MACE 2 (Safety MACE) <sup>3</sup>	4.5% (102)	4.3% (32)
Death	2.1% (47)	1.9% (14)
- Cardiac	2.0% (44)	1.7% (13)
- Noncardiac	0.1% (3)	0.1% (1)
Reinfarction	1.7% (37)	2.2% (16)
- Q wave	1.2% (28)	1.6% (12)
- Non Q wave	0.4% (10)	0.5% (4)
Death or reinfarction	3.6% (80)	3.5% (26)
Ischemic TVR	2.3% (51)	2.6% (19)
Ischemic TLR	2.1% (46)	2.6% (19)
Stroke	0.5% (11)	0.5% (4)
Major bleeding (non-CABG)	7.1% (159)	5.6% (42)
Target Lesion stent thrombosis	2.3% (50)	2.7% (20)
<b>1 Year Clinical Endpoints</b>		
Net Adverse Clinical Events <sup>1</sup>	15.8% (355)	16.3% (121)
MACE 1 <sup>2</sup>	10.6% (237)	12.4% (92)
MACE 2 (Safety MACE) <sup>3</sup>	8.1% (181)	8.0% (59)
Death	3.5% (78)	3.5% (26)
- Cardiac	2.4% (54)	2.7% (20)
- Noncardiac	1.1% (24)	0.8% (6)
Reinfarction	3.7% (81)	4.5% (33)
- Q wave	2.0% (45)	1.9% (14)
- Non Q wave	1.8% (39)	2.6% (19)
Death or reinfarction	6.8% (152)	7.0% (52)
Ischemic TVR	5.9% (129)	8.8% (64)
Ischemic TLR	4.6% (101)	7.4% (54)
Stroke	1.0% (23)	0.7% (5)
Major bleeding (non-CABG)	7.7% (172)	6.6% (49)
Target Lesion stent thrombosis	3.1% (69)	3.4% (25)
<b>2 Year Clinical Endpoints</b>		
Net Adverse Clinical Events <sup>1</sup>	21.5% (480)	26.0% (191)
MACE 1 <sup>2</sup>	16.8% (373)	22.2% (162)
MACE 2 (Safety MACE) <sup>3</sup>	11.0% (245)	11.2% (82)
Death	4.3% (96)	5.3% (39)
- Cardiac	2.7% (60)	3.3% (24)
- Noncardiac	1.7% (36)	2.1% (15)
Reinfarction	5.7% (123)	6.0% (43)
- Q wave	3.1% (67)	2.8% (20)
- Non Q wave	3.0% (64)	3.2% (23)
Death or reinfarction	9.4% (210)	9.8% (72)
Ischemic TVR	10.9% (236)	16.7% (119)
Ischemic TLR	8.3% (180)	14.2% (101)
Stroke	1.4% (30)	1.1% (8)
Major bleeding (non-CABG)	8.0% (178)	7.0% (52)
Target Lesion stent thrombosis	4.2% (91)	4.1% (30)

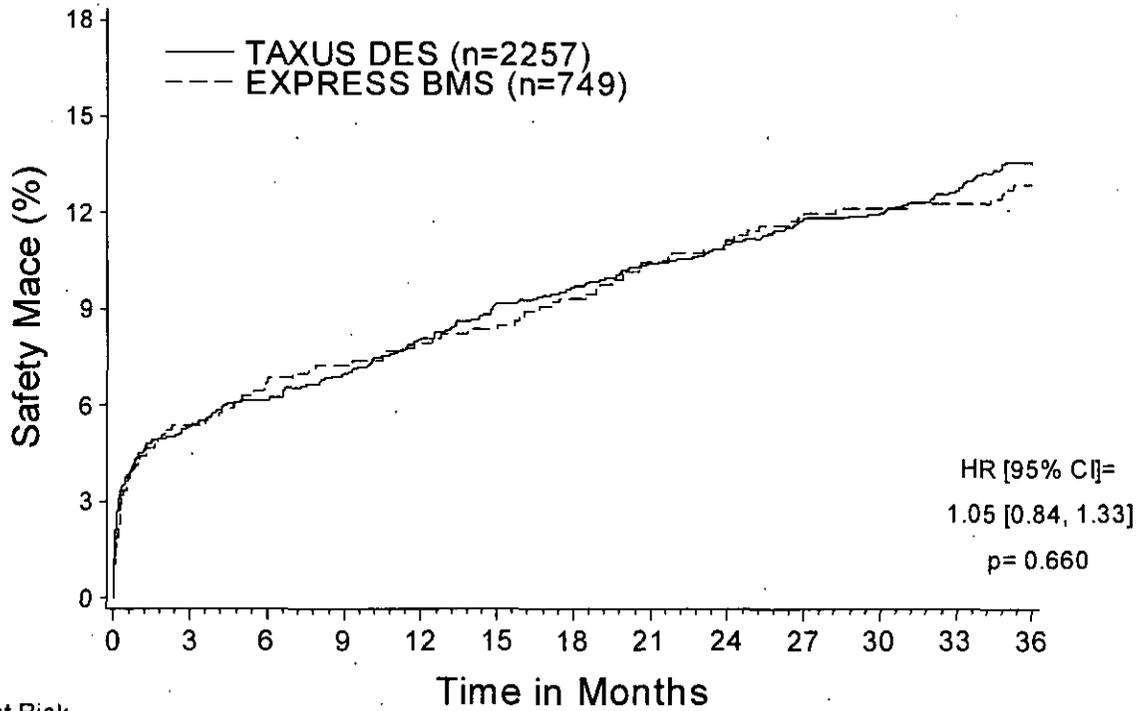
**Table 9.6.4: HORIZONS AMI Kaplan-Meier Estimates of Clinical Endpoints at 30 Day, 1, 2, and 3 Years (ITT Population)**

	TAXUS Express (N=2257)	Bare Metal Express (N=749)
<b>3 Year Clinical Endpoints</b>		
Net Adverse Clinical Events <sup>1</sup>	24.5% (544)	28.0% (205)
MACE 1 <sup>2</sup>	20.0% (441)	24.0% (175)
MACE 2 (Safety MACE) <sup>3</sup>	13.6% (300)	12.9% (94)
Death	5.6% (123)	6.6% (48)
- Cardiac	3.2% (71)	3.8% (28)
- Noncardiac	2.4% (52)	2.9% (20)
Reinfarction	7.0% (150)	6.6% (47)
- Q wave	3.5% (75)	2.8% (20)
- Non Q wave	4.0% (84)	3.8% (27)
Death or reinfarction	11.8% (260)	11.5% (84)
Ischemic TVR	12.4% (265)	17.6% (125)
Ischemic TLR	9.4% (202)	15.1% (107)
Stroke	1.6% (35)	1.4% (10)
Major bleeding (non-CABG)	8.4% (188)	7.3% (54)
Target Lesion stent thrombosis	4.8% (103)	4.3% (31)

<sup>1</sup> Net Adverse Clinical Events includes MACE1 and non-CABG related major bleeding.  
<sup>2</sup> MACE1 includes death, reinfarction, stroke, or ischemic target vessel revascularization.  
<sup>3</sup> MACE2 includes death, reinfarction, stent thrombosis, or stroke.

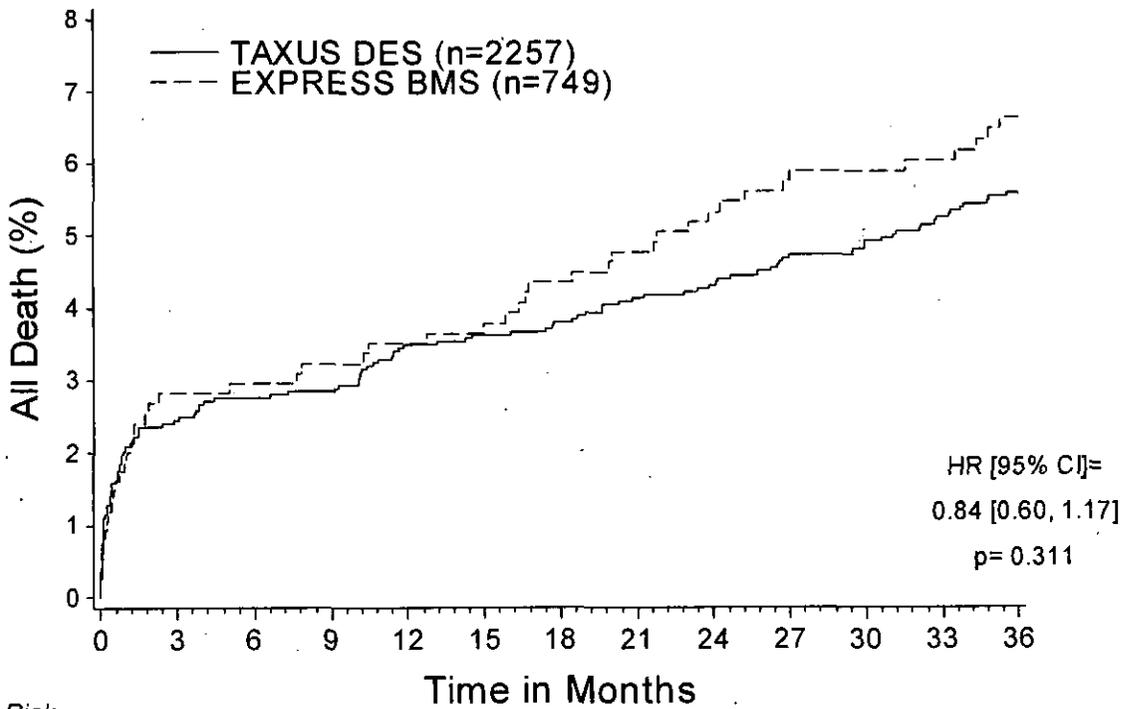


**Figure 9.6.1: HORIZONS AMI Cumulative Rates of Ischemic Target Lesion Revascularization to 3 Years For All Patients and Patients Not in the Protocol-Required Angiographic Subset**



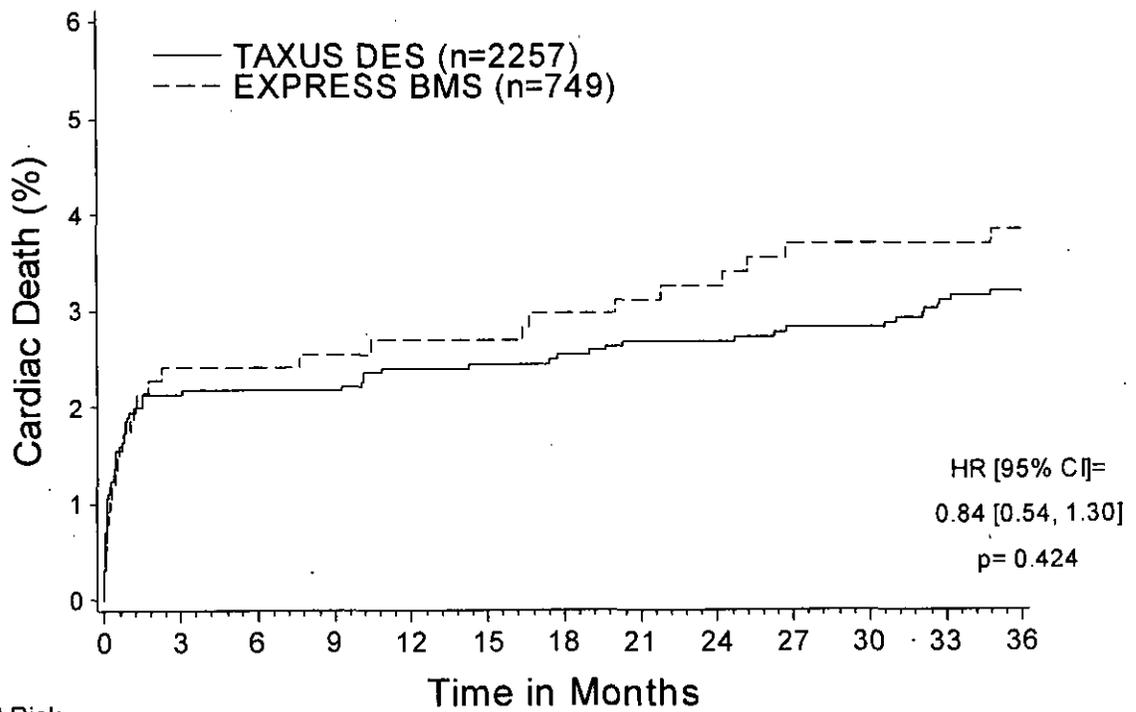
Number at Risk							
TAXUS DES	2257	2094	2037	1971	1928	1875	1289
EXPRESS BMS	749	684	669	648	634	615	412

**Figure 9.6.2: HORIZONS AMI Cumulative Rates of Safety MACE (Death, Reinfarction, Stent Thrombosis or Stroke) to 3 Years**



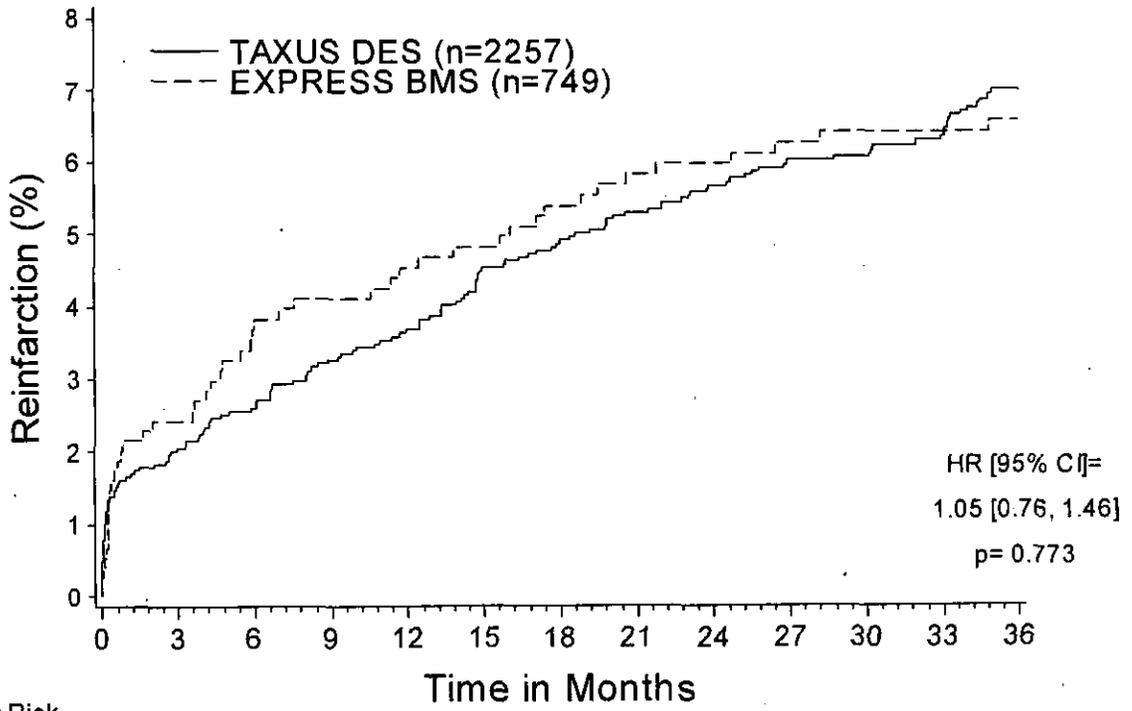
Number at Risk							
TAXUS DES	2257	2170	2138	2097	2072	2026	1409
EXPRESS BMS	749	713	702	683	674	657	443

**Figure 9.6.3: HORIZONS AMI Cumulative Rates of All Death to 3 Years**



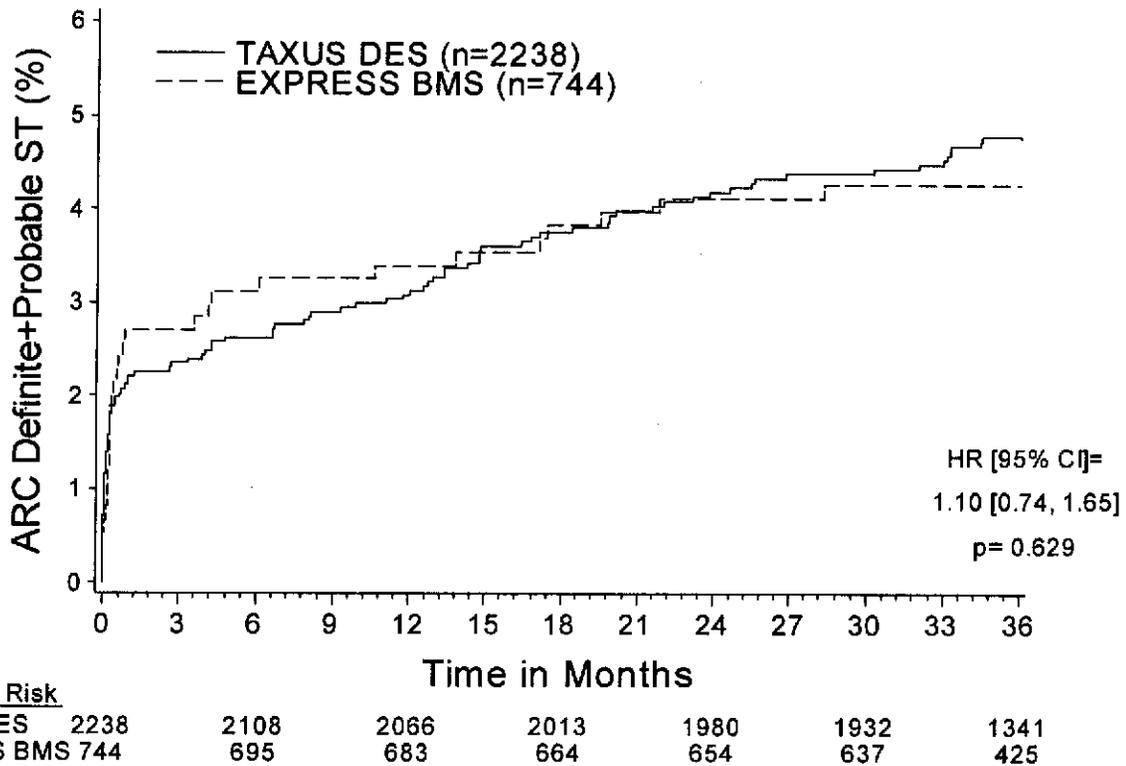
Number at Risk							
TAXUS DES	2257	2170	2138	2097	2072	2026	1409
EXPRESS BMS	749	713	702	683	674	657	443

**Figure 9.6.4: HORIZONS AMI Cumulative Rates of Cardiac Death to 3 Years**



Number at Risk							
TAXUS DES	2257	2118	2066	2002	1961	1910	1316
EXPRESS BMS	749	690	676	654	643	624	419

**Figure 9.6.5: HORIZONS AMI Cumulative Rates of Reinfarction to 3 Years**



**Figure 9.6.6: HORIZONS AMI Cumulative Rates of ARC Definite and Probable Stent Thrombosis to 3 Years**

**Table 9.6.5: HORIZONS AMI 13 Month Angiographic and IVUS Results)**

QCA	TAXUS Express (N=910 Patients / 1081 Lesions)	Bare Metal Express (N=293 Patients / 332 lesions)
Follow-up MLD in-stent (mm)	2.36 ± 0.75 (1062)	1.98 ± 0.82 (328)
Follow-up MLD in-segment (mm)	2.09 ± 0.68 (1062)	1.84 ± 0.76 (328)
Follow-up %DS in-stent	18.7 ± 22.8 (1062)	32.6 ± 24.9 (328)
Follow-up %DS in-segment	28.8 ± 19.6 (1062)	37.4 ± 22.0 (328)
Late Loss in-stent (mm)	0.41 ± 0.64 (1062)	0.82 ± 0.70 (328)
Late Loss in-segment (mm)	0.30 ± 0.56 (1062)	0.59 ± 0.64 (328)
Binary restenosis, in-stent	8.2% (87/1062)	21.0% (69/328)
Binary restenosis, in-segment	9.6% (102/1062)	23.2% (76/328)
IVUS	TAXUS Express (N=196 pts / 219 lesions)	Bare Metal Express (N=62 pts / 67 lesions)
Neointimal Volume (mm <sup>3</sup> )	19.4 ± 21.6 (191)	37.4 ± 30.0 (65)
Percent net volume obstruction (%)	7.9 ± 7.4 (191)	19.8 ± 15.8 (65)
Incomplete Apposition (late)	58.3% (95/163)	33.3% (12/36)
Incomplete Apposition (late-acquired)	42.9% (70/163)	19.4% (7/36)

QCA = quantitative coronary angiography, MLD = minimal lumen diameter, %DS = percent diameter stenosis  
Follow-up QCA results on stented lesions only (per lesion)

**Results in Males and Females:** The HORIZONS AMI trial data were retrospectively evaluated for possible sex-based differences in baseline characteristics and clinical outcomes, as well as for any interaction between treatment and sex/gender. The HORIZONS AMI trial was not designed or powered to study safety or effectiveness in sex-specific subgroups, so these analyses were performed *post hoc* and are considered hypothesis generating.

In the HORIZONS AMI population, of patients randomized to TAXUS Express DES 1738/2257 (77%) subjects were male and 519/2257 (23%) subjects were female. The proportions in the Express BMS group were similar (76% male, 24% female). According to the Nationwide Inpatient Sample (a large database of inpatient admissions from 1988 to 2004), men had almost 2 times the age-adjusted STEMI rate as women (men 62.4%, women 37.6%)<sup>9</sup>. The gender proportions enrolled in this trial are similar to other trials in the STEMI population<sup>10,11</sup>.

In subjects treated with TAXUS Express DES, 12-month TLR rates were 6.8% in females and 3.9% in males and Safety MACE rates were 10.1% in females and 7.5% in males. In subjects treated with Express BMS, 12-month TLR rates were 12.1% in females and 6.0% in males and Safety MACE rates were 12.3% in females and 6.6% in males (Table 9.6.6). Primary and secondary endpoint outcomes data stratified by gender are shown in tables 9.6.6 and 9.6.7. HORIZONS AMI clinical results at 30 Days, 1 Year, 2 Year and 3 Year in male and female patients are reported in Table 9.6.8. Within the female group, cardiac death was numerically higher through 30 days in those treated with TAXUS Express versus bare metal Express, but the numerical difference between groups narrowed over time. Other trials of interventional treatment for AMI have shown female sex to be associated with higher mortality rates compared to men,<sup>12,13</sup> but differences appear to be largely explained by baseline risk factors such as BSA and angiographic disease severity. Rates of reinfarction and stent thrombosis in females were numerically lower in TAXUS Express DES versus bare metal Express at 30 days and through 3 years. Formal interaction testing revealed no difference (at a significance level of p=0.15) between males and females in treatment effect at any time point, suggesting the conclusions of the overall study can be generalized for males and females.

**Table 9.6.6: HORIZONS AMI Primary Endpoints by Gender**

	<b>TAXUS Express (N=2257)</b>	<b>Bare Metal Express (N=749)</b>
<b>1 Year Ischemic TLR</b>		
<b>Male (N=2307)</b>	(N=1738) 3.9% (66)	(N=569) 6.0% (33)
<b>Female (N=699)</b>	(N=519) 6.8% (34)	(N=180) 12.1% (21)
	<b>TAXUS Express (N=2257)</b>	<b>Bare Metal Express (N=749)</b>
<b>Safety MACE<sup>1</sup></b>		
<b>Male (N=2307)</b>	(N=1738)	(N=569)

<sup>9</sup> Movahed M, Ramaraj R, Hashemzadeh, M, et. al. Rate of Acute ST-Elevation Myocardial Infarction in the United States from 1988 to 2004 (from the Nationwide Inpatient Sample), *Am J Cardiol.* 2009;104:5-8.

<sup>10</sup> GUSTO Investigators, An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction, *N Engl J Med*; 1993; 329, 673-82.

<sup>11</sup> Lansky AJ, Pietras C, Costa RA, et. al. Gender Differences in Outcomes After Primary Angioplasty Versus Primary Stenting With and Without Abciximab for Acute Myocardial Infarction: Results of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Trial; *Circulation*; 2005: 111:1611-18.

<sup>12</sup> Lansky AJ, Pietras C, Costa RA, et. al. Gender Differences in Outcomes After Primary Angioplasty Versus Primary Stenting With and Without Abciximab for Acute Myocardial Infarction: Results of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Trial; *Circulation*; 2005: 111:1611-18.

<sup>13</sup> Berger JS, Elliott L, Gallup, et al. Sex Differences in Mortality Following Acute Coronary Syndrome; *JAMA.* 2009;302(8):874-882

	7.5% (129)	6.6% (37)
<b>Female (N=699)</b>	<b>(N=519)</b>	<b>(N=180)</b>
	10.1% (52)	12.3% (22)

<sup>1</sup> Safety MACE includes death, reinfarction, stroke or stent thrombosis

**Table 9.6.7: HORIZONS AMI Secondary Endpoint by Gender**

Binary Restenosis at 13 Months (Per Lesion)	TAXUS Express (N=2257)	Bare Metal Express (N=749)
<b>Male (N=2307)</b>	<b>(N=1738)</b>	<b>(N=569)</b>
	9.6% (83/863)	22.6% (55/243)
<b>Female (N=699)</b>	<b>(N=519)</b>	<b>(N=180)</b>
	11.5% (25/218)	23.6% (21/89)

**Table 9.6.8: HORIZONS AMI Clinical Endpoints, All TAXUS Express Male and Female Patients at 30 Days, 1 Year, 2 Year and 3 Year (Stent ITT Population)**

Endpoint	TAXUS Express Male Patients (N=1738)	TAXUS Express Female Patients (N=519)	Bare Metal Express Male Patients (N=569)	Bare Metal Express Female Patients (N=180)
<b>30 Day</b>				
Net Adverse Clinical Events <sup>1</sup>	8.6% (149)	16.2% (84)	7.2% (41)	16.1% (29)
MACE 1 <sup>2</sup>	4.1% (71)	7.4% (38)	3.5% (20)	7.8% (14)
MACE 2 (Safety MACE) <sup>3</sup>	3.9% (68)	6.6% (34)	3.2% (18)	7.8% (14)
Death	1.5% (26)	4.1% (21)	1.6% (9)	2.8% (5)
- Cardiac	1.4% (24)	3.9% (20)	1.6% (9)	2.2% (4)
- Noncardiac	0.1% (2)	0.2% (1)	0.0% (0)	0.6% (1)
Reinfarction	1.6% (27)	2.0% (10)	1.6% (9)	3.9% (7)
- Q wave	1.2% (21)	1.4% (7)	1.2% (7)	2.8% (5)
- Non Q wave	0.4% (7)	0.6% (3)	0.4% (2)	1.1% (2)
Death or reinfarction	2.9% (51)	5.6% (29)	2.8% (16)	5.6% (10)
Ischemic TVR	2.0% (35)	3.5% (18)	2.1% (12)	3.9% (7)
Ischemic TLR	1.8% (32)	3.1% (16)	2.1% (12)	3.9% (7)
Stroke	0.6% (10)	0.2% (1)	0.2% (1)	1.7% (3)
Major bleeding (non-CABG)	6.1% (105)	10.7% (55)	4.6% (26)	10.6% (19)
Target Lesion stent thrombosis	2.0% (35)	2.8% (14)	2.1% (12)	4.5% (8)
<b>1 Year</b>				
Net Adverse Clinical Events <sup>1</sup>	13.3% (231)	23.7% (122)	13.7% (77)	24.5% (44)
MACE 1 <sup>2</sup>	9.3% (161)	14.8% (76)	10.4% (58)	19.0% (34)
MACE 2 (Safety MACE) <sup>3</sup>	7.5% (129)	10.1% (52)	6.6% (37)	12.3% (22)
Death	2.9% (50)	5.4% (28)	2.8% (16)	5.6% (10)
- Cardiac	1.8% (32)	4.3% (22)	2.3% (13)	3.9% (7)
- Noncardiac	1.1% (18)	1.2% (6)	0.5% (3)	1.8% (3)
Reinfarction	3.6% (62)	3.8% (19)	3.8% (21)	6.8% (12)
- Q wave	2.1% (36)	1.8% (9)	1.6% (9)	2.8% (5)
- Non Q wave	1.7% (28)	2.2% (11)	2.2% (12)	4.0% (7)
Death or reinfarction	6.2% (108)	8.6% (44)	6.0% (34)	10.0% (18)
Ischemic TVR	5.0% (85)	8.9% (44)	7.2% (40)	13.8% (24)

Ischemic TLR	3.9% (66)	6.8% (34)	6.0% (33)	12.1% (21)
Stroke	0.9% (16)	1.4% (7)	0.4% (2)	1.7% (3)
Major bleeding (non-CABG)	6.4% (110)	12.0% (61)	5.0% (28)	11.7% (21)
Target Lesion stent thrombosis	3.1% (52)	3.4% (17)	2.9% (16)	5.1% (9)
<b>2 Year</b>				
Net Adverse Clinical Events <sup>1</sup>	19.4% (333)	28.7% (147)	24.5% (135)	30.7% (55)
MACE 1 <sup>2</sup>	15.9% (271)	20.0% (102)	21.4% (117)	24.7% (44)
MACE 2 (Safety MACE) <sup>3</sup>	10.5% (179)	12.9% (58)	10.5% (58)	13.4% (24)
Death	3.7% (63)	6.5% (33)	5.1% (28)	6.2% (11)
- Cardiac	2.2% (38)	4.3% (22)	2.9% (16)	4.5% (8)
- Noncardiac	1.5% (25)	2.3% (11)	2.3% (12)	1.8% (3)
Reinfarction	5.8% (96)	5.5% (27)	5.3% (29)	8.0% (14)
- Q wave	3.3% (55)	2.4% (12)	2.6% (14)	2.4% (6)
- Non Q wave	2.8% (46)	3.7% (18)	2.8% (15)	4.6% (8)
Death or reinfarction	9.0% (153)	11.2% (57)	9.4% (52)	11.2% (20)
Ischemic TVR	10.4% (173)	12.9% (63)	16.0% (86)	18.5% (32)
Ischemic TLR	7.7% (128)	10.2% (50)	13.6% (73)	16.2% (28)
Stroke	1.3% (22)	1.6% (8)	1.0% (5)	1.7% (3)
Major bleeding (non-CABG)	6.5% (113)	12.4% (63)	5.4% (30)	12.3% (22)
Target Lesion stent thrombosis	4.1% (69)	4.2% (21)	3.6% (20)	5.7% (10)
<b>3 Year</b>				
Net Adverse Clinical Events <sup>1</sup>	22.3% (381)	31.9% (163)	26.7% (148)	31.9% (57)
MACE 1 <sup>2</sup>	18.9% (321)	23.7% (120)	23.4% (129)	25.9% (46)
MACE 2 (Safety MACE) <sup>3</sup>	12.9% (220)	15.8% (80)	12.5% (69)	14.0% (25)
Death	5.0% (85)	7.5% (38)	6.4% (35)	7.4% (13)
- Cardiac	2.8% (47)	4.7% (24)	3.6% (20)	4.5% (8)
- Noncardiac	2.3% (38)	2.9% (14)	2.8% (15)	3.0% (5)
Reinfarction	6.9% (115)	7.2% (35)	6.1% (33)	8.0% (14)
- Q wave	3.7% (62)	2.6% (13)	2.6% (14)	3.4% (6)
- Non Q wave	3.6% (59)	5.3% (25)	3.6% (19)	4.6% (8)
Death or reinfarction	11.2% (190)	13.8% (70)	11.4% (63)	11.8% (21)
Ischemic TVR	11.7% (194)	14.6% (71)	17.1% (92)	19.2% (33)
Ischemic TLR	8.7% (145)	11.7% (57)	14.5% (78)	16.9% (29)
Stroke	1.6% (26)	1.9% (9)	1.3% (7)	1.7% (3)
Major bleeding (non-CABG)	7.0% (120)	13.4% (68)	5.7% (32)	12.3% (22)
Target Lesion stent thrombosis	4.6% (77)	5.3% (26)	3.8% (21)	5.7% (10)

<sup>1</sup> Net Adverse Clinical Events includes MACE1 and non-CABG related major bleeding.

<sup>2</sup> MACE1 includes death, reinfarction, stroke, or ischemic target vessel revascularization.

<sup>3</sup> MACE2 includes death, reinfarction, stent thrombosis, or stroke.

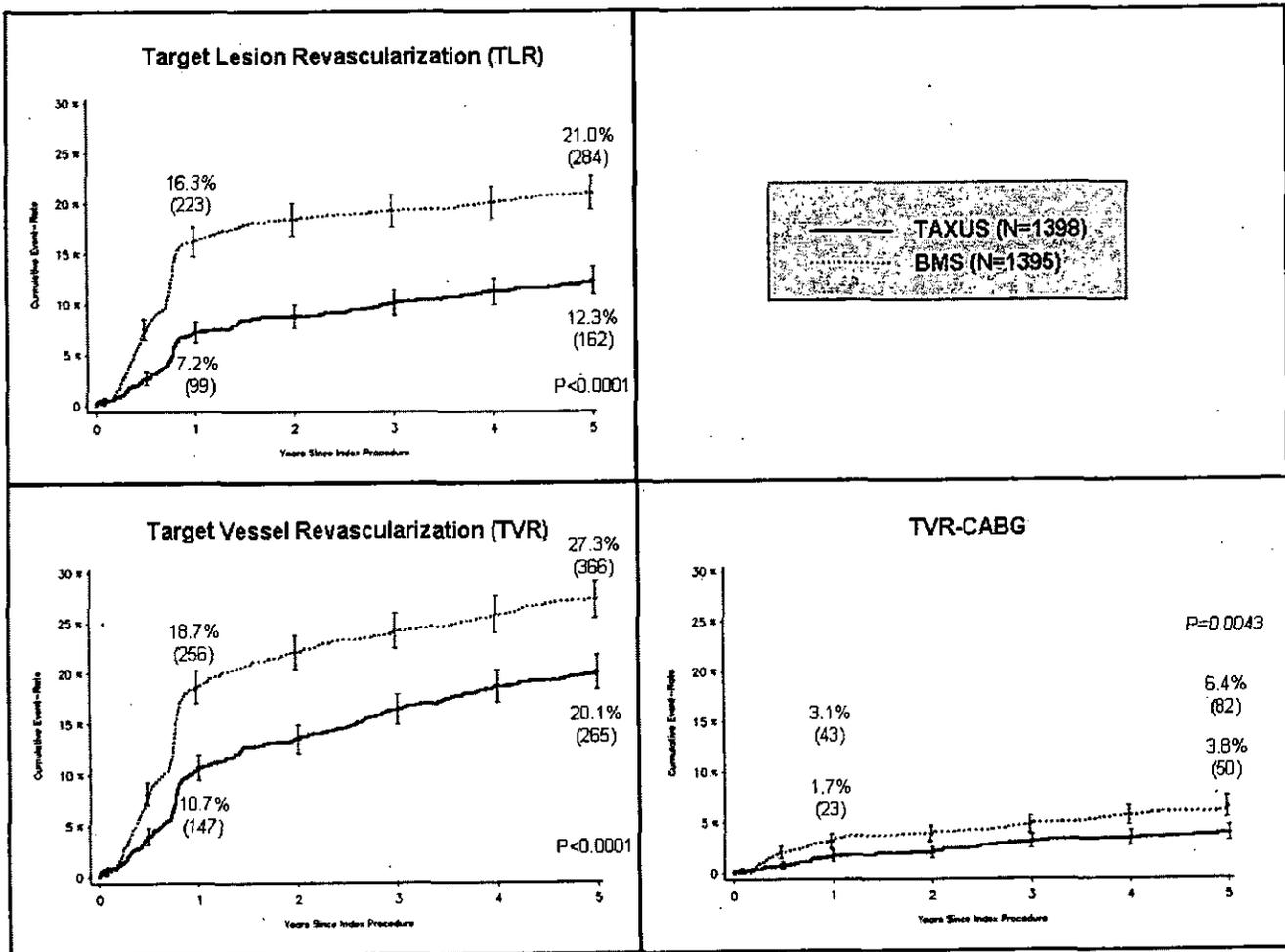
**9.7 Pooled Results of the TAXUS SR stent versus BMS (TAXUS I, II-SR, IV, and V de novo)**

In order to better estimate the incidence of low frequency events or outcomes in specific patient subgroups, a patient-level pooled analysis was conducted of all randomized, blinded, controlled trials comparing TAXUS SR versus its respective bare metal control group in elective PCI patients. Data from the TAXUS I, II-SR, IV, and V de novo randomized trials (as per Section 7.1) were pooled to allow the broadest comparison of the TAXUS SR stent to bare metal stent (BMS) controls in 2793 patients, with a median of 5 years of follow-up. The patient level data was included until the latest available time point depending on the follow-up status for each trial (TAXUS I, II, and IV and TAXUS V de novo to 5 years). Follow-up was 92.6% (2587/2793) complete at the end of 5 years.

**Table 9.7.1: TAXUS SR ITT Patients Disposition Table (N=2793; TAXUS I, II-SR, IV, and V de novo)**

Days post-procedure	0-30	31-180	181-365	366-730	731-1095	1096-1460	1461-1825
TAXUS Stents	1398	1388	1365	1344	1304	1252	1192
Bare Metal Stent	1395	1387	1369	1349	1311	1262	1210

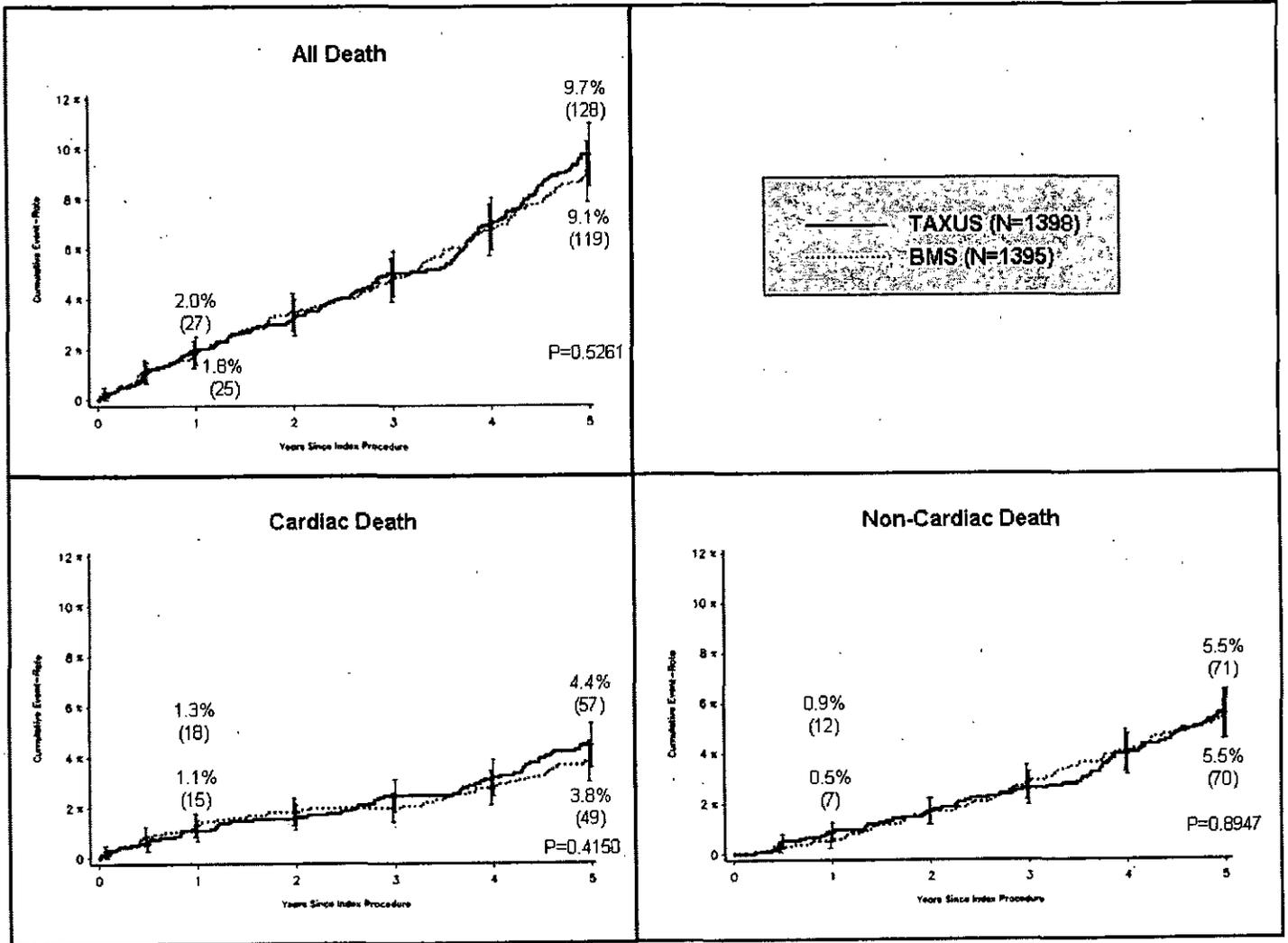
It is acknowledged that the results of such retrospective pooled analyses are hypothesis-generating in nature. Definitive proof of the presence or absence of any differences between such subgroups requires prospectively powered assessment in dedicated clinical trials. The results of the pooled analysis show a notable reduction in repeat revascularization in TAXUS compared to BMS that is maintained throughout long-term follow-up. For example, the target vessel revascularization rate is significantly lower in TAXUS versus Control at 1 year, and remains so throughout 5-year follow-up. This difference is predominantly driven by a 41% reduction in revascularizations within the target lesion (stented segment plus 5 mm proximal and distal edge), as shown in Figure 9.7.1.



Percentages shown are Kaplan-Meier estimates. % (n) are indicated, with "n" being number of patients with events. P-Value from Log-rank test. P-Values are not adjusted for multiple comparisons.

**Figure 9.7.1: Efficacy – Target Vessel Revascularization (TVR) in TAXUS pooled analysis (TAXUS I, II-SR, IV, V de novo; N=2793)**

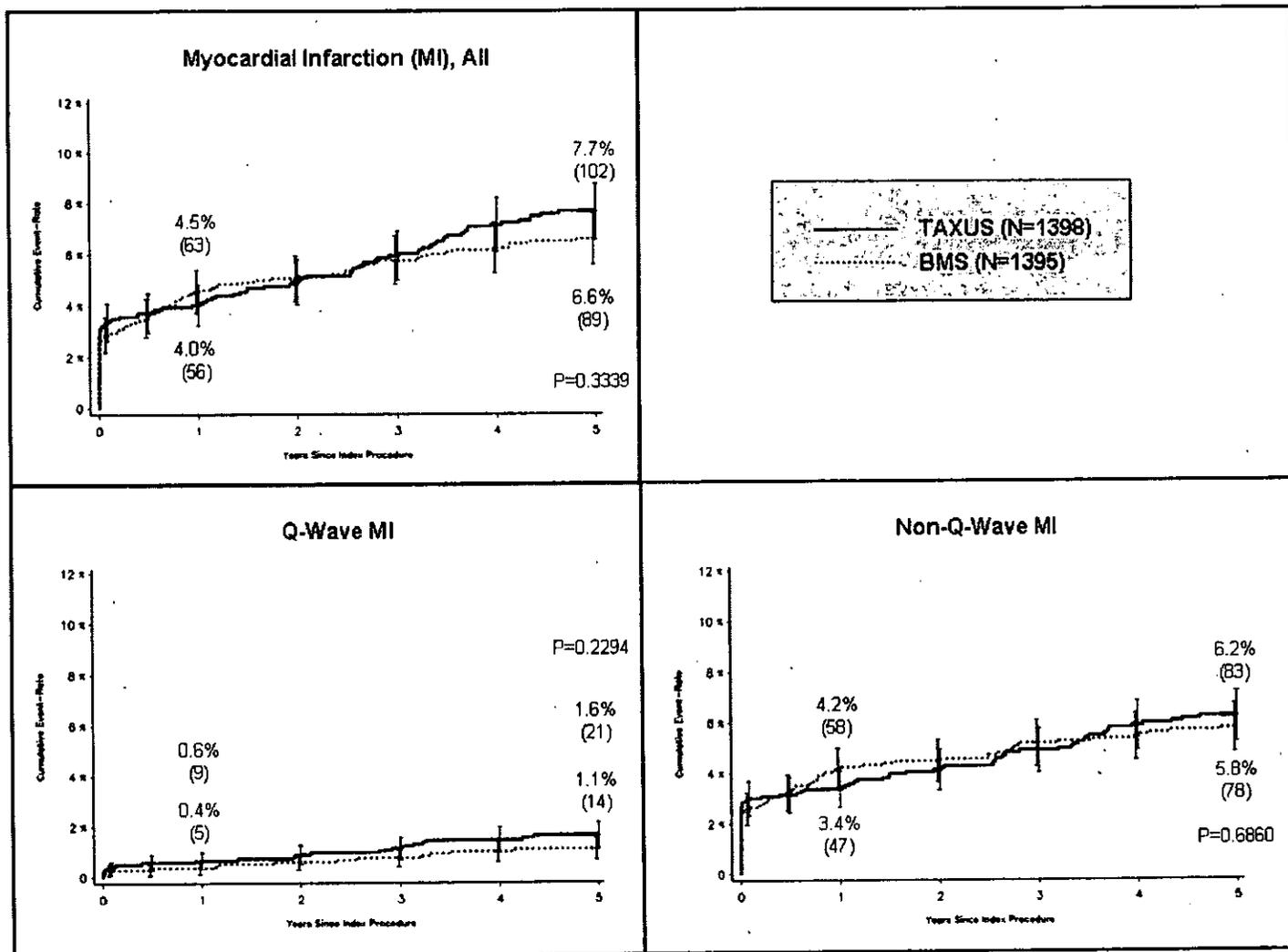
The TAXUS stent is more effective than bare metal stents in reducing the need for revascularization, and as shown in Figure 9.7.2, it does so with no significant increase in mortality rate. While the original study protocols focused on cardiac death as a secondary endpoint, the pooled analysis addressed total death, as well as cardiac death and non-cardiac death as its components. For the endpoints of all death, cardiac death and non-cardiac death, no significant differences between treatment groups are seen.



Percentages shown are Kaplan-Meier estimates. % (n) are indicated, with "n" being number of patients with events. P-Values from Log-rank test. P-Values are not adjusted for multiple comparisons.

**Figure 9.7.2: Safety – Mortality in TAXUS pooled analysis (TAXUS I, II-SR, IV, V de novo; N=2793)**

MI rates were also examined in the pooled analysis. The rate of all MI (Q-wave MI and non-Q-wave MI), Q-wave MI, and non-Q-wave MI were not significantly different between the TAXUS and BMS Control groups.



Percentages shown are Kaplan-Meier estimates. % (n) are indicated, with "n" being number of patients with events. P-Values from Log-rank test. P-Values are not adjusted for multiple comparisons

**Figure 9.7.3: Safety – Myocardial Infarction (MI) in TAXUS pooled analysis (TAXUS I, II-SR, IV, V de novo; N=2793)**

**9.7.1 Stent thrombosis in TAXUS pooled analysis (TAXUS I, II-SR, IV, V de novo; N=2793)**

Acknowledging subtle differences in protocol definitions for stent thrombosis in individual trials, as well as the risk of potential underreporting of various components (e.g., events after revascularization, potential events in patients reported with unexplained cardiac death after 30 days, etc.), the FDA recommended an additional categorization of all events using the proposed definitions by the Academic Research Consortium (ARC)<sup>14</sup>. Stent thrombosis was defined (per protocol) in the TAXUS IV pivotal trial as the occurrence of any of the following:

<sup>14</sup> Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circ* 2007;115:2344-51.

1. Clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis:
  - a) Angiographic documentation of a complete occlusion (TIMI flow of 0 or 1) of a previously successfully treated artery (TIMI flow of 2 to 3 immediately after stent placement and diameter stenosis  $\leq$  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 first 30 days (without other obvious cause) is considered a surrogate for stent thrombosis when angiography is not available.

All events were recategorized according to the FDA recommendation using the stent thrombosis definitions proposed by ARC. This was performed by an independent event committee blinded to the treatment groups of the individual patients. They categorized each incident of stent thrombosis by timing, level of probability (definite, probable, possible), and relation to the original index procedure (primary, secondary after revascularization). These categories are defined as follows:

**Timing:**

- |                             |  |
|-----------------------------|--|
| Acute stent thrombosis:     | 0 – 24 hours post- stent implantation        |
| Subacute stent thrombosis:  | > 24 hours – 30 days post-stent implantation |
| Late stent thrombosis:      | > 30 days – 1 year post-stent implantation   |
| Very late stent thrombosis: | > 1 year post-stent implantation             |

**Level of probability:**

- **Definite ST**  
Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation.
- **Probable ST**  
Probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:
  - 1) Any unexplained death within the first 30 days.
  - 2) 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 stent thrombosis and in the absence of any other obvious cause.
- **Possible ST**  
Possible stent thrombosis is considered to have occurred with any unexplained death following 30 days after the intracoronary stenting until the end of trial follow-up.

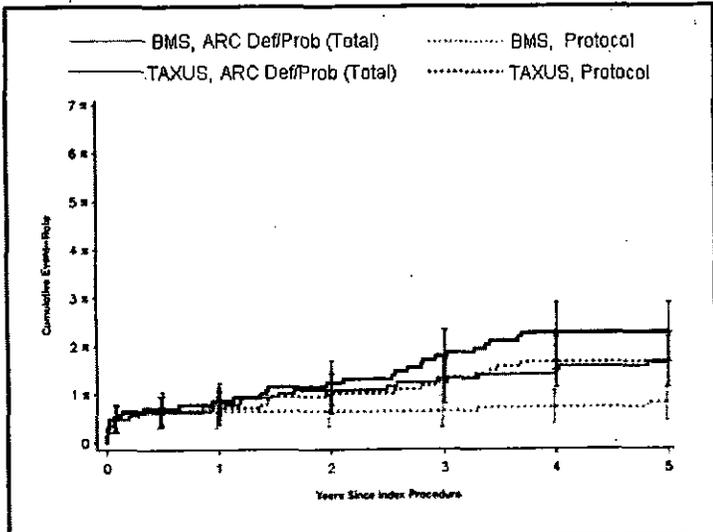
**Relation to original procedure**

- Primary - ST after index procedure without any preceding TLR
- Secondary - ST after index procedure with intervening TLR
- Total - Primary plus secondary stent thromboses

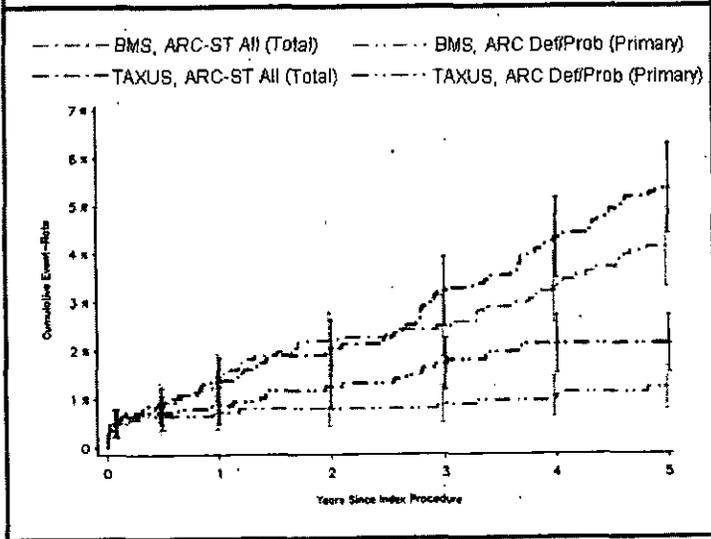
There are several components of the ARC definitions of stent thrombosis, based on certainty (Definite, Probable, or also adding broader and less-specific Possible stent thrombosis), and on whether stent thrombosis events occurring post-TLR should be included (ARC Total) or excluded from analysis (ARC Primary and protocol definitions). Current practice favors the ARC Definite+Probable Total

definition based on an intent-to-treat analysis, but in the interest of completeness, all definition variants are reported for the pooled TAXUS data displayed below (Figure 9.7.4).

As defined per protocol, there is no statistically significant difference between TAXUS and Control in the 5-year cumulative stent thrombosis rates; nor is there a statistically significant difference between treatment groups in the cumulative 5-year stent thrombosis rate significantly higher for TAXUS using the ARC Definite+Probable (Primary) definition ( $p=0.0682$ ). In addition, using the ARC All (including definite, probable, and possible) and more importantly the standard ARC Definite+Probable (Total) definitions, there also are no statistically significant differences in 5-year cumulative stent thrombosis ( $p=0.1616$  and  $p=0.2597$ , respectively). For very late stent thrombosis (those occurring after 1 year), a small numerical excess can be seen with TAXUS versus BMS control, which represents a significant increase by both the TLR censored ARC Primary Definite+Probable ( $p=0.0312$ ) and the protocol ( $p=0.0071$ ) definitions, but which did not reach statistical significance using the standard ARC Definite+Probable (Total) definition ( $p=0.1845$ ).



	5-yr cumulative	After 1 year † BMS vs. TAXUS (difference)
ARC ST Definite/Probable (Total)	BMS: 1.7% (22) TAXUS: 2.3% (30) Log-Rank P=0.2597	11 vs. 18 (0.5%) Log-Rank P=0.1845
Protocol	BMS: 0.8% (11) TAXUS: 1.7% (22) Log-Rank P=0.0537	2 vs. 12 (0.7%) Log-Rank P=0.0071



	5-yr cumulative	After 1 year † BMS vs. TAXUS (difference)
ARC All (Total) †	BMS: 4.1% (54) TAXUS: 5.3% (69) Log-Rank P=0.1616	35 vs. 50 (1.2%) Log-Rank P=0.0913
ARC Definite/ Probable (Primary) ‡	BMS: 1.2% (16) TAXUS: 2.1% (28) Log-Rank P=0.0682	6 vs. 16 (0.8%) Log-Rank P=0.0312

		ARC Def/Prob (Total)	Protocol	ARC All, (Total) †	ARC Def/Prob (Primary) §	ARC Def/Prob (Total)	Protocol	ARC All, (Total) †	ARC Def/Prob (Primary) §
		5-Year Cumulative				Years 1-5 ‡			
TAXUS	# Entered	1398	1398	1398	1398	1344	1344	1344	1344
	# Events	30	22	69	28	18	12	50	16
Bare Metal	# Entered	1395	1395	1395	1395	1349	1349	1349	1349
	# Events	22	11	54	16	11	2	35	6

Event rates are Kaplan-Meier estimates. P-Values are not adjusted for multiple comparisons.

Analysis included data from TAXUS I, II-SR, IV, and V de novo.

† ARC All (Total) includes definite, probable and possible.

‡ For analyses beyond 1 year ST events that occurred in the first year were excluded and the first event beyond 1 year was considered.

§ Data is TLR-censored for ARC def/prob primary. ARC definitions are provided in Section 9.7.1

**Figure 9.7.4: Stent thrombosis Rates for the TAXUS vs. BMS Pooled Analysis (TAXUS I, II-SR, IV, novo; N=2793) vs. BMS by Protocol and ARC Definitions**

**9.7.2 Diabetic Patients in TAXUS SR pooled analysis (TAXUS I, II SR, IV, and V de novo; N=715)**

Patients with diabetes mellitus represent a high-risk group for clinical events following percutaneous coronary intervention. While some of the individual trials included stratification of diabetic status as part of the randomization process (TAXUS IV and TAXUS V de novo), these trials were not adequately powered to determine the rate of low frequency events or compare their incidence to a bare metal control group. Diabetics were defined as medically treated (all patients treated with oral medication and/or insulin) for diabetes mellitus.

The clinical trials conducted on the TAXUS SR stent system were not designed to specifically support an approval for use in diabetic patients. The following table includes pooled patient level data from TAXUS I, II-SR, IV, and V de novo in diabetic patients. Additional safety information on use of the TAXUS stent in diabetic patients is presented in Section 9.8 ARRIVE Clinical Registry.

**Table 9.7.2: Pooled TAXUS SR Clinical Results for Medically Treated Diabetic Patients (TAXUS I, II-SR, IV, and V de novo)**

	9 months			5 years* (final planned follow-up)		
	TAXUS Stents (N=356)	Bare Metal Stents (N=359)	P-Value	TAXUS Stents (N=356)	Bare Metal Stents (N=359)	P-Value
<b>EFFICACY</b>						
TVR, Overall	8.6% (30)	16.1% (57)	0.0020	25.6% (85)	33.7% (114)	0.0117
TLR, Overall	5.5% (19)	14.7% (52)	< 0.0001	13.5% (45)	25.4% (87)	< 0.0001
TLR, PCI	5.2% (18)	11.9% (42)	0.0012	12.6% (42)	20.6% (71)	0.0027
TLR, CABG	0.3% (1)	2.8% (10)	0.0066	0.9% (3)	6.4% (20)	0.0004
Non-TLR, Overall	4.3% (15)	2.3% (8)	0.1316	16.5% (54)	14.5% (47)	0.3776
Non-TLR, PCI	3.2% (11)	1.7% (6)	0.2103	12.1% (39)	12.4% (40)	0.9803
Non-TLR, CABG	1.1% (4)	0.6% (2)	0.4053	5.6% (18)	2.8% (9)	0.0726
<b>SAFETY</b>						
Total Death	2.0% (7)	2.2% (8)	0.8155	13.8% (46)	11.2% (38)	0.3324
Cardiac Death or MI	4.2% (15)	6.7% (24)	0.1497	14.0% (46)	10.1% (35)	0.2052
Cardiac Death	1.1% (4)	1.4% (5)	0.7561	7.7% (25)	4.3% (14)	0.0662
MI	3.4% (12)	5.3% (19)	0.2093	8.6% (28)	7.1% (25)	0.6659
Q-wave MI	0.3% (1)	0.6% (2)	0.5747	1.3% (4)	1.2% (4)	0.9809
Non-Q-wave MI	3.1% (11)	4.8% (17)	0.2574	7.3% (24)	6.3% (22)	0.7507
Stent Thrombosis	0.6% (2)	1.4% (5)	0.2668	1.2% (4)	1.4% (5)	0.7552

Kaplan-Meier rate % (n). P-Value from Log-rank test.

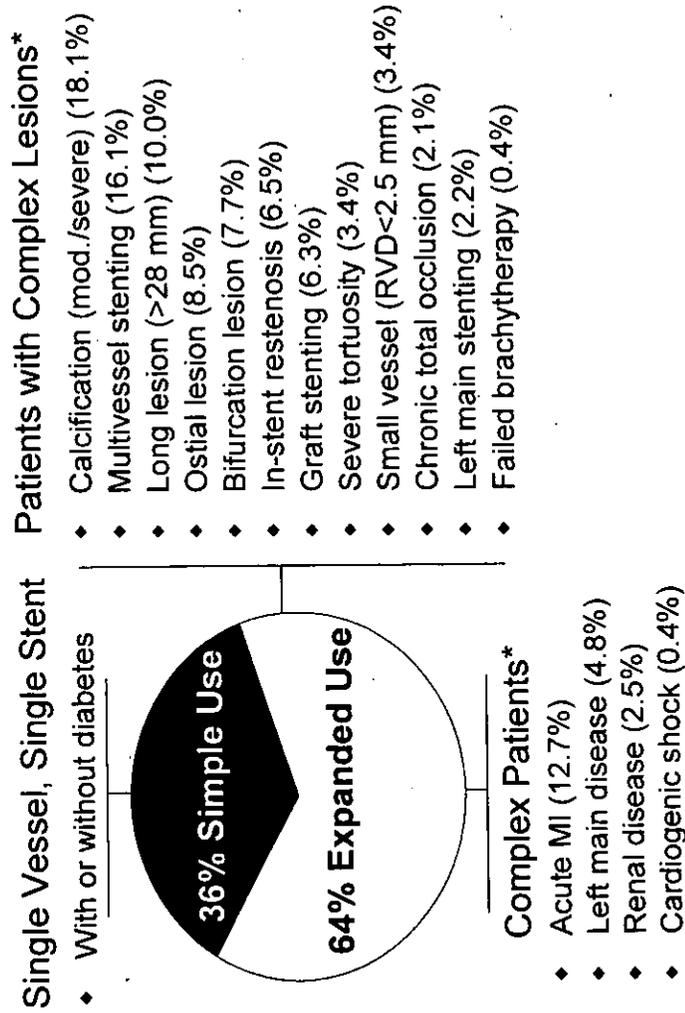
This trial was not adequately powered to compare the rate of low frequency events to a bare metal control group, nor was it sized to determine the rate of low frequency events with a pre-specified precision.

\*TAXUS I, II, and IV and TAXUS V de novo to 5 years.

### 9.8 ARRIVE Clinical Registry

The TAXUS Clinical Trial program was complemented by the ARRIVE real-world registry program. The goals of this program were: (1) to estimate the incidence of clinical outcomes outside of controlled clinical trials in a real-world setting (safety surveillance), and (2) to confirm the predictability of real-world outcomes post-approval through the pre-approval clinical trial program. The ARRIVE program itself consisted of ARRIVE 1 (an FDA-mandated peri-approval registry) and ARRIVE 2 (a voluntary post-approval registry). Both registries were enrolled within the U.S.

The ARRIVE program helped to compile real-world usage of the TAXUS Express stent in consecutively consented and treated patients. When combining all patients from ARRIVE 1 and ARRIVE 2, 36% of all analyzed patients (2698/7492) had single vessel, single stent lesions that met the inclusion criteria of TAXUS IV, the pivotal trial for TAXUS approval (Figure 9.8.1). The remaining 64% of all patients from ARRIVE 1 and ARRIVE 2 (4794/7492) had more complex disease. Thus, 64% of ARRIVE patients represent an expanded use of the TAXUS stent not formally assessed within the pivotal dataset.



\*A patient may belong to more than one expanded-use group.

Figure 9.8.1: Lesion complexity in ARRIVE 1 and 2 combined (N=7,492)

### 9.8.1 ARRIVE 1

ARRIVE 1 was a peri-approval FDA-mandated safety surveillance program designed to compile real-world use, safety, and clinical outcomes data for the TAXUS® Express<sup>2</sup>® Coronary Stent System. Through a web-based registry, investigators enrolled up to 75 consenting, consecutive patients receiving TAXUS stents at 50 U.S. sites. Clinical or telephone follow-up at 30 days, at 6 months, and at 1 and 2 years collected data on TAXUS-related death, MI, stent thrombosis, re-intervention, and hypersensitivity events. Re-intervention triggered an additional 12-month observation for subsequent events. All reported cardiac events were adjudicated by an independent CEC to determine relationship to the study device.

The ARRIVE 1 analysis population includes 2487 patients with 3630 lesions, 2958 vessels, and 4068 stents. Patient follow-up out to 2 years has been completed in the entire patient population. Baseline demographics and procedural characteristics (Table 9.8.1), as well as safety results (Table 9.8.2), are presented below.

In addition to the protocol-specified (and CEC-adjudicated) definitions of stent thrombosis used to generate the results in Table 9.7.2 below, the FDA requested an additional retrospective assessment of all events using the proposed ARC definitions (see Section 9.7.1). These results are also displayed below (Table 9.8.3).

**Table 9.8.1: ARRIVE 1 - Baseline Demographics and Procedural Characteristics**

Analysis Group: 2487 patients; 3630 lesions; 2958 vessels; 4068 stents

Patient Demographics		Procedural Characteristics
Male	68.0% (1691/2487)	Vessels Treated
Age (yr)	63.7±11.5 (2487)	1
Diabetes	30.4% (756/2487)	2
Oral Medication Treated	24.5% (610/2487)	≥ 3
Insulin Treated	9.8% (243/2487)	Target Vessels
Multi-vessel Disease	38.7% (962/2487)	RCA
Prior MI	36.8% (916/2487)	LAD
Prior PCI	36.1% (889/2465)	CX
Prior CABG	20.8% (517/2483)	LM
		Graft
		Stenting
Reference Vessel Diameter (mm)	3.0±0.4	Direct stenting (per lesion)
Lesion Length (mm)	16.1±9.3	TAXUS stents per patient
Lesion Type		Patients with > 1 TAXUS stent
A	13.4% (485/3627)	Stent length per patient (mm)
B1	34.5% (1251/3627)	Stent length per lesion (mm)
B2	31.3% (1136/3627)	
C	20.8% (755/3627)	

Numbers are % (Count/Sample Size) or Mean±SD.  
 Denominators may not reflect overall number of patients due to missing or incomplete data.  
 Patients from 2 sites are excluded from analysis due to Good Clinical Practices (GCP) non-compliance.

**Table 9.8.2: ARRIVE 1 Principal Safety Results Summary to 2 years (N=2487)**

Analysis Group: 2487 patients; 3630 lesions; 2958 vessels; 4068 stents	
	Event Rate
TAXUS-related cardiac event (Cardiac death, MI, TAXUS-related re-intervention)	9.9% (230/2323)
Cardiac death	1.3% (30/2323)
MI	2.4% (55/2323)
Q-wave MI	0.9% (21/2323)
Non Q-wave MI	1.5% (36/2323)
TAXUS-related re-intervention	8.1% (189/2323)
All Death <sup>†</sup>	6.0% (140/2323)
Stent thrombosis (per protocol)	2.9% (67/2323)

Numbers are % (count/sample size).

<sup>†</sup> Includes non-stent-related deaths.

Patients from 2 sites are excluded from analysis due to GCP non-compliance.

The ARRIVE registries were not designed to compare the rate of low frequency events to a control group, nor were the registries designed to determine the rate of low frequency events with a pre-specified precision.

**Table 9.8.3: Stent Thrombosis by Time Interval in ARRIVE 1 (N=2487)**

	Per protocol*	ARC Definite & Probable Total <sup>§</sup>
0 days – 1 day	0.2% (4/2487)	0.2% (4/2487)
0 days – 30 days	1.3% (33/2486)	1.4% (34/2486)
31 days – 365 days	0.8% (20/2420)	0.8% (20/2420)
366 days – 730 days	0.6% (14/2271)	0.7% (16/2271)
0 days – 365 days	2.2% (53/2411)	2.2% (54/2411)
0 days – 730 days	2.9% (67/2323)	3.0% (70/2323)

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

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)

§ ARC definitions are provided in Section 9.7.1.

Patients from 2 sites are excluded from analysis due to (GCP) non-compliance.

The ARRIVE registries were not designed to compare the rate of low frequency events to a control group, nor were the registries designed to determine the rate of low frequency events with a pre-specified precision.

### 9.8.2 ARRIVE 2

ARRIVE 2 is a BSC-initiated, post-approval safety surveillance program. Through a web-based registry, investigators enrolled up to 100 consenting, consecutive patients receiving TAXUS stents at 53 US sites. Clinical or telephone follow-up occurred at 30 days, at 6 months, and at 1 and 2 years to collect data on TAXUS-related death, MI, stent thrombosis, re-intervention, and hypersensitivity events. Re-intervention triggered an additional 12-month observation for subsequent events. All reported cardiac events were adjudicated by an independent CEC to determine relationship to the study device.

The ARRIVE 2 analysis population includes 5005 patients with 7038 lesions, 5837 vessels, and 7815 stents. Patient follow-up out to 2 years has been completed in the entire patient population. Baseline demographics and procedural characteristics (Table 9.8.4), as well as safety results (Table 9.8.5), are listed below.

In addition to the protocol-specified (and CEC-adjudicated) definitions of stent thrombosis used to generate the results in Table 9.8.5 below, the FDA requested an additional retrospective assessment of all events using the proposed ARC definitions (see Section 9.7.1). These results are also presented (Table 9.8.6).

**Table 9.8.4: ARRIVE 2 - Baseline Demographics and Procedural Characteristics**

Analysis Group: 5005 patients; 7038 lesions; 5837 vessels, 7815 Stents

Patient Demographics		Vessels Treated	Procedural Characteristics
Male	67.0% (3352/5005)	1	84.5% (4227/5005)
Age (yr)	64.5±11.8 (5005)	2	14.5% (726/5005)
Diabetes	32.2% (1612/5005)	≥3	1.0% (52/5005)
Oral medication treated	22.1% (1108/5005)	<b>Target Vessels</b>	
Insulin treated	10.4% (521/5005)	RCA	33.3% (2342/7038)
Multi-vessel disease	36.0% (1803/5005)	LAD	35.4% (2490/7038)
Prior MI	36.1% (1806/5005)	CX	24.2% (1700/7038)
Prior PCI	37.1% (1836/4943)	LM	1.4% (102/7038)
Prior CABG	19.7% (985/4988)	Graft	5.7% (404/7038)
<b>Lesion Characteristics</b>		<b>Stenting</b>	
Reference vessel diameter (mm)	3.0±0.4 (7036)	Direct stenting (per lesion)	47.6% (2384/5005)
Lesion length (mm)	15.4±9.2 (7009)	TAXUS stents per patient	1.6±0.9 (5005)
<b>Lesion Type</b>		Stent length per lesion (mm)	20.8±11.1 (6940)
A	14.3% (1006/7035)		
B1	36.4% (2561/7035)		
B2	31.1% (2190/7035)		
C	18.2% (1278/7035)		

Numbers are % (count/sample size) or mean±SD (n).

Denominators may not reflect number of overall patients due to missing or incomplete data.

Nine (9) patients were excluded from ARRIVE 2 analysis due to simultaneous enrollment in another randomized clinical trial, and 2 more were excluded due to treatment with a TAXUS stent for a dissection rather than a primary event.

**Table 9.8.5: ARRIVE 2 Principal Safety Results Summary to 2 Years (N=5005)**

Analysis Group: 5005 patients; 7038 lesions; 5837 vessels, 7815 Stents	
	Event Rate
TAXUS-related cardiac event (cardiac death, MI, TAXUS-related re-intervention)	9.0% (423/4712)
Cardiac death	1.1% (54/4712)
MI <sup>‡</sup>	2.2% (106/4712)
Q-wave MI (only)	0.8% (37/4712)
Non Q-wave MI (only)	1.4% (65/4712)
TAXUS-related re-intervention	7.6% (356/4712)
All death <sup>†</sup>	6.8% (321/4712)
Stent thrombosis (per protocol)	2.3% (107/4712)

Numbers are % (count/sample size).

<sup>‡</sup> Three additional patients had a Q-wave and a non Q-wave MI.

<sup>†</sup> Includes non-stent-related deaths.

Nine (9) patients were excluded from ARRIVE 2 analysis due to simultaneous enrollment in another randomized clinical trial, and 2 more were excluded due to treatment with a TAXUS stent for a dissection rather than a primary event.

The ARRIVE registries were not designed to compare the rate of low frequency events to a control group, nor were the registries designed to determine the rate of low frequency events with a pre-specified precision.

**Table 9.8.6: Stent Thrombosis by Time Interval in ARRIVE 2 (N=5005)**

	Per protocol*	ARC Definite & Probable Total <sup>§</sup>
0 days – 1 day	0.2% (12/5005)	0.3% (13/5005)
0 days – 30 days	0.8% (40/5005)	0.9% (43/5005)
31 days – 365 days	0.7% (32/4912)	0.6% (31/4912)
366 days – 730 days	0.8% (35/4611)	0.9% (40/4611)
0 days – 365 days	1.5% (72/4863)	1.5% (74/4863)
0 days – 730 days	2.3% (107/4712)	2.4% (114/4712)

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

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)

§ ARC definitions are provided in Section 9.7.1

Nine (9) patients were excluded from ARRIVE 2 analysis due to simultaneous enrollment in another randomized clinical trial and 2 more were excluded due to treatment with a TAXUS stent for a dissection rather than a primary event. The ARRIVE registries were not designed to compare the rate of low frequency events to a control group, nor were the registries designed to determine the rate of low frequency events with a pre-specified precision.

### **9.9 Subgroup analysis of the ARRIVE registries**

A subgroup analysis was conducted on the ARRIVE 1 and ARRIVE 2 patients. The two ARRIVE registries were designed to allow data pooling. Statistical comparisons (baseline demographic and lesion data, procedural, and post-procedural characteristics) between ARRIVE 1 and ARRIVE 2 indicated data could be pooled. Results for pooled ARRIVE 1 and ARRIVE 2 from 0-1 and 1-2 years are presented in Tables 9.9.1 and 9.9.2, respectively.

**Table 9.9.1: Subgroup Outcomes in Pooled ARRIVE 1 and 2 (0-1 year)**

	ARRIVE 1 & 2 Overall n=7492	Simple-use n=2698	Long Lesions (>28 mm) n=748	Small Vessels (RVD <2.5 mm) n=251	Multivessel Stenting n=1208	Multiple Stents Per Patient n=2877	Bifurcation Lesions n=574	AMI n=953	All Diabetics n=2305	Insulin Treated Diabetics n=746	Non-Insulin Treated Diabetics n=1559	ISR n=489	Vein Graft n=474
<b>Efficacy</b>													
TAXUS-related re-intervention	5.1% (373/7274)	3.4% (89/2623)	8.9% (64/721)	7.5% (18/240)	7.8% (92/1174)	7.2% (206/2862)	8.6% (48/558)	4.2% (38/905)	4.7% (107/2296)	5.3% (39/729)	4.3% (68/1567)	7.1% (34/479)	5.6% (26/465)
<b>Safety</b> <sup>†</sup>													
All death*	3.5% (257/7274)	2.3% (60/2623)	4.7% (34/722)	3.3% (8/240)	4.3% (51/1174)	3.7% (105/2862)	5.0% (28/558)	3.9% (35/905)	5.3% (122/2296)	5.9% (43/729)	5.0% (79/1567)	4.4% (21/479)	5.2% (24/465)
Cardiac death	1.0% (72/7274)	0.6% (15/2623)	1.5% (11/722)	1.7% (4/240)	2.0% (23/1174)	1.4% (39/2862)	2.2% (12/558)	1.0% (9/905)	1.6% (37/2296)	2.2% (16/729)	1.3% (21/1567)	0.8% (4/479)	1.1% (5/465)
MI	1.6% (116/7274)	1.3% (33/2623)	4.2% (30/722)	2.5% (6/240)	3.1% (36/1174)	2.4% (69/2862)	2.2% (12/558)	1.5% (14/905)	1.8% (41/2296)	2.7% (20/729)	1.3% (21/1567)	2.1% (10/479)	1.7% (8/465)
Q-wave	0.6% (43/7274)	0.5% (12/2623)	2.1% (15/722)	0.8% (2/240)	1.3% (15/1174)	1.0% (29/2862)	0.5% (3/558)	0.1% (1/905)	0.7% (15/2296)	0.8% (6/729)	0.6% (9/1567)	0.6% (3/479)	0.4% (2/465)
<b>Stent thrombosis</b>													
Per Protocol <sup>‡</sup>	1.7% (125/7274)	0.9% (24/2623)	3.7% (27/721)	3.3% (8/240)	2.7% (32/1174)	2.6% (75/2862)	2.9% (16/558)	2.3% (21/905)	2.0% (45/2296)	2.9% (21/729)	1.5% (24/1567)	1.7% (8/479)	2.4% (11/465)
Definite/ Probable Total <sup>‡</sup>	1.8% (128/7274)	0.9% (24/2623)	4.0% (29/722)	3.3% (8/240)	2.8% (33/1174)	2.7% (77/2862)	2.9% (16/558)	2.7% (24/905)	2.1% (48/2296)	3.3% (24/729)	1.5% (24/1567)	2.1% (10/479)	2.4% (11/465)

<sup>†</sup> Stent-related events

\* Includes non-stent-related deaths.

<sup>‡</sup> Simple-use cases excluded one or more of the following: acute myocardial infarction (AMI); bifurcation, cardiogenic shock, chronic total occlusion, failed brachytherapy, vein graft stenting, in-stent restenosis, large vessel (RVD > 3.75 mm), left main disease/stenting, long lesion (> 28 mm), moderate/severe calcification, multivessel stenting, ostial lesion, renal disease, severe tortuosity, small vessel (RVD < 2.5 mm). Expanded-use cases are those not classified as simple-use.

<sup>†</sup> Per protocol, stent thrombosis (in target vessel) was defined as either:

- Angiographically confirmed - thrombus detected in any stent placed in the target vessel(s), or
- 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)

<sup>‡</sup> Academic Research Consortium (ARC) definitions are provided in Section 9.7.1

Patients from two ARRIVE 1 sites are excluded from analysis due to GCP non-compliance.

The ARRIVE registries were not designed to compare the rate of low frequency events to a control group, nor were the registries designed to determine the rate of low frequency events with a pre-specified precision.

Table 9.9.2: Subgroup Outcomes in Pooled ARRIVE 1 and 2 (1-2 years)													
	ARRIVE 1 & 2 Overall n=7492	Simple-use n=2698	Long lesions (>28 mm) n=748	Small vessels (RVD <2.5 mm) n=251	Multivessel Stenting n=1208	Multiple Stents Per Patient n=2877	Bifurcation Lesions n=574	AMI n=953	All Diabetics n=2305	Insulin Treated Diabetics n=746	Non-Insulin Treated Diabetics n=1559	ISR n=489	Vein Graft n=474
<b>Efficacy</b>													
TAXUS-related re-intervention	2.5% (172/6882)	1.9% (48/2520)	4.0% (27/673)	1.3% (3/225)	4.3% (47/1088)	3.7% (99/2697)	3.9% (20/519)	1.4% (12/844)	3.3% (69/2123)	3.7% (25/671)	3.0% (44/1452)	4.4% (20/450)	4.4% (19/435)
<b>Safety<sup>†</sup></b>													
All death*	3.0% (204/6882)	1.9% (48/2520)	4.3% (29/673)	4.0% (9/225)	3.1% (34/1088)	2.9% (79/2697)	2.5% (13/519)	2.8% (24/844)	4.4% (94/2123)	5.8% (39/671)	3.8% (55/1452)	4.0% (18/450)	6.0% (26/435)
Cardiac death	0.2% (12/6882)	0.0% (1/2520)	0.1% (1/673)	0.0% (0/225)	0.3% (3/1088)	0.1% (4/2697)	0.2% (1/519)	0.2% (2/844)	0.2% (5/2123)	0.1% (1/671)	0.3% (4/1452)	0.2% (1/450)	0.7% (3/435)
MI	0.7% (45/6882)	0.4% (11/2520)	1.5% (10/673)	0.0% (0/225)	1.1% (12/1088)	1.0% (28/2697)	1.3% (7/519)	0.9% (8/844)	0.6% (13/2123)	0.9% (6/671)	0.5% (7/1452)	1.1% (5/450)	1.8% (7/435)
Q-wave	0.3% (19/6882)	0.2% (6/2520)	0.7% (5/673)	0.0% (0/225)	0.3% (3/1088)	0.4% (11/2697)	0.4% (2/519)	0.4% (3/844)	0.1% (2/2123)	0.0% (0/671)	0.1% (2/1452)	0.4% (2/450)	0.5% (2/435)
<b>Stent thrombosis</b>													
Per Protocol <sup>†</sup>	0.7% (49/6882)	0.5% (13/2520)	1.6% (11/673)	0.0% (0/225)	0.8% (9/1088)	1.0% (28/2697)	1.3% (7/519)	0.7% (6/844)	0.7% (15/2123)	0.6% (4/671)	0.8% (11/1452)	1.3% (6/450)	1.6% (7/435)
Definite/Probable Total <sup>†</sup>	0.8% (56/6882)	0.4% (11/2520)	1.8% (12/673)	0.0% (0/225)	1.5% (16/1088)	1.3% (34/2697)	1.5% (8/519)	1.1% (9/844)	0.9% (19/2123)	0.9% (6/671)	0.9% (13/1452)	1.8% (8/450)	2.3% (10/435)

<sup>†</sup> Stent-related events

\* Includes non-stent-related deaths.

† Simple-use cases excluded one or more of the following: acute myocardial infarction (AMI); bifurcation, cardiogenic shock, chronic total occlusion, failed brachytherapy, vein graft stenting, in-stent restenosis, large vessel (RVD>3.75), left main disease/stenting, long lesion (>28 mm), moderate/severe calcification, multivessel stenting, ostial lesion, renal disease, severe tortuosity, small vessel (RVD<2.5 mm). Expanded-use cases are those not classified as simple-use.

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

- Angiographically confirmed - thrombus detected in any stent placed in the target vessel(s), or

- 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).

† Academic Research Consortium (ARC) definitions are provided in Section 9.7.1 (Cutlip DE, et al. Circulation 2007;115:2344).

Patients from two ARRIVE 1 sites are excluded from analysis due to GCP non-compliance.

The ARRIVE registries were not designed to compare the rate of low frequency events to a control group, nor were the registries designed to determine the rate of low frequency

events with a pre-specified precision.

**Table 9.9.3: Subgroup Outcomes in Pooled ARRIVE 1 and 2 (0-2 years)**

	ARRIVE 1 & 2 Overall n=7492	Simple-use † n=2698	Long lesions (>28 mm) n=747	Small vessels (RVD <2.5 mm) n=251	Multivessel Stenting n=1208	Multiple Stents Per Patient n=2956	Bifurcated Lesions n=575	AMI n=954	All Diabetics n=2368	Insulin Treated Diabetics n=764	Non-Insulin Treated Diabetics n=1604	ISR n=489	Vein Graft n=474
<b>Efficacy</b>													
TAXUS-related re-intervention	7.7% (545/7035)	5.4% (137/2545)	13.1% (91/696)	9.1% (21/230)	12.3% (139/1128)	11.1% (305/2760)	12.7% (68/535)	5.8% (50/855)	8.0% (176/2206)	9.1% (64/706)	7.5% (112/1500)	11.7% (54/462)	9.8% (45/457)
<b>Safety<sup>‡</sup></b>													
All death*	6.6% (461/7035)	4.2% (108/2545)	9.1% (63/696)	7.4% (17/230)	7.5% (85/1128)	6.7% (184/2760)	7.6% (41/538)	6.9% (59/855)	9.8% (216/2206)	11.6% (82/706)	8.9% (134/1500)	8.4% (39/462)	10.9% (50/457)
Cardiac death	1.2% (84/7035)	0.6% (16/2545)	1.7% (12/696)	1.7% (4/230)	2.3% (26/1128)	1.6% (43/2760)	2.4% (13/538)	1.3% (11/855)	1.9% (42/2206)	2.4% (17/706)	1.7% (25/1500)	1.1% (5/462)	1.8% (8/457)
MI	2.3% (161/7035)	1.7% (44/2545)	5.7% (40/696)	2.6% (6/230)	4.3% (48/1128)	3.5% (97/2760)	3.5% (19/538)	2.6% (22/855)	2.4% (54/2206)	3.7% (26/706)	1.9% (28/1500)	3.2% (15/462)	3.3% (15/457)
Q-wave	0.9% (62/7035)	0.7% (18/2545)	2.9% (20/696)	0.9% (2/230)	1.6% (18/1128)	1.4% (40/2760)	0.9% (5/538)	0.5% (4/855)	0.8% (17/2206)	0.8% (6/706)	0.7% (11/1500)	1.1% (5/462)	0.9% (4/457)
<b>Stent thrombosis</b>													
Per Protocol†	2.5% (174/7035)	1.5% (37/2545)	5.5% (38/696)	3.5% (8/230)	3.6% (41/1128)	3.7% (103/2760)	4.3% (23/535)	3.2% (27/855)	2.7% (60/2206)	3.5% (25/706)	2.3% (35/1500)	3.0% (14/462)	3.9% (18/457)
Definite/Probable Total‡	2.6% (184/7035)	1.4% (35/2545)	5.9% (41/697)	3.5% (8/230)	4.3% (49/1128)	4.0% (111/2760)	4.5% (24/538)	3.9% (33/855)	3.0% (67/2206)	4.2% (30/706)	2.5% (37/1500)	3.9% (18/463)	4.6% (21/457)

† Stent-related events

\* Includes non-stent-related deaths.

‡ Simple-use cases excluded one or more of the following: acute myocardial infarction (AMI); bifurcation, cardiogenic shock, chronic total occlusion, failed brachytherapy, vein graft stenting, in-stent restenosis, large vessel (RVD > 3.75 mm), left main disease/stenting, long lesion (> 28 mm), moderate/severe calcification, multivessel stenting, ostial lesion, renal disease, severe tortuosity, small vessel (RVD < 2.5 mm). Expanded-use cases are those not classified as simple-use.

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

- Angiographically confirmed - thrombus detected in any stent placed in the target vessel(s), or

- 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)

‡ Academic Research Consortium (ARC) definitions are provided in Section 9.7.1 (Cutlip DE, et al. Circulation 2007;115:2344).

Patients from two ARRIVE 1 sites are excluded from analysis due to GCP non-compliance.

The ARRIVE registries were not designed to compare the rate of low frequency events to a control group, nor were the registries designed to determine the rate of low frequency events with a pre-specified precision.

## 9.10 Sex-Specific Information from Pooled Analysis

In the United States, an estimated 17,600,000 adults age 20 and older (9.1% of men and 7.0% of women) suffer from coronary artery disease (CAD)<sup>15</sup>. Once diagnosed and treated, poorer revascularization outcomes have been reported in women due to smaller coronary arteries and increased prevalence of baseline comorbidities including advanced age, diabetes, hypertension, and peripheral vascular disease compared with men<sup>16,17</sup>.

To evaluate for sex-specific differences in long-term outcomes after percutaneous coronary intervention with the paclitaxel-eluting coronary stent, Boston Scientific conducted a retrospective pooled analysis of patients enrolled in five randomized trials (TAXUS I, II SR, IV, V *de novo*, and TAXUS ATLAS Workhorse), and two 'real world' registries (ARRIVE 1 and 2). Of the 2,271 patients pooled from the randomized trials, 665 (29.3%) were women. The proportion of women included in these studies is similar to that reported in literature.<sup>16,18</sup>

Despite significantly more adverse baseline risk factors in women (which was also observed in the TAXUS stent program, see Table 9.10.1), recent randomized trials of drug-eluting stents have demonstrated comparable safety and effectiveness outcomes in men and women<sup>19, 19</sup>. As shown in Table 9.10.2 and Figure 9.10.1, clinical event rates were generally similar between men and women. Information on bleeding is not available, as these data were not collected in the randomized trials. Overall, the influence of gender on long-term drug-eluting stent outcomes has not been fully elucidated.<sup>20</sup>

The clinical trials and registries conducted with paclitaxel-eluting stents were not designed or powered to specifically analyze for differences by sex/gender.

**Table 9.10.1: Baseline Clinical and Lesion Characteristics for Patients Receiving PES<sup>1</sup> in Randomized Trials**

Variable	Women (N=665)	Men (N=1606)	P value
Age, (yr)	64.9±11.1 (665)	61.4±10.7 (1606)	<0.001
Weight (lbs)	171.3±37.1 (397)	200.8±38.4 (970)	<0.001
<b>Cardiac History</b>			
Stable Angina	55.1% (365/663)	57.8% (929/1606)	0.22
Unstable Angina	37.4% (248/663)	31.5% (496/1577)	0.006
Silent Ischemia	10.1% (67/665)	12.5% (201/1602)	0.10

<sup>15</sup> Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart Disease and Stroke Statistics—2010 Update. A Report From the American Heart Association. *Circulation*. 2010;121(7):e46-e215.

<sup>16</sup> Berenguer A, Mainar V, Bordes P, Valencia J, Gomez S, Lozano T. Incidence and predictors of restenosis after sirolimus-eluting stent implantation in high-risk patients. *Am Heart J* 2005;150:536-42.

<sup>17</sup> Seth A, Serruys PW, Lansky A, et al. A pooled gender based analysis comparing the Xience V everolimus-eluting stent and the TAXUS paclitaxel-eluting stent in male and female patients with coronary artery disease, results of the SPIRIT II and SPIRIT III studies: two-year analysis. *EuroIntervention* 2010;5:788-27.

<sup>18</sup> Women and Heart Disease Fact Sheet, Women's Heart Foundation, [www.womensheart.org](http://www.womensheart.org)

<sup>19</sup> Lansky AJ, Costa RA, Mooney M, et al. Gender-based outcomes after paclitaxel-eluting stent implantation in patients with coronary artery disease. *J Am Coll Cardiol* 2005;45:1180-5.

<sup>20</sup> Mikhail GW, Gerber RT, Cox DA, et al. Influence of Gender on Long-Term Outcomes after Percutaneous Coronary Intervention with the Paclitaxel-Eluting Coronary Stent: Results of the 'TAXUS Woman' Analysis. *J Am Coll Cardiol Intv*. 2010;3:1250-9.

**Table 9.10.1: Baseline Clinical and Lesion Characteristics for Patients Receiving PES<sup>1</sup> in Randomized Trials**

Variable	Women (N=665)	Men (N=1606)	P value
Congestive Heart Failure	7.7% (51/664)	3.9% (63/1605)	<0.001
Previous Myocardial Infarction	25.8% (171/663)	31.8% (501/1577)	0.005
Previous Percutaneous Coronary Intervention	28.0% (174/622)	33.8% (500/1481)	0.01
Previous Coronary Artery Bypass Graft	5.9% (39/663)	9.3% (146/1577)	0.008
<b>Cardiac Risk Factors</b>			
Current Smoking	20.8% (138/665)	23.5% (378/1606)	0.15
Diabetes, Medically Treated	33.5% (223/665)	21.9% (352/1606)	<0.001
Hypertension	78.0% (519/665)	69.5% (1116/1606)	<0.001
Hyperlipidemia	71.7% (477/665)	72.8% (1166/1602)	0.61
History of Coronary Artery Disease	62.0% (372/600)	52.6% (762/1450)	<0.001
<b>Comorbid Conditions</b>			
Peripheral Vascular Disease	10.2% (63/ 615)	7.6% (112/1475)	0.046
Previous Transient Ischemic Attack	3.7% (7/187)	2.9% (14/475)	0.60
Previous Cerebrovascular Accident	6.0% (27/453)	3.8% (41/1080)	0.06
Renal Disease	5.1% (23/ 453)	3.9% (42/1080)	0.29
<b>Lesion Characteristics (by QCA)</b>			
Reference Vessel Diameter (mm)	2.63± 0.46 (659)	2.79± 0.52 (1597)	<0.001
Minimum Lumen Diameter (mm)	0.87± 0.35 (658)	0.89±0.35 (1569)	0.24
Diameter Stenosis (%)	67.09± 11.54 (658)	67.98±11.14 (1569)	0.09
Lesion Length (mm)	14.65±7.31 (659)	14.72±7.31 (1592)	0.84
Left Anterior Descending Vessel Location	39.0% (259/664)	41.2% (661/1603)	0.33
Bend > 45 degrees	23.8% (148/622)	22.2% (328/1476)	0.43
Tortuosity	11.9% (74/622)	10.5% (155/1475)	0.35
<b>Modified ACC/AHA Lesion Type</b>			
A	8.0% (50/622)	7.1% (105/1478)	0.45
B1	22.5% (140/622)	24.4% (361/1478)	0.35
B2	41.6% (259/622)	38.6% (571/1478)	0.20
C	27.8% (173/622)	29.8% (441/1478)	0.35
B2/C	69.5% (432/622)	68.5% (1012/1478)	0.66

<sup>1</sup> PES = paclitaxel-eluting stent. The TAXUS NIRx stent was utilized in the TAXUS I and TAXUS II trials, the TAXUS Express stent was utilized in the TAXUS IV and TAXUS V de novo trials, and the TAXUS Liberté stent was utilized in the TAXUS ATLAS Workhorse trial.

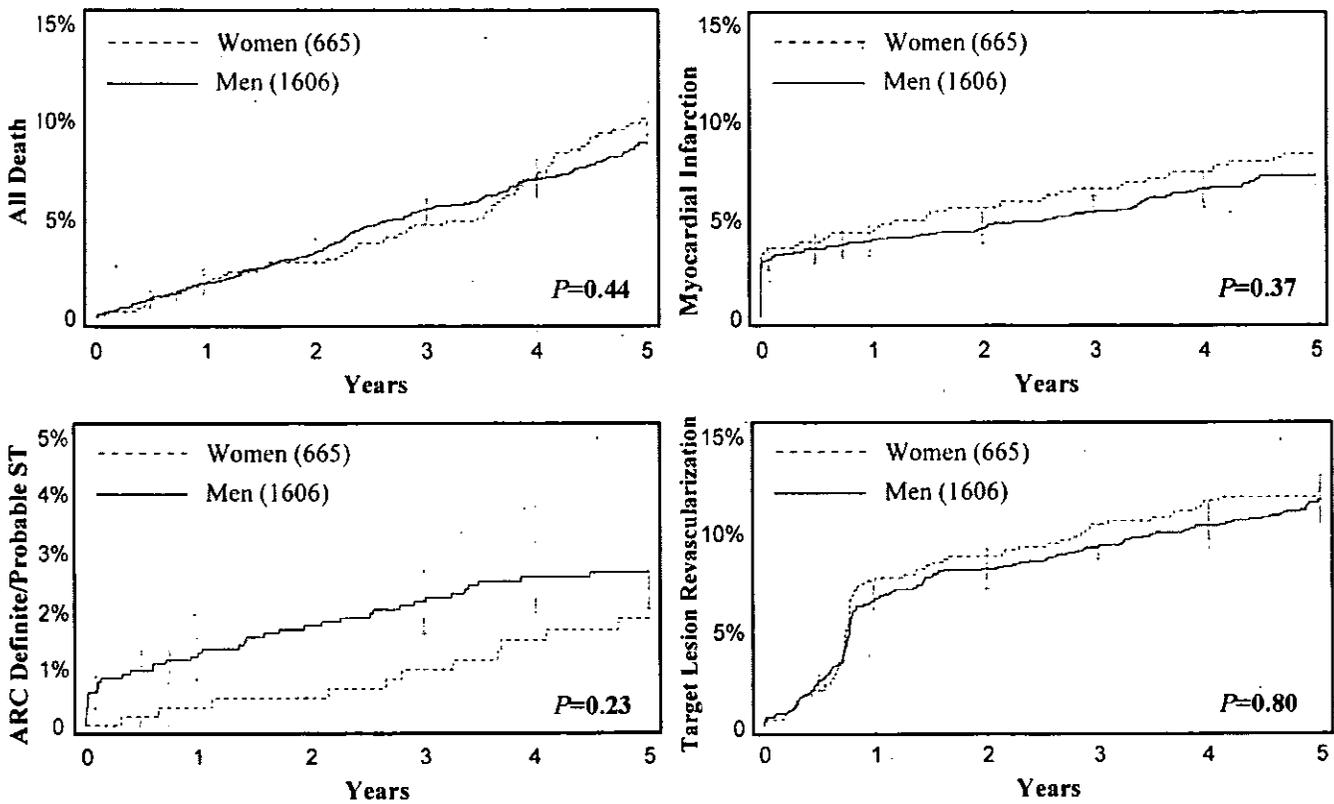
Numbers are % (count/sample size) or mean ± standard deviation (n). P values for continuous variables were calculated by the Student t-test and for categorical variables were calculated by the Chi-square test. Abbreviations: ACC=American College of Cardiology; AHA=American Heart Association; PES= paclitaxel-eluting stent; QCA=quantitative coronary angiography.

**Table 9.10.2: Clinical Outcomes at 5 Years for Patients Receiving PES in Randomized Trials**

Variable	Male (N=1606)	Female (N= 665)
TVR, Overall	19.8% (291/1470)	20.8% ( 124/595)
TLR, Overall	11.9% (175/1470)	12.4% (74/595)
TLR, PCI	10.5% (155/1470)	11.8% (70/595)
TLR, CABG	1.6% (23/1470)	1.0% (6/595)
Non-TLR	10.2% (150/1470)	11.4% (68/595)

**Table 9.10.2: Clinical Outcomes at 5 Years for Patients Receiving PES in Randomized Trials**

Variable	Male (N=1606)	Female (N= 665)
Non-TLR, PCI	7.8% (114/1470)	8.7% (52/595)
Non-TLR, CABG	2.8% (41/1470)	3.0% (18/595)
Total Death	9.1% (134/1470)	10.4% (62/595)
Cardiac Death or MI	11.3% (166/1470)	12.3% (73/595)
Cardiac Death	4.6% (68/1470)	5.0% (30/595)
MI	7.4% (109/1470)	8.7% (52/595)
Q-wave MI	1.8% (27/1470)	1.2% (7/595)
Non-Q-wave MI	5.8% (85/1470)	7.6% (45/595)
ARC Stent Thrombosis Definite or Probable	2.9% (40/1360)	2.0% (11/541)
Definite	2.1% (29/1360)	1.1% (6/541)
Probable	1.0% (13/1360)	0.9% (5/541)



**Figure 9.10.1: Kaplan-Meier Estimates of 5-year Cumulative Rates of Clinical Outcomes for Women versus Men for Patients Receiving Paclitaxel-eluting Stents in the Randomized Trials**

## 10 Individualization of Treatment

See also **Precautions - Section 5.6; Use in Special Populations and Section 5.7, Lesion/Vessel Characteristics.**

The risks and benefits should be carefully considered for each patient before use of the TAXUS<sup>®</sup> Express<sup>2®</sup> Stent System. Patient selection factors to be assessed should include a judgment regarding risk of prolonged antiplatelet therapy. For Elective PCI Procedures, based on randomized clinical trial protocols, a P2Y<sub>12</sub> inhibitor should be given for at least 6 months after paclitaxel-eluting stent (PES) implantation and ideally up to 12 months in patients who are not at high risk of bleeding. For PCI in ST-elevated MI Patients, a P2Y<sub>12</sub> inhibitor should be given for at least 12 months; however if the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by P2Y<sub>12</sub> inhibitor therapy, earlier discontinuation should be considered. Aspirin should be administered concomitantly with the P2Y<sub>12</sub> inhibitor and then continued indefinitely. Stenting is generally avoided in those patients at heightened risk of bleeding (e.g., those patients with recently active gastritis or peptic ulcer disease) in which anticoagulation therapy would be contraindicated.

Premorbid conditions that increase the risk of poor initial results or the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed.

## 11 Patient Counseling Information

Physicians should consider the following in counseling patients about this product:

- Discuss the risks associated with stent placement.
- Discuss the risks associated with a paclitaxel-eluting stent.
- Discuss the risks/benefits issues for this particular patient.
- Discuss alteration to current lifestyle immediately following the procedure and over the long term.

The following information is included in the package (or on-line) for physicians to provide to their patients.

- A Patient Information Guide which includes information on coronary artery disease, the implant procedure and the TAXUS Express<sup>2</sup> Stent System.
- A Patient Implant Card that includes both patient information and stent implant information.
- An angioplasty and stent education guide (available online or by request) which includes information on coronary artery disease, the implant procedure, and frequently asked questions.

## 12 How Supplied

**STERILE:** This product is sterilized with ethylene oxide gas. It is intended for single use only. Do not resterilize. Non-pyrogenic. Do not use if package is opened or damaged.

**CONTENTS** for (1) TAXUS Express<sup>2</sup> or TAXUS Express<sup>2</sup> Atom™ Over-the-Wire Stent System

- One (1) TAXUS Express<sup>2</sup> Over-the-Wire Stent System
- One (1) e-Directions for Use Manual
- One (1) Patient Guide with Patient Implant Card

**CONTENTS** for (1) TAXUS Express<sup>2</sup> or TAXUS Express<sup>2</sup> Atom™ Monorail® Stent System

- One (1) TAXUS Express<sup>2</sup> Monorail Stent System
- One (1) e-Directions for Use Manual
- Two (2) CLIPIT® hypotube clips
- One (1) Flushing needle with luer fitting
- One (1) Patient Guide with Patient Implant Card

**STORAGE:** Protect from light. Do not remove from carton until ready for use. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature].

**DISPOSAL INSTRUCTIONS:** After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

## **13 Operators Instructions**

### **13.1 Inspection Prior to Use**

Carefully inspect the sterile package before opening. Do not use after the "Use By" date. If the integrity of the sterile package has been compromised prior to the product "Use By" date (e.g. damage of the package), contact your local Boston Scientific representative for return information. Do not use if any defects are noted.

**NOTE:** At any time during use of the Monorail® Stent System, if the stainless steel proximal shaft has been bent or kinked, do not continue to use the catheter.

### **13.2 Materials Required (not included in Stent System package)**

#### **Quantity Material**

Appropriate guide catheter (see Table 1-1, TAXUS® Express<sup>2</sup> Stent System Product Description)

2-3 20 ml (cc) syringe

1,000u / 500cc Normal heparinized saline

1 ≤ 0.014 in. / 0.36 mm guidewire

1 Rotating hemostatic valve

Diluted contrast medium 1:1 with normal heparinized saline

1 Inflation device

1 Torque device

1 Pre-deployment dilation catheter

1 Three-way stopcock

1 Appropriate arterial sheath

### **13.3 Preparation**

#### **13.3.1 Packaging Removal**

##### **Step Action**

1. Carefully remove the delivery system from its protective tubing for preparation of the delivery system. When using a Monorail system, do not bend or kink hypotube during removal.
2. Remove the product mandrel and stent protector by grasping the catheter just proximal to the stent (at the proximal balloon bond site), and with the other hand, grasp the stent protector and gently remove distally. If unusual resistance is felt during product mandrel and stent protector removal, do not use this product and replace with another. Follow product returns procedure for the unused device.
3. A Monorail Catheter may be coiled once and secured using the coil clip (CLIPIT<sup>®</sup>) provided in the catheter package. Only the proximal shaft should be inserted into the CLIPIT device; the clip is not intended for the distal end of the catheter.

**NOTE: Care should be taken not to kink or bend the shaft upon application or removal of the coil clip.**

### **13.3.2 Guidewire Lumen Flush**

#### **Step Action**

1. (Over-the-Wire only) Flush stent system guidewire lumen with normal heparinized saline through the back port of the manifold.
2. (Monorail<sup>®</sup> system only) Flush stent system guidewire lumen with normal heparinized saline using the flushing needle supplied for the Monorail system at the distal end.
3. Verify that the stent is positioned between the proximal and distal balloon markers. Check for bends, kinks and other damage. Do not use if any defects are noted.

**NOTE: Avoid manipulation of the stent during flushing of the guidewire lumen, as this may disrupt the placement of the stent on the balloon.**

### **13.3.3 Balloon Preparation**

#### **Step Action**

1. Stent contact with any fluid is not recommended, as there is a possibility of initiating drug release. However, if it is absolutely necessary to flush the stent with saline, contact time should be limited (1 minute maximum).
2. Prepare inflation device/syringe with diluted contrast medium.
3. Attach inflation device/syringe to stopcock; attach to inflation port. Do not bend the hypotube when connecting to inflation device/syringe.
4. With tip down, orient stent system vertically.
5. Open stopcock to stent system; pull negative for 15 seconds; release to neutral for contrast fill.
6. Close stopcock to stent system; purge inflation device/syringe of all air.
7. Repeat steps 4 through 6 until all air is expelled. If bubbles persist, do not use product.
8. If a syringe was used, attach a prepared inflation device to stopcock.
9. Open stopcock to stent system.
10. Leave on neutral.

### **13.3.4 Delivery Procedure**

#### **Step Action**

1. Prepare the vascular access site according to standard PTCA practice.

2. Predilate the lesion/vessel with appropriate diameter balloon.
3. Maintain neutral pressure on inflation device attached to stent system.
4. Backload stent system onto proximal portion of guidewire while maintaining guidewire position across target lesion.
5. Fully open rotating hemostatic valve to allow for easy passage of the stent and prevent damage to the stent.
6. Carefully advance the stent system into the hub of the guide catheter. When using a Monorail<sup>®</sup> system, be sure to keep the hypotube straight. Ensure guide catheter stability before advancing the stent system into the coronary artery.

**NOTE:** If unusual resistance is felt before the stent exits the guide catheter, do not force passage. Resistance may indicate a problem, and use of excessive force may result in stent damage or stent dislodgment from the balloon. Maintain guidewire placement across the lesion, and remove the stent system and guide catheter as a single unit.

7. Advance the stent system over the guidewire to target lesion under direct fluoroscopic visualization. Utilize the proximal and distal radiopaque balloon markers as a reference point. If the position of the stent is not optimal, it should be carefully repositioned or removed (See also **Precautions - 5.12, Stent System Removal**). The inside edges of the marker bands indicate both the stent edges and balloon shoulders. Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion segment of the vessel.

**NOTE:** If unusual resistance is felt at any time during lesion access before stent implantation, the stent system and the guide catheter should be removed as a single unit. (See also **Precautions - 5.12, Stent System Removal**).

8. Sufficiently tighten the rotating hemostatic valve. The stent is now ready to be deployed.

### 13.3.5 Deployment Procedure

#### Step Action

1. Inflate the delivery system expanding the stent to a minimum pressure of 9 atm (nominal pressure). Higher pressure may be necessary to optimize stent apposition to the arterial wall. Accepted practice generally targets an initial deployment pressure that would achieve a stent inner diameter of about 1.1 times the reference vessel diameter (see Table 13-1). Balloon pressure must not exceed rated burst pressure of 18 atm. (see Table 13-1).
2. Maintain inflation pressure for 15-30 seconds for full expansion of the stent.
3. Deflate balloon by pulling negative pressure on inflation device until balloon is fully deflated.
4. Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall contact should be verified through routine angiography or

intravascular ultrasound (IVUS).

5. If stent sizing/apposition requires optimization, readvance the stent system balloon, or another high-pressure, non-compliant balloon catheter of the appropriate size, to the stented area using standard angioplasty techniques.
6. Inflate the balloon to the desired pressure while observing under fluoroscopy. Deflate the balloon (refer to product labeling and/or Table 13-1 for proper stent inflation pressure).
7. If more than one TAXUS<sup>®</sup> Express<sup>®</sup> Stent is needed to cover the lesion and balloon treated area, it is recommended to allow for approximately 4 mm of stent-to-stent overlap, to avoid the potential for gap restenosis, the stents be adequately overlapped. To ensure that there are no gaps between stents, the balloon marker bands of the second TAXUS Express Stent should be positioned inside of the deployed stent prior to expansion.
8. Reconfirm stent position and angiographic result. Repeat inflations until optimal stent deployment is achieved.

### 13.3.6 Removal Procedure

#### Step Action

1. Ensure balloon is fully deflated before delivery system withdrawal.
2. Fully open rotating hemostatic valve.
3. While maintaining guidewire position and negative pressure on inflation device, withdraw delivery system.
4. Monorail<sup>®</sup> catheters may be coiled once and secured using the coil clip (CLIPIT<sup>®</sup>) (see **Operator's Instructions - Section 13.3.1, Packaging Removal**).
5. Repeat angiography to assess the stented area. If an adequate expansion has not been obtained, exchange back to the original stent delivery catheter or exchange to another balloon catheter of appropriate balloon diameter to achieve proper stent apposition to the vessel wall.

### 13.4 Post-Deployment Dilatation of Stented Segments

**Precaution: Do not dilate the stent beyond the limits stated below.**

Nominal Stent Diameter	Dilatation Limits
2.25 mm – 3.5 mm	4.25 mm
4.0 mm	5.75 mm

All efforts should be taken to assure that the stent is not under-dilated. If the deployed stent size is still inadequate with respect to vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. The stent may be further expanded using a low-profile, high-pressure, and non-compliant balloon catheter. If this is required, the stented segment should be re-crossed carefully with a prolapsed guidewire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

### 13.5 In Vitro Information

#### 13-1. Typical TAXUS<sup>®</sup> Express<sup>2</sup><sup>®</sup> Stent System Compliance

Pressure (Atm)		2.25 mm Stent I.D. (mm)	2.50 mm Stent I.D. (mm)	2.75 mm Stent I.D. (mm)	3.00 mm Stent I.D. (mm)	3.50 mm Stent I.D. (mm)	4.00 mm Stent I.D. (mm)
9.0	Stent Nominal	2.31	2.56	2.75	2.99	3.48	4.07
10.0		2.35	2.62	2.81	3.06	3.56	4.13
11.0		2.39	2.67	2.87	3.13	3.63	4.20
12.0		2.43	2.72	2.92	3.18	3.70	4.26
13.0		2.46	2.76	2.97	3.24	3.75	4.32
14.0		2.50	2.79	3.01	3.28	3.81	4.36
15.0		2.53	2.82	3.04	3.33	3.85	4.40
16.0		2.55	2.85	3.08	3.36	3.89	4.44
17.0		2.57	2.88	3.10	3.39	3.93	4.48
18.0*		2.59*	2.90*	3.13*	3.42*	3.97*	4.52*

\* Rated Burst Pressure. DO NOT EXCEED.

## 14 Warranty

Boston Scientific Corporation (BSC) warrants that reasonable care has been used in the design and manufacture of this instrument. **This warranty is in lieu of and excludes all other warranties not expressly set forth herein, whether express or implied by operation of law or otherwise, including, but not limited to, any implied warranties of merchantability or fitness for a particular purpose.** Handling, storage, cleaning and sterilization of this instrument as well as other factors relating to the patient, diagnosis, treatment, surgical procedures, and other matters beyond BSC's control directly affect the instrument and the results obtained from its use. BSC's obligation under this warranty is limited to the repair or replacement of this instrument and BSC shall not be liable for any incidental or consequential loss, damage, or expense directly or indirectly arising from the use of this instrument. BSC neither assumes, nor authorizes any other person to assume for it, any other or additional liability or responsibility in connection with this instrument. **BSC assumes no liability with respect to instruments reused, reprocessed or re-sterilized and makes no warranties, express or implied, including but not limited to merchantability or fitness for a particular purpose, with respect to such instruments.** NIRx<sup>™</sup> is a trademark and NIR<sup>®</sup> is a registered trademark of Medinol Ltd., Jerusalem, Israel.

# Boston Scientific

Boston Scientific Corporation  
One Boston Scientific Place  
Natick, MA 01760-1537  
USA  
USA Customer Service 888-272-1001

EU Authorized Representative:  
Boston Scientific International S.A.  
55 avenue des Champs Pierreux  
TSA 551101  
92729 NANTERRE CEDEX  
FRANCE

A N G I  T E C H