

TAXUS[®] Express²™
and TAXUS Express² Atom™

Paclitaxel-Eluting Coronary Stent System
Monorail® 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.

DIRECTIONS FOR USE

CONFIDENTIAL

**Boston
Scientific**

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1 TAXUS™ Express2™ and TAXUS Express2 Atom™ Paclitaxel-Eluting Coronary Stent System

The TAXUS Express² (2.50 mm - 4.0 mm) and TAXUS Express² Atom (2.25 mm) Paclitaxel-Eluting Coronary Stent Systems (hereinafter referred to as TAXUS Express² Stent System) is a device / drug combination product comprised of two regulated components: a device (Express² Coronary Stent System) and a drug product (a formulation of paclitaxel contained in a polymer coating). The characteristics of the TAXUS Express² Stent System are described in Table 1-1.

Table 1-1. TAXUS Express² Stent System Product Description

	TAXUS Express² Monorail® Stent Delivery System	TAXUS Express² 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® stent	
Drug Product	A conformal coating of a polymer carrier loaded with 1 µg/mm ² paclitaxel in a slow release (SR)* formulation applied to the stent with a maximum nominal drug content of 282 µg on the largest stent (4.00x32mm).	
Delivery System		
Working Length	140 cm	135 cm
Delivery System Y-Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 25 cm from tip. Designed for guidewire ≤ 0.014"	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤ 0.014"
Stent Delivery	A compliant balloon, nominally 0.3 mm longer than the stent, with two radiopaque markers.	
Balloon		
Balloon Inflation	Nominal Inflation Pressure: 9 ATM; Rated Burst Inflation Pressure: 18 ATM	
Pressure		
Guide Catheter Inner Diameter	≥ 0.058"	≥ 0.066"
Catheter Shaft Outer Diameter	1.8F proximally, 2.7F distally (Ø up to 3.0mm, and 8-20mm long stents with Ø > 3.0mm) 2.0F proximally, 2.7F distally (24-32mm long stents with Ø > 3.0mm)	3.2F proximally, 2.7F distally

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

1.1 Device Component Description

The device component consists of the Express Stent mounted onto the Express² Stent Delivery System (SDS). The 2.25 – 4.00 mm diameter 316L stainless steel stents use two designs. The 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). For the 4.00 mm diameter stent, the nominal Paclitaxel content is 282 µg. This product contains no detectable latex.

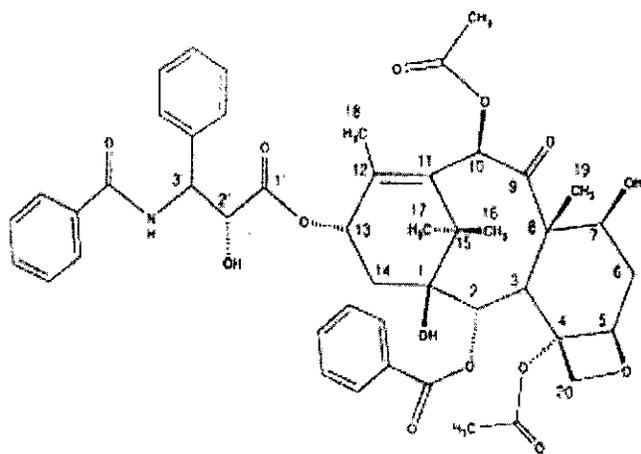
1.2 Drug Component Description

The stent component of the TAXUS Express² 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™ Express® Stent is paclitaxel. It is a white powder, isolated from a spectrum of Taxus species and hybrids. The chemical name of paclitaxel is: Benzenepropanoic acid, β-(benzoylamino)-α-hydroxy-, 6,12-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-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2aR- [2αα,4β,4aβ,6β,9α (αR*,βS*),11α,12α,12aα,12bα]]-. The chemical structure of paclitaxel is shown below.

Figure 1.1. The Chemical Structure of Paclitaxel

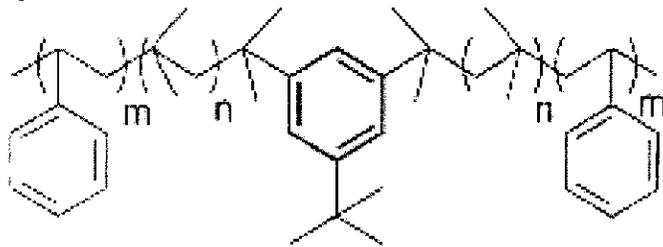


Paclitaxel is a diterpenoid with a characteristic taxane skeleton of 20 carbon atoms, a molecular weight of 853.91 g/mol and a molecular formula of C₄₇H₅₁NO₁₄. It is highly lipophilic, insoluble in water, but freely soluble in methanol, ethanol, chloroform, ethyl acetate and dimethyl sulfoxide.

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 (Mn-number average molecular weight) of 80,000 to 130,000 g/mol and a polydispersity index of 1.0 to 2.0. The polymer is mixed with the drug paclitaxel and then applied to the stents. There is no primer or topcoat layer. The drug/polymer coating is adhered to the entire surface (i.e, luminal and abluminal) of the stent. The structural formula for the polymer is shown below.

Figure 1.2. The Chemical Structure of Translute™ Polymer Carrier



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

1.2.3 Product Matrix and Paclitaxel Content

Table 1-2. TAXUS™ Express^{2™} 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	204
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™ Express²™ 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 Express² Paclitaxel-Eluting Coronary Stent System is indicated for improving luminal diameter for the treatment of de novo lesions in native coronary arteries ≥ 2.25 to ≤ 4.00 mm in diameter in lesions ≤ 28 mm in length, and within bare metal stent restenotic lesions ≥ 2.5 to ≤ 3.75 mm in diameter and ≤ 28 mm in length.

3 Contraindications

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

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

Coronary Artery Stenting is contraindicated for use in:

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

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. Additional data from longer-term follow-up in the randomized clinical trials on the TAXUS Stent and analyses of DES-related stent thrombosis are expected and should be considered in making treatment decisions as data become available.
- 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.

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.

The optimal duration of antiplatelet therapy, specifically clopidogrel, is unknown 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 ACC/AHA/SCAI 2005 Guideline for anti-thrombotic adjunctive therapies for Percutaneous Coronary Intervention (PCI), Section 5.2.1.

5.2.1 Oral Antiplatelet Therapy

Continuation of combination treatment with aspirin and clopidogrel after PCI appears to reduce rates of cardiovascular ischemic events. On the basis of randomized clinical trial protocols, aspirin 325 mg daily should be given for at least 6 months after paclitaxel-eluting stent (PES) implantation, after which daily chronic aspirin should be continued indefinitely at a dose of 75 to 162 mg. Likewise, clopidogrel

75 mg daily should be given for at least 6 months after PES implantation and ideally up to 12 months in patients who are not at high risk of bleeding. To reduce the incidence of bleeding complications associated with dual antiplatelet therapy, lower-dose aspirin (75 to 162 mg daily) is recommended for long-term therapy.

<http://www.acc.org/qualityandscience/clinical/guidelines/percutaneous/update/index.pdf>

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.

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 eluting polymer.

In the TAXUS V de novo study, the use of ≥ 2 planned TAXUS Stents (including overlapping and non-overlapping placement) in patients with single lesions >26mm by visual estimate was associated with a numerically higher rate of peri-procedural (≤ 30 days) non-Q-wave myocardial infarction (Non-Q wave MI; CK levels $> 2.0 \times$ 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 ≤ 30 days in either arm. In TAXUS V patients treated with ≥ 2 planned study stents in lesions >26mm who were MI-free at 30 days, there were 3 total deaths, 3 cardiac deaths, and 1 MI (0 Q-wave and 1 non-Q wave) in TAXUS patients (N= 102) through 2 years follow-up compared with 6 total deaths, 1 cardiac death, and 1 MIs (0 Q-wave and 1 non-Q wave) in BMS patients (N= 112). In TAXUS V patients treated with ≥ 2 planned stents in lesions >26mm by visual estimate and who had MI within 30 days (N= 11 TAXUS; N= 3 BMS), there were 0 deaths to 2 years, with 0 new MI events from 30 days to 2 years in either treatment arm.

In TAXUS V patients treated with ≥ 2 planned study stents in lesions >26mm, TAXUS patients had a reduced target vessel revascularization (TVR) rate (15.9%) compared to BMS patients (34.9%) through 2-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 periprocedural Non-Q wave MI. Updates to the product label will be made as additional information becomes available.

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™ Express® 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

Clinical studies of the TAXUS Express Stent did not find any differences in safety and effectiveness for male and female patients.

5.6.4 Ethnicity

Clinical studies of the TAXUS Express Stent did not include sufficient numbers of patients to assess for differences in safety and effectiveness due to ethnicity, either by individual category or when grouped by Caucasian and non-Caucasian.

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

Clinical studies of the TAXUS Express Stent did not find that patients age 65 years and over differed with regard to safety and effectiveness compared to younger patients.

7 Lesion/Vessel Characteristics

The safety and effectiveness of the TAXUS™ Express® Stent have not been established in the cerebral, carotid, or peripheral vasculature or the following patient populations:

- Patients 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 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 a recent acute myocardial infarction where there is evidence of thrombus or poor flow.
- 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.

9 Magnetic Resonance Imaging (MRI)

Through non-clinical testing, the TAXUS Express Stent has been shown to be MRI safe at field strengths of 3 Tesla or less, and a maximum whole body averaged specific absorption rate (SAR) of 2.0 W/kg for 15 minutes of MRI. The TAXUS Express Stent should not migrate in this MRI environment. MRI at 3T or less may be performed immediately following the implantation of the TAXUS Express Stent. Non-clinical testing has not been performed to rule out the possibility of stent migration at field strengths higher than 3 Tesla.

In this testing, the stent produced a maximum temperature rise of 0.65 degrees C at a maximum whole body averaged SAR of 2.0 W/kg for 15 minutes of MRI. The effect of heating in the MRI environment was similar for overlapping bare metal stents (2 to 5 mm overlap at the ends), made of the same stainless steel material and having the same stent design. The effect of heating in the MRI environment on stents with fractured struts is not known. The temperature rise of 0.65 degrees C for 15 minutes is calculated to result in an increase in cumulative drug release of 0.001% of the total dose. MR imaging quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.

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 Reuse Precaution Statement, Section 15.)
- 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 14.1-1, TAXUS™ Express²™ Stent System Stent and Balloon 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 5-1 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 5-1 System Deflation Time Specifications

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

*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™ 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.
- 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 detectable systemic levels, standard pharmacokinetic parameters were not estimated.

6.3 Drug Interactions

Paclitaxel is metabolized in the liver via CYP2C8 to 6- α -hydroxypaclitaxel and via CYP3A4 to 3'- p -hydroxypaclitaxel and 6- α , 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™ Express® Stent coated with 282 μ g 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 55 and 300 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 55 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[®] 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 I¹ is a randomized, double-blind, controlled feasibility Phase I study comparing the 1 µg/mm² SR formulation of the paclitaxel-eluting TAXUS[®] NIRx[™] Stent with the NIR[™] 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 protocol mandated clinical follow-up for 5 years after the index procedures has been finalized.

TAXUS II² 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

¹ Bullesfeld L, Gerckens U, Müller 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.
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.

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. Follow-up through 4 years is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing. For TAXUS II, results are only presented for the SR treatment group (Cohort I) and corresponding control (see section 9).

TAXUS IV³ is a randomized, double-blind, controlled pivotal Phase III U.S. study of the safety and performance of the SR formulation TAXUS[®] Express^{2™} 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[™] Stent or the uncoated Express[™] 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. Follow-up through 4 years is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

TAXUS V *de novo*⁴ is a randomized, double-blind, controlled expansion study of the safety and performance of the SR formulation TAXUS[®] Express^{2™} Paclitaxel-Eluting Coronary Stent in *de novo* lesions in small and large diameter vessels, as well as long lesions. TAXUS V *de novo* was designed to expand the data set beyond the standard-risk, *de novo* coronary artery lesions studied in the pivotal TAXUS IV trial. 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. Follow-up through 2 years is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

TAXUS V – In-stent restenosis (ISR) was a randomized, open-label, controlled study of the safety and performance of the 1 µg /mm² (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 end point for the study was the 9-month ischemia-driven TVR rate. Secondary end points 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 was performed at 1, 4, 9, 12, and 24 months post-procedure with yearly clinical follow-up through 5 years. Follow-up through 24 months is currently available.

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.

⁴ Stone GW, Ellis SG, Cannon L, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: A randomized controlled trial. *JAMA*. 2005;294(10):1215-1223.

Table 7.1: TAXUS Slow Release Formulation Trials

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

*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 sites in the 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 the Clinical Events Committee (CEC) with 100% of cardiac adverse event (AE) data verified against source documents.

8 Adverse Events

8.1 Observed Adverse Events

Observed adverse event experience comes from four clinical studies, TAXUS V *de novo*, IV, II, and I. Principal adverse events for these trials are shown in Table 8.1. 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 2 Years**		TAXUS V <i>de novo</i> to 2 Years**		TAXUS IV to 4 Years†		TAXUS II SR to 4 Years		TAXUS I to 5 Years	
	TAXUS Express	Brachy	TAXUS Express	Control	TAXUS Express	Control	TAXUS NIRx	Control	TAXUS NIRx	Control
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% (19/662)	2.5% (16/652)	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)	0.0% (0/30)
9-Month MACE, overall	11.1% (24/216)	20.1% (39/194)	15.0% (84/560)	21.2% (120/567)	8.5% (56/662)	15.0% (98/652)	NA	NA	3.2% (1/31)	10.0% (3/30)
Cardiac Death	0.0% (0/216)	0.5% (1/194)	0.5% (3/560)	0.9% (5/567)	1.4% (9/662)	1.1% (7/652)	NA	NA	0.0% (0/31)	0.0% (0/30)
MI	3.7% (8/216)	4.6% (9/194)	5.4% (30/560)	4.6% (26/567)	3.5% (23/662)	3.7% (24/652)	NA	NA	0.0% (0/31)	0.0% (0/30)
Q-Wave MI	0.5% (1/216)	0.0% (0/194)	0.5% (3/560)	0.2% (1/567)	0.8% (5/662)	0.3% (2/652)	NA	NA	NA	NA
Non-Q-Wave MI	3.2% (7/216)	4.6% (9/194)	4.8% (27/560)	4.4% (25/567)	2.7% (18/662)	3.4% (22/652)	NA	NA	NA	NA
TVR, Overall	9.7% (21/216)	17.5% (34/194)	12.1% (68/560)	17.3% (98/567)	4.7% (31/662)	12.0% (78/652)	NA	NA	3.2% (1/31)	10.0% (3/30)

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 2 Years**		TAXUS V <i>de novo</i> to 2 Years**		TAXUS IV to 4 Years†		TAXUS II SR to 4 Years		TAXUS I to 5 Years	
	TAXUS Express	Brachy	TAXUS Express	Control	TAXUS Express	Control	TAXUS NIRx	Control	TAXUS NIRx	Control
TLR, Overall*	6.0% (13/216)	13.9% (27/194)	8.6% (48/560)	15.7% (89/567)	3.0% (20/662)	11.3% (74/652)	NA	NA	0.0%(0/31)	10.0% (3/30)
Non-TLR, Overall*	4.6% (10/216)	6.2% (12/194)	4.8% (27/560)	4.2% (24/567)	1.7% (11/662)	1.1% (7/652)	NA	NA	3.2% (1/31)	0.0% (0/30)
1-Year MACE	16.4% (35/214)	24.9% (47/189)	18.9% (105/556)	25.9% (146/563)	10.6% (70/662)	19.8% (129/652)	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% (159/544)	14.7% (95/645)	25.2% (161/640)	14.2% (18/127)	26.9% (36/134)	3.2% (1/31)	10.0% (3/30)
3-Year MACE	NA	NA	NA	NA	18.9% (116/614)	29.0% (178/613)	15.7% (20/127)	29.8% (39/131)	3.2% (1/31)	10.0% (3/30)
4-Year MACE	NA	NA	NA	NA	22.1% (133/601)	31.5% (190/604)	19.5% (24/123)	30.8% (41/133)	3.2% (1/31)	13.3% (4/30)
Cardiac Death	NA	NA	NA	NA	3.0% (18/601)	4.0% (24/604)	1.6% (2/123)	2.3% (3/133)	0.0% (0/31)	0.0% (0/30)
MI	NA	NA	NA	NA	7.2% (43/601)	7.1% (43/604)	4.9% (6/123)	6.8% (9/133)	0.0% (0/31)	0.0% (0/30)
Q-Wave MI	NA	NA	NA	NA	1.3% (8/601)	1.0% (6/604)	1.6% (2/123)	3.0% (4/133)	NA	NA
Non-Q-Wave MI	NA	NA	NA	NA	6.0% (36/601)	6.5% (39/604)	4.1% (5/123)	3.8% (5/133)	NA	NA
TVR, Overall	NA	NA	NA	NA	16.0% (96/601)	26.0% (157/604)	16.3% (20/123)	24.1% (32/133)	3.2% (1/31)	13.3% (4/30)
TLR, Overall*	NA	NA	NA	NA	7.8% (47/601)	20.2% (122/604)	7.3% (9/123)	15.0% (20/133)	0.0% (0/31)	10.0% (3/30)
Non-TLR, Overall*	NA	NA	NA	NA	9.0% (54/601)	9.3% (56/604)	5.7% (7/123)	10.5% (14/133)	3.2% (1/31)	3.3% (1/30)
5-Year MACE	NA	NA	NA	NA	NA	NA	NA	NA	9.7% (3/31)	13.3% (4/30)
Stent Thrombosis 4 Years	NA	NA	NA	NA	1.6% (9/579)	1.1% (6/569)	2.5% (3/119)	0.0% (0/129)	0.0% (0/31)	0.0% (0/30)
Stent Thrombosis 5 Years	NA	NA	NA	NA	NA	NA	NA	NA	0.0% (0/31)	0.0% (0/30)

* For TAXUS II rates reflect PCI only.

** After 2 years the TAXUS V study population was reduced to a pre-specified cohort, which consists 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 4 years, the safety population is comprised of 1290 (n=649 for TAXUS, n=641 for BMS).

Stent Thrombosis defined per protocol (See Section 9.4). NA= Not Applicable; variable and/or time point not calculated.

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

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

- Allergic/immunologic reaction to drug (paclitaxel or structurally-related compounds) or the polymer stent coating (or its individual components) or 316L stainless steel (or any of its components)
- Alopecia
- Anemia

- Blood product transfusion
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage or necrosis
- Myalgia / arthralgia
- Peripheral neuropathy

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

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9 Clinical Studies

1. Results of the TAXUS IV Pivotal Clinical Trial

Primary Objective: To demonstrate superiority of the TAXUS[®] Express[™] Stent compared to a matched uncoated control stent for reduction of the 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), and had documented angina pectoris or functional ischemia.

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

Follow-up included clinical assessments at 1, 4, and 9 months. In addition, patients agreed to annual telephone follow-up for clinical parameters through 5 years post-procedure. Follow-up through 2 years was available in 1238/1314 (94.2%) of patients. After the 2-year follow-up, the TAXUS IV study population was reduced to a pre-specified cohort, which consists of all patients who received a study stent at baseline (Safety Population). At 4 years, the safety population is comprised of 1290 (n=649 for TAXUS, n=641 for Control) and follow-up is available for 1230 patients (95.4%).

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

The primary endpoint data (9-months) and latest available follow-up (48 months) results are presented below (Table 9.1.1, Table 9.1.2, and Figure 9.1.1), as well as stent thrombosis data through 48 months (Table 9.1.3).

Table 9.1.1: TAXUS IV Clinical Results

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

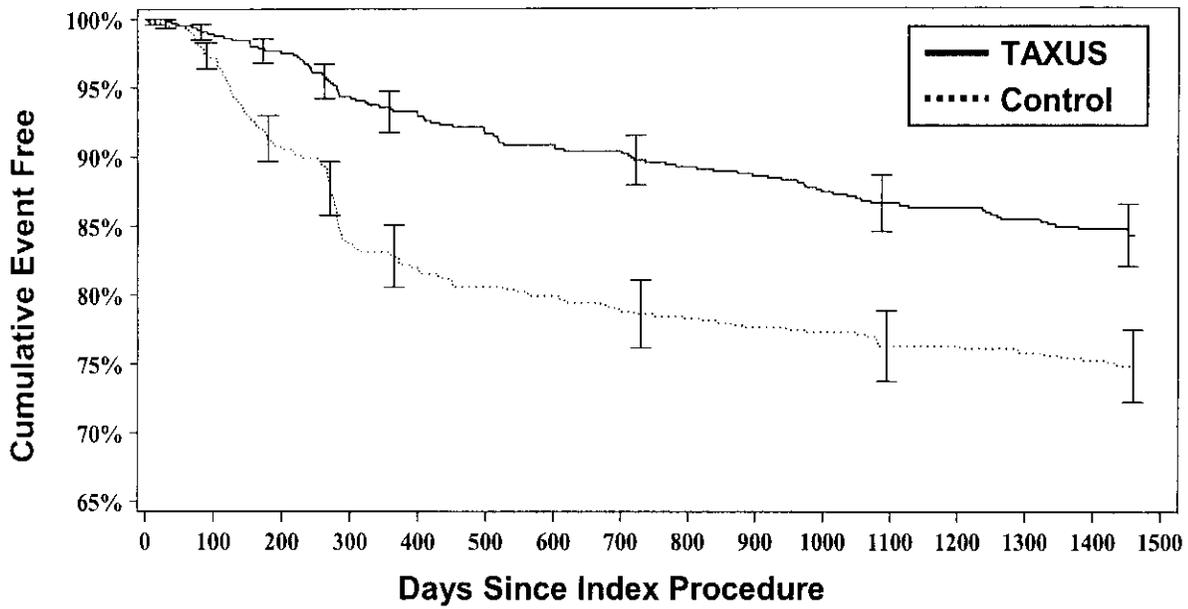
[§] 9-month primary endpoint.

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

P-values are not adjusted for multiple comparisons.

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

Figure 9.1.1: TAXUS IV Freedom from TVR to 4 Years, Event-Free Survival \pm 1.5 SE, Safety Population, All Patients (N=1290)



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

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

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 9.1.3. TAXUS IV Protocol Defined Stent Thrombosis* through 4 Years Safety Population

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

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

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

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

Numbers are % (Count/Sample Size).

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

P-values are not adjusted for multiple comparisons.

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

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[®] NIRx[™] Paclitaxel-Eluting Coronary Stent System (1 µg/mm² 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[®] NIRx[™] (SR) Stent or an uncoated NIR[™] 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. Follow-up through 48 months (+ 60 days) is currently available for 260/267 (97.4%) patients.

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).

The primary endpoint (6 months) data and latest available follow-up (48 months) results are presented below (Table 9.2.1 and Figure 9.2.1).

Table 9.2.1: TAXUS II Clinical Results

	6 months			4 years (latest available follow-up)		
	TAXUS (N=131)	Control (N=136)	P-Value	TAXUS (N=131)	Control (N=136)	P-Value
EFFICACY						
TVR, Overall	7.7% (10/130)	14.3% (19/133)	0.1148*	16.3% (20/123)	24.1% (32/133)	0.1212
TVR, TLR (PCI)	4.6% (6/130)	12.0% (16/133)	0.0432*	7.3% (9/123)	15.0% (20/133)	0.0515
TVR, CABG	0.8% (1/130)	0.8% (1/133)	1.0000*	4.1% (5/123)	4.5% (6/133)	0.8604
TVR, Non-TLR (PCI)	3.1% (4/130)	2.3% (3/133)	0.7203*	5.7% (7/123)	10.5% (14/133)	0.1590
Non-TLR, CABG	NA	NA	NA	NA	NA	NA
SAFETY						
Total Death	0.0% (0/131)	0.7% (1/136)	1.0000*	5.6% (7/126)	3.7% (5/134)	0.4835
Cardiac Death or MI	1.5% (2/130)	6.0% (8/133)	0.1029*	6.5% (8/123)	9.0% (12/133)	0.4531
Cardiac Death	0.0% (0/130)	0.8% (1/133)	1.0000*	1.6% (2/123)	2.3% (3/133)	1.0000*
MI	1.5% (2/130)	5.3% (7/133)	0.1724*	4.9% (6/123)	6.8% (9/133)	0.5203
Q-wave MI	0.0% (0/130)	1.5% (2/133)	0.4982*	1.6% (2/123)	3.0% (4/133)	0.6852*
Non-Q-wave MI	1.5% (2/130)	3.8% (5/133)	0.4470*	4.1% (5/123)	3.8% (5/133)	1.0000*
Per Protocol Stent Thrombosis	0.8% (1/131)	0.0% (0/136)	0.4906*	2.5% (3/119)	0.0% (0/129)	0.1090*
PRIMARY ENDPOINT						
Change in Neointimal Volume (IVUS) (%) [†]	7.85±10.0 2 (111)	23.56±1 8.57 (117)	<0.0001 [§]	NA	NA	NA

*Fisher's Exact test was used. The Chi-Square test for homogeneity or Student's t-test was used for all other p-values.

[§] Student's t-test was used.

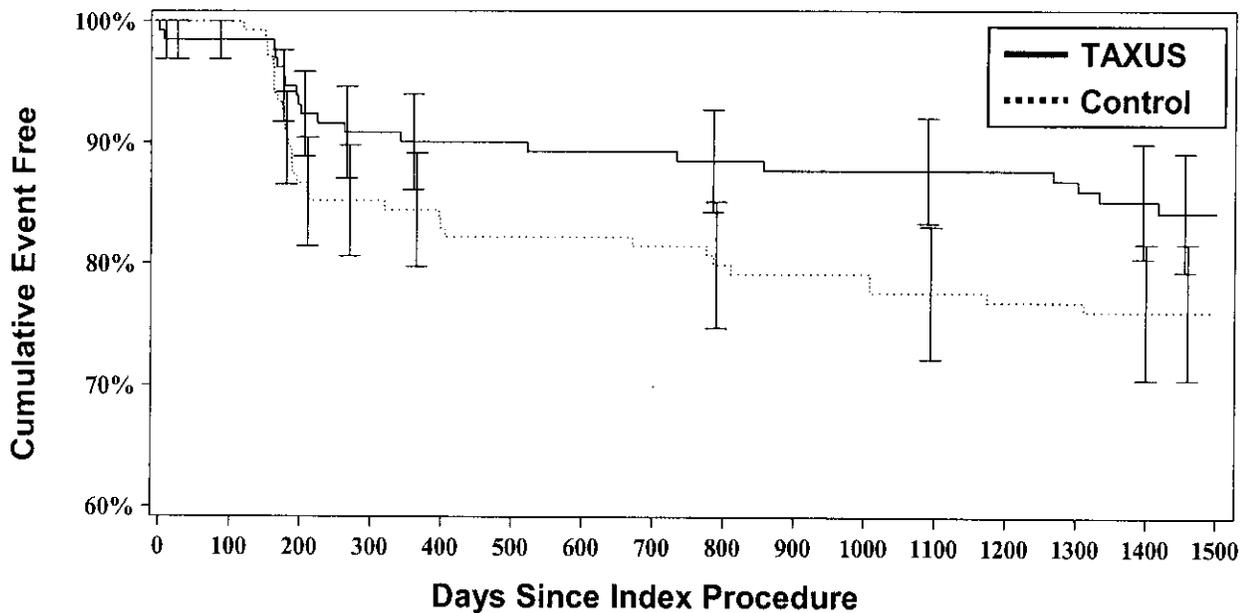
[†] Primary endpoint data are +/- standard deviation (count).

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 4 Years, Event-Free Survival \pm 1.5 SE, Safety Population (N=267)



	Event Rate	Event Free	P-value*
Control	23.9%	76.1%	0.0830
TAXUS	15.8%	84.2%	

* 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 /mm² 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. Clinical follow-up is available through 5 years. Angiography and IVUS were performed at the 6-month follow-up visit for all patients.

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 follow-up)		
	TAXUS (N=31)	Control (N=30)	P-Value	TAXUS (N=31)	Control (N=30)	P-Value
PRIMARY ENDPOINT						
MACE	0.0% (0/31)	0.0% (0/30)	Undef	9.7% (3/31)	13.3% (4/30)	0.7072*
EFFICACY						
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*
SAFETY						
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

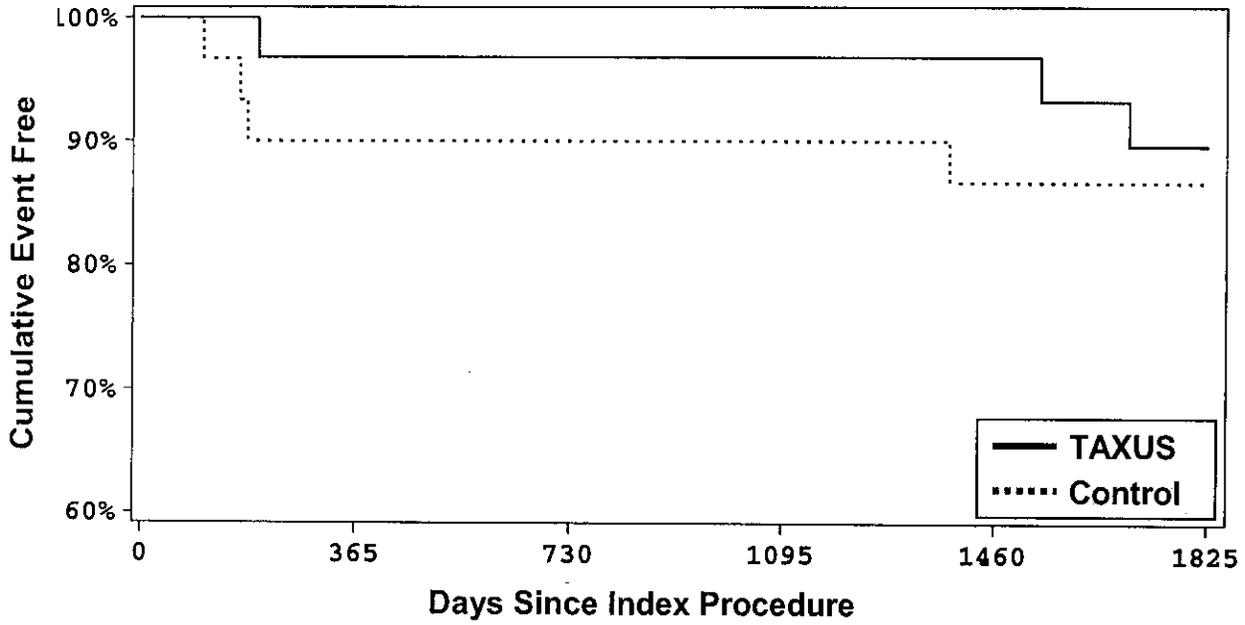
*Fisher's Exact test was used.

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.

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[®] Express^{2™} Stent compared to the uncoated Express Stent in long lesion lengths, small and large vessel diameters and with multiple overlapping stents in the treatment of de novo coronary artery lesions.

Design: This was a multicenter, prospective, randomized, double-blind study in patients at 66 U.S. sites. Eligible patients were those presenting for stenting of *de novo* lesions of a single, native coronary artery (RVD ≥ 2.25 and ≤ 4.00 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. ≥ 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 ≤ 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 ≥ 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 2 years is currently available in 1052/1108 (94.9%) of patients eligible for 2-year follow-up.

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

Patient subgroup characteristics are presented in Table 9.4.1. The primary endpoint data (9-months) and latest available follow-up (2 years) results are presented below for the overall population in Table 9.4.2 and Figure 9.4.1. The high-risk small vessel (2.25 mm stent diameter) and planned multiple stent subgroups and large vessel (4.0 mm stent diameter), are presented in Tables 9.4.3, 9.4.4 and 9.4.5 respectively.

Table 9.4.1: TAXUS V de novo Baseline Characteristics

	TAXUS	Control	P-Value*
Intent-to-Treat, All Patients (N=1156)			
Patients with Medically Treated Diabetes	31.7% (183/577)	29.9% (173/579)	0.5242
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
Patients with Implanted Stent Diameter of 2.25 mm, Intent-to-Treat (N=203)			
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
Patients with Implanted Stent Diameter of 4.0 mm (Large Vessel Subgroup) Intent-to-Treat (N=202)			
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
Patients with Lesion Length >26 mm by Visual Estimate and ≥2 Planned Stents Intent-to-Treat (N=233)			
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).

Table 9.4.2: TAXUS V de novo Clinical Results

	9 months (ITT Population)			2 years (latest available follow-up) (Safety Population)		
	TAXUS (N=577)	Control (N=579)	P-Value	TAXUS (N=575)	Control (N=571)	P-Value
EFFICACY						
TVR, Overall [§]	12.1% (68/560)	17.3% (98/567)	0.0184*	18.6% (101/542)	25.4% (138/544)	0.0074
TLR, Overall	8.6% (48/560)	15.7% (89/567)	0.0003*	13.3% (72/542)	21.5% (117/544)	0.0004
TLR, PCI	7.9% (44/560)	13.9% (79/567)	0.0011*	12.5% (68/542)	19.5% (106/544)	0.0018
TLR, CABG	0.7% (4/560)	1.8% (10/567)	0.1770*	0.7% (4/542)	2.4% (13/544)	0.0283
Non-TLR, Overall	4.8% (27/560)	4.2% (24/567)	0.6691*	7.9% (43/542)	8.6% (47/544)	0.6730
Non-TLR, PCI	4.5% (25/560)	3.2% (18/567)	0.2793*	7.2% (39/542)	6.8% (37/544)	0.7991
Non-TLR, CABG	0.4% (2/560)	1.1% (6/567)	0.2874*	0.9% (5/542)	1.8% (10/544)	0.1961

Table 9.4.2: TAXUS V de novo Clinical Results

	TAXUS (N=577)	Control (N=579)	P-Value		TAXUS (N=575)	Control (N=571)	P-Value
SAFETY							
Total Death	1.3% (7/559)	1.4% (8/566)	1.0000*		3.3% (18/541)	3.8% (21/548)	0.6539
Cardiac Death or MI	5.7% (32/560)	5.5% (31/567)	0.8973*		7.2% (39/542)	6.1% (33/544)	0.4545
Cardiac Death	0.5% (3/560)	0.9% (5/567)	0.7256*		1.7% (9/542)	1.5% (8/544)	0.8010
MI	5.4% (30/560)	4.6% (26/567)	0.5853*		5.9% (32/542)	4.8% (26/544)	0.4098
Q-wave MI	0.5% (3/560)	0.2% (1/567)	0.3712*		0.6% (3/542)	0.4% (2/544)	0.6863*
Non-Q-wave MI	4.8% (27/560)	4.4% (25/567)	0.7777*		5.4% (29/542)	4.4% (24/544)	0.4728
Per Protocol Stent Thrombosis	0.7% (4/557)	0.7% (4/562)	1.0000*		0.8% (4/529)	0.8% (4/530)	1.0000*

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

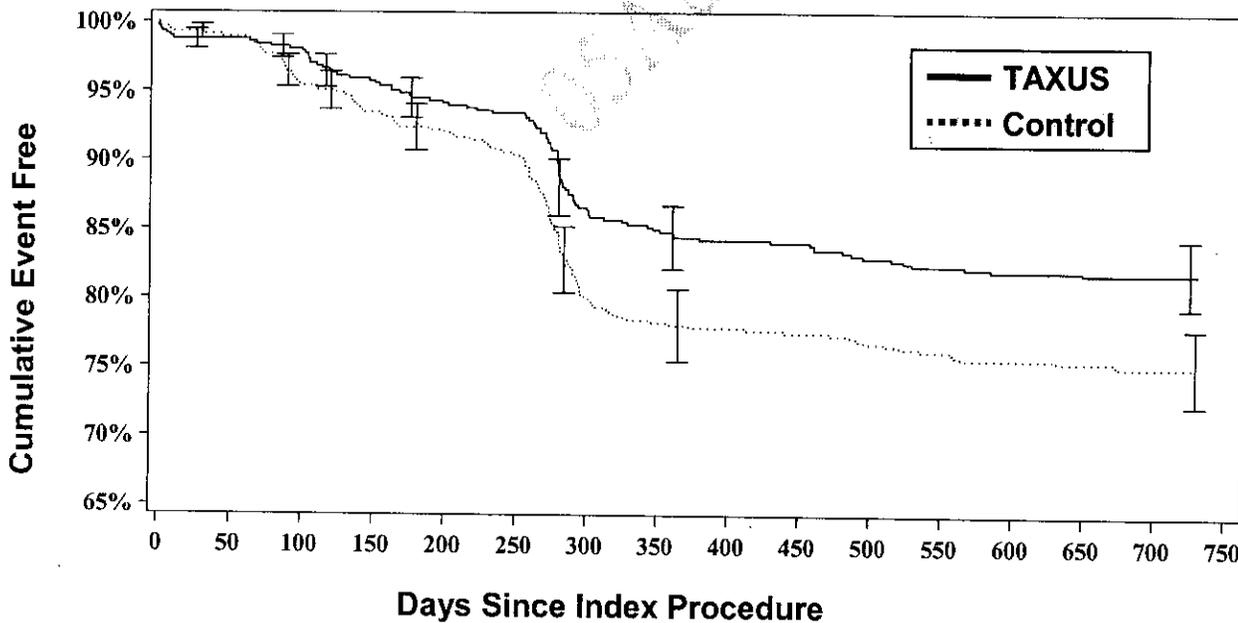
* P-values are two-sided from Fisher's exact test; p-values without * are from the Chi-square test.

§ 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 2 Years, Event-Free Survival ± 1.5 SE, Safety Population, All Patients (N=1146)



	Event Rate at 2 years	Event-Free Rate at 2 years	P-value*
Control	24.9%	75.1%	0.0053
TAXUS	18.2%	81.8%	

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

Table 9.4.3: TAXUS V de novo 2.25 mm Diameter Stent Clinical Results

	9 months (ITT Population)			2 years (latest available follow-up) (Safety Population)		
	TAXUS (N=108)	Control (N=95)	P-Value	TAXUS (N=108)	Control (N=95)	P-Value
EFFICACY						
TVR, Overall	16.0% (17/106)	24.7% (23/93)	0.1565*	25.0% (26/104)	34.1% (31/91)	0.1649
TLR, Overall	10.4% (11/106)	21.5% (20/93)	0.0332*	17.3% (18/104)	27.5% (25/91)	0.0876
TLR, PCI	9.4% (10/106)	19.4% (18/93)	0.0647*	16.3% (17/104)	24.2% (22/91)	0.1727
TLR, CABG	0.9% (1/106)	2.2% (2/93)	0.5999*	1.0% (1/104)	3.3% (3/91)	0.3408*
Non-TLR, Overall	8.5% (9/106)	8.6% (8/93)	1.0000*	12.5% (13/104)	13.2% (12/91)	0.8862
Non-TLR, PCI	8.5% (9/106)	6.5% (6/93)	0.7889*	12.5% (13/104)	9.9% (9/91)	0.5655
Non-TLR, CABG	0.0% (0/106)	2.2% (2/93)	0.2171*	1.0% (1/104)	3.3% (3/91)	0.3408*
SAFETY						
Total Death	1.9% (2/105)	2.1% (2/94)	1.0000*	5.8% (6/104)	4.4% (4/91)	0.7532*
Cardiac Death or MI	6.6% (7/106)	3.2% (3/93)	0.3420*	8.7% (9/104)	3.3% (3/91)	0.1204
Cardiac Death	1.9% (2/106)	1.1% (1/93)	1.0000*	3.8% (4/104)	1.1% (1/91)	0.3742*
MI	5.7% (6/106)	2.2% (2/93)	0.2876*	5.8% (6/104)	2.2% (2/91)	0.2878*
Q-wave MI	0.9% (1/106)	0.0% (0/93)	1.0000*	1.0% (1/104)	0.0% (0/91)	1.0000*
Non-Q-wave MI	4.7% (5/106)	2.2% (2/93)	0.4519*	4.8% (5/104)	2.2% (2/91)	0.4521*
Per protocol Stent Thrombosis	1.0% (1/104)	1.1% (1/92)	1.0000*	1.0% (1/99)	1.1% (1/88)	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 9.4.4: Patients with Lesion Length > 26 mm by Visual Estimate and ≥ 2 Planned Stents Clinical Results

	TAXUS (N=118)	Control (N=115)	P value
30 Days (ITT Population)			
EFFICACY			
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
SAFETY			
Total Death	0.0% (0/117)	0.0% (0/115)	Undef
Cardiac Death or MI	9.4% (11/117)	2.6% (3/115)	0.0502
Cardiac Death	0.0% (0/117)	0.0% (0/115)	Undef
MI	9.4% (11/117)	2.6% (3/115)	0.0502
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)	0.0834
Per Protocol Stent Thrombosis	0.0% (0/117)	0.0% (0/115)	Undef
Stent Thrombosis (ARC ⁵ definite/probable)	0.0% (0/117)	0.0% (0/115)	Undef
6-Months (ITT Population)			
EFFICACY			
TVR, Overall	12.9% (15/116)	24.8% (28/113)	0.0275
TLR, Overall	11.2% (13/116)	23.9% (27/113)	0.0145
TLR, PCI	9.5% (11/116)	21.2% (24/113)	0.0166
TLR, CABG	1.7% (2/116)	2.7% (3/113)	0.6806
Non-TLR, Overall	4.3% (5/116)	3.5% (4/113)	1.0000
Non-TLR, PCI	4.3% (5/116)	1.8% (2/113)	0.4461
Non-TLR, CABG	0.0% (0/116)	1.8% (2/113)	0.2424
SAFETY			
Total Death	0.9% (1/115)	2.6% (3/115)	0.6217
Cardiac Death or MI	10.3% (12/116)	4.4% (5/113)	0.1290
Cardiac Death	0.9% (1/116)	0.9% (1/113)	1.0000
MI	9.5% (11/116)	3.5% (4/113)	0.1068
Q-wave MI	0.9% (1/116)	0.0% (0/113)	1.0000
Non-Q-wave MI	8.6% (10/116)	3.5% (4/113)	0.1665
Per Protocol Stent Thrombosis	0.0% (0/115)	0.0% (0/112)	Undef
Stent Thrombosis (ARC definite/probable)	0.9% (1/115)	0.9% (1/112)	1.0000
1.5 Years (latest available follow-up) (Safety Population)			
EFFICACY			

⁵ "Academic Research Consortium (Circulation. 2007;115[17]:2344-2351)"

Table 9.4.4: Patients with Lesion Length > 26 mm by Visual Estimate and ≥ 2 Planned Stents Clinical Results

	TAXUS (N=118)	Control (N=115)	P value
TVR, Overall	15.9% (18/113)	34.9% (38/109)	0.0012
TLR, Overall	13.3% (15/113)	31.2% (34/109)	0.0013
TLR, PCI	11.5% (13/113)	28.4% (31/109)	0.0016
TLR, CABG	1.8% (2/113)	3.7% (4/109)	0.4395*
Non-TLR, Overall	6.2% (7/113)	8.3% (9/109)	0.5525
Non-TLR, PCI	5.3% (6/113)	4.6% (5/109)	0.8041
Non-TLR, CABG	0.9% (1/113)	3.7% (4/109)	0.2063*
SAFETY			
Total Death	2.7% (3/112)	5.3% (6/113)	0.4989*
Cardiac Death or MI	13.3% (15/113)	4.6% (5/109)	0.0238
Cardiac Death	2.7% (3/113)	0.9% (1/109)	0.6218*
MI	10.6% (12/113)	3.7% (4/109)	0.0453
Q-wave MI	0.9% (1/113)	0.0% (0/109)	1.0000*
Non-Q-wave MI	9.7% (11/113)	3.7% (4/109)	0.0719
Per Protocol Stent Thrombosis	0.0% (0/109)	0.0% (0/107)	Undef
Stent Thrombosis (ARC definite/probable)	0.9% (1/110)	0.9% (1/107)	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 9.4.5: TAXUS V de novo Large Vessel Subgroup (4.0mm diameter stent) Clinical Results

	9 months (ITT Population)			2 years (latest available follow-up) (Safety Population)		
	TAXUS (N=99)	Control (N=103)	P-Value	TAXUS (N=99)	Control (N=103)	P-Value
EFFICACY						
TVR, Overall	4.3% (4/93)	7.9% (8/101)	0.3775*	9.0% (8/89)	13.8% (13/94)	0.3044
TLR, Overall	0.0% (0/93)	5.0% (5/101)	0.0603*	4.5% (4/89)	5.3% (5/94)	1.0000*
TLR, PCI	0.0% (0/93)	5.0% (5/101)	0.0603*	4.5% (4/89)	5.3% (5/94)	1.0000*
TLR, CABG	0.0% (0/93)	0.0% (0/101)	Undef	0.0% (0/89)	0.0% (0/94)	Undef
Non-TLR, Overall	4.3% (4/93)	4.0% (4/101)	1.0000*	5.6% (5/89)	11.7% (11/94)	0.1453
Non-TLR, PCI	4.3% (4/93)	4.0% (4/101)	1.0000*	5.6% (5/89)	11.7% (11/94)	0.1453
Non-TLR, CABG	0.0% (0/93)	0.0% (0/101)	Undef	0.0% (0/89)	0.0% (0/94)	Undef
SAFETY						
Total Death	1.1% (1/94)	2.0% (2/101)	1.0000*	3.4% (3/89)	6.1% (6/98)	0.5018*
Cardiac Death or MI	3.2% (3/93)	6.9% (7/101)	0.3351*	4.5% (4/89)	7.4% (7/94)	0.4010
Cardiac Death	0.0% (0/93)	1.0% (1/101)	1.0000*	1.1% (1/89)	1.1% (1/94)	1.0000*
MI	3.2% (3/93)	5.9% (6/101)	0.5009*	3.4% (3/89)	6.4% (6/94)	0.4983*
Q-wave MI	0.0% (0/93)	0.0% (0/101)	Undef	0.0% (0/89)	0.0% (0/94)	Undef
Non-Q-wave MI	3.2% (3/93)	5.9% (6/101)	0.5509*	3.4% (3/89)	6.4% (6/94)	0.4983*
Per Protocol Stent Thrombosis	0.0% (0/93)	0.0% (0/100)	Undef	0.0% (0/88)	0.0% (0/92)	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 ≥ 2.5 and ≤ 3.75 mm) with a target lesion ≤ 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.

The primary endpoint data (9 months) and latest available follow-up (24 months) 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)			2 years (latest available follow-up) (Safety Population)		
	TAXUS (N=220)	Brachy (N=201)	P-Value	TAXUS (N=217)	Brachy (N=193)	P-Value
EFFICACY						
TVR, Overall[§]	9.7% (21/216)	17.5% (34/194)	0.0206 ^a -2.3% ^b	16.7% (35/209)	27.6% (51/185)	0.0095

Table Table 9.5.1: TAXUS V ISR Clinical Results

TLR, Overall	6.0% (13/216)	13.9% (27/194)	0.0071	9.6% (20/209)	21.6% (40/185)	0.0009
TLR, PCI	4.2% (9/216)	12.4% (24/194)	0.0023	7.2% (15/209)	20.5% (38/185)	0.0001
TLR, CABG	2.3% (5/216)	2.6% (5/194)	1.0000*	2.9% (6/209)	3.2% (6/185)	0.8300
Non-TLR, Overall	4.6% (10/216)	6.2% (12/194)	0.4851	9.1% (19/209)	10.3% (19/185)	0.6923
Non-TLR, PCI	2.8% (6/216)	3.6% (7/194)	0.6318	5.7% (12/209)	6.5% (12/185)	0.7577
Non-TLR, CABG	1.9% (4/216)	2.6% (5/194)	0.7409*	3.3% (7/209)	3.8% (7/185)	0.8161
SAFETY						
Total Death	0.0% (0/216)	0.5% (1/193)	0.4719*	1.0% (2/210)	1.1% (2/185)	1.0000*
Cardiac Death or MI	3.7% (8/216)	5.2% (10/194)	0.4740	4.8% (10/209)	7.6% (14/185)	0.2491
Cardiac Death	0.0% (0/216)	0.5% (1/194)	0.4732*	0.5% (1/209)	1.1% (2/185)	0.6025*
MI	3.7% (8/216)	4.6% (9/194)	0.6352	4.3% (9/209)	6.5% (12/185)	0.3363
Q-wave MI	0.5% (1/216)	0.0% (0/194)	1.0000*	0.5% (1/209)	0.5% (1/185)	1.0000*
Non-Q-wave MI	3.2% (7/216)	4.6% (9/194)	0.4654	3.8% (8/209)	6.5% (12/185)	0.2302
Per Protocol Stent thrombosis**	1.4% (3/216)	NA	NA	1.9% (4/208)	NA	NA

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

^a Primary Endpoint at 9 months.

^a p-value for two-sided Z test

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

Decision rule:

- 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.

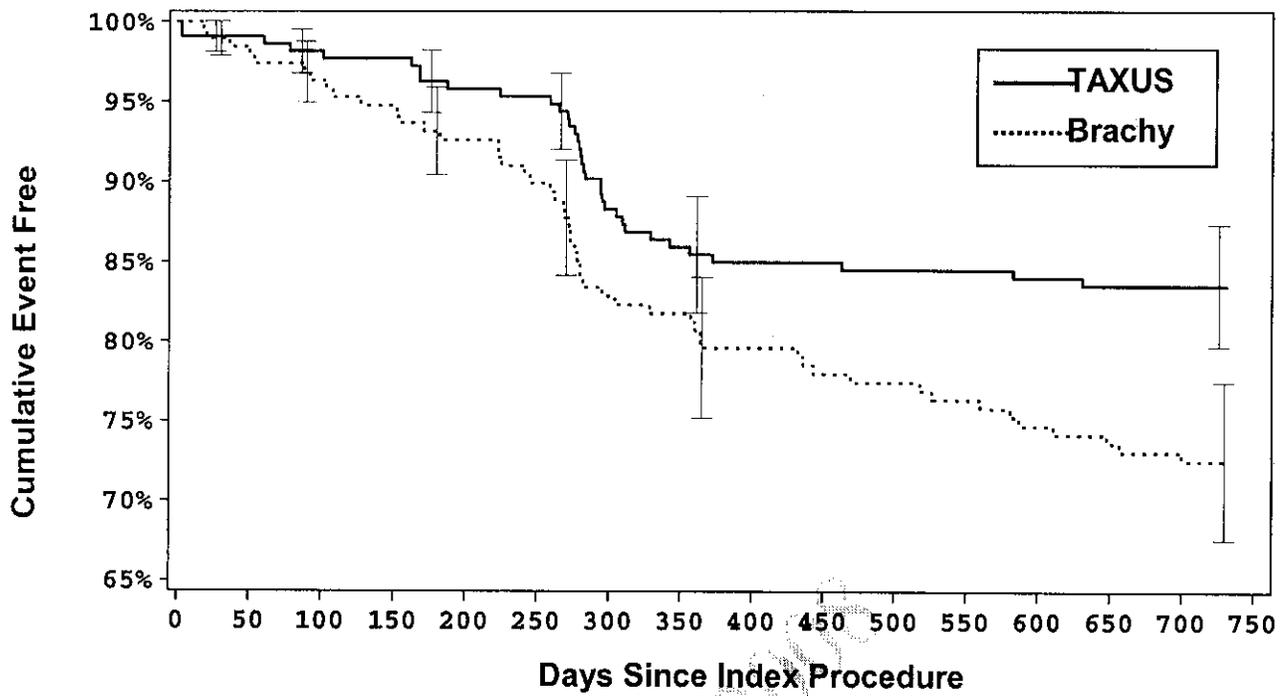
P-values are not adjusted for multiple comparisons.

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)

Figure 9.5.1: TAXUS V ISR Freedom from TVR to 2 Years, Event-Free Survival \pm 1.5 SE, Safety Population, All Patients (N=410)



	Event Rate	Event Free	P-value*
Brachy	27.5%	72.5%	0.0086
TAXUS	16.5%	83.5%	

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

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

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

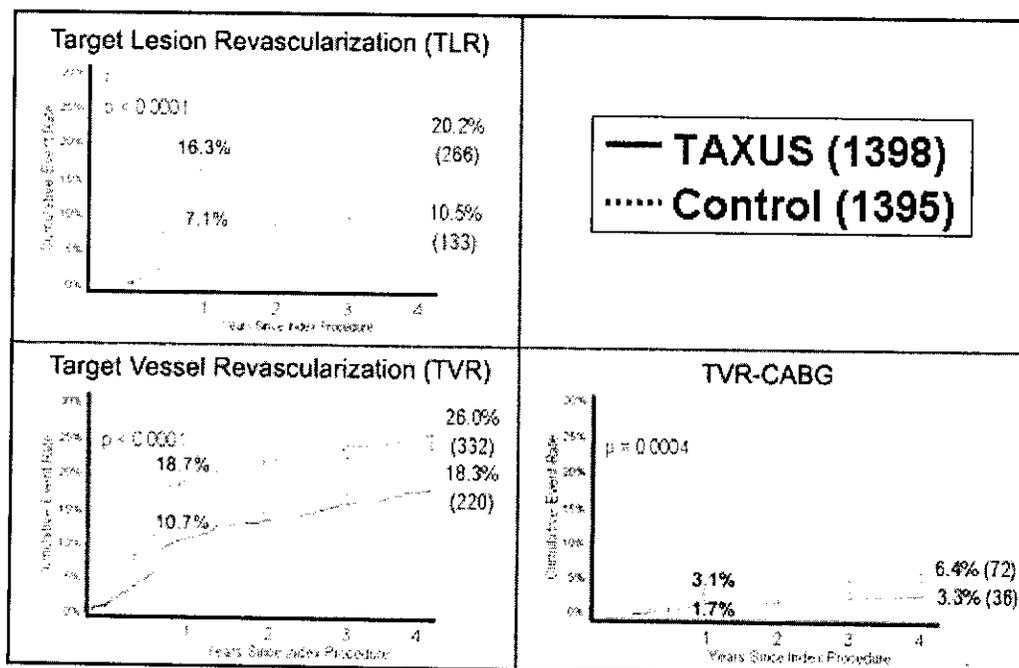
In order to better estimate the incidence of low frequency events or outcomes in various specific patient subgroups, a patient level pooled analysis was conducted of all randomized, blinded, controlled trials comparing TAXUS SR versus its respective bare metal control group. Data from the TAXUS I, II-SR, 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 4 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 to 5 years, TAXUS II and IV to 4 years, TAXUS V de novo to 2 years). Follow-up was 95.6% complete at the end of 4 years.

Table 9.6.1: 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
TAXUS	1398	1388	1365	1341	779	749
BMS	1395	1387	1369	1349	779	758

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 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 4 year follow-up. This difference is predominantly driven by a 48% reduction in revascularizations within the target lesion (stented segment plus 5 mm proximal and distal 'ge), as shown in Figure 9.6.1.

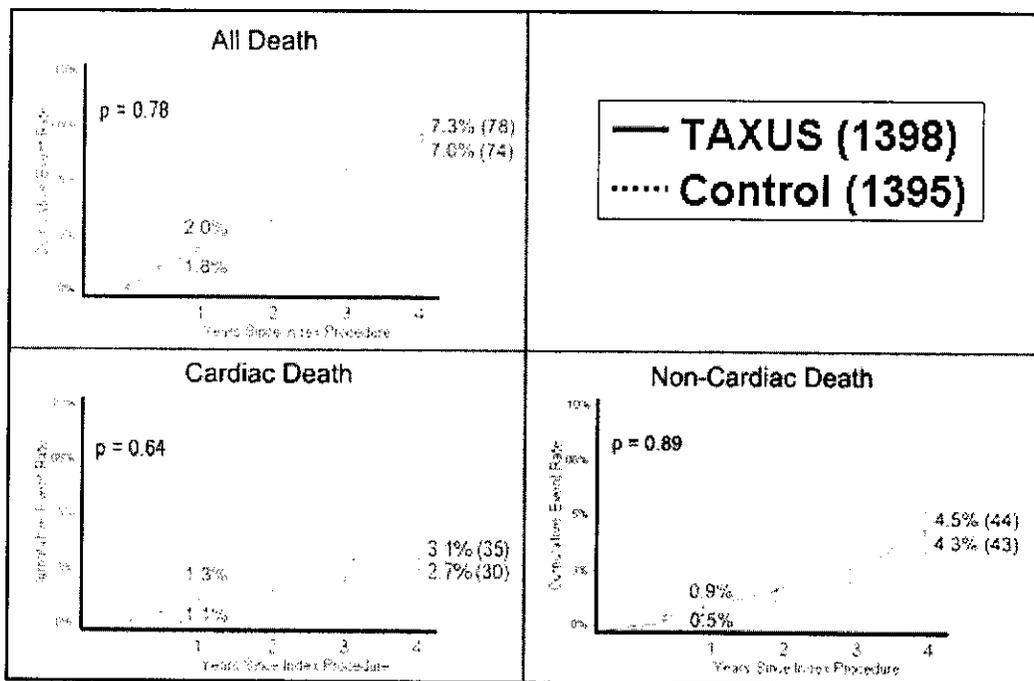
Figure 9.6.1: Efficacy – Target Vessel Revascularization (TVR) in TAXUS pooled analysis (TAXUS I, II-SR, IV, V de novo; N=2793)



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.

The TAXUS stent is more effective than bare metal stents in reducing the need for revascularization, and as shown in Figure 9.6.2, 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. All death as well as its individual components is well-balanced between groups with no significant differences.

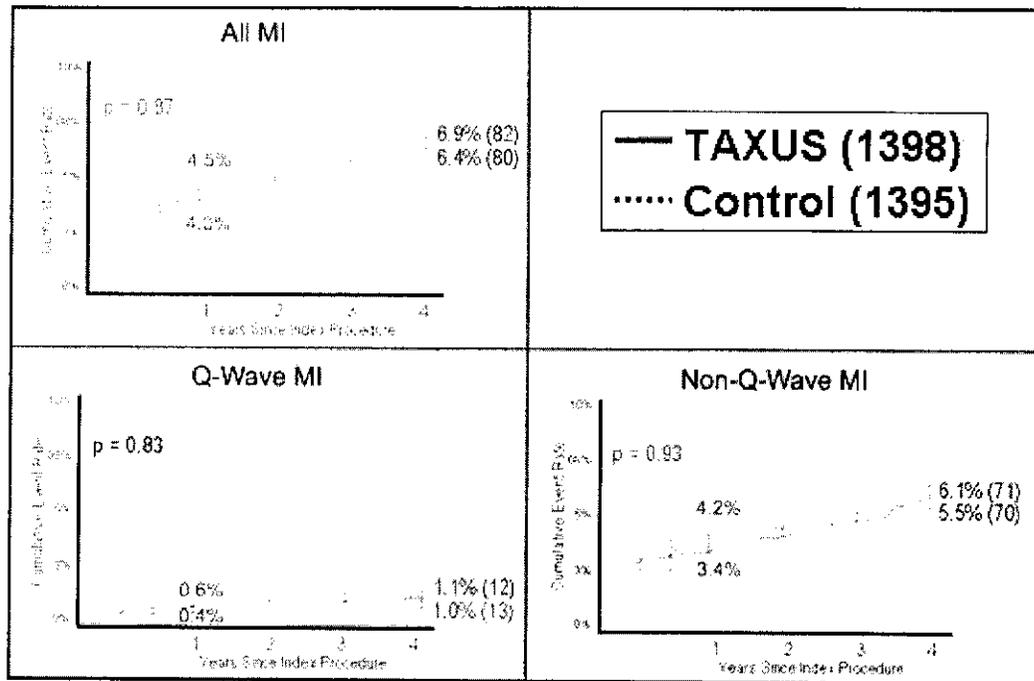
Figure 9.6.2: Safety – Mortality in TAXUS pooled analysis (TAXUS I, II-SR, IV, V de novo; N=2793)



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.

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 are well-balanced between the TAXUS and BMS Control groups.

Figure 9.6.3: Safety – Myocardial Infarction (MI) in TAXUS pooled analysis (TAXUS I, II-SR, IV, V de novo; N=2793)



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

9.6.1 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)⁶. Stent thrombosis was defined (per protocol) in the TAXUS IV pivotal trial as the occurrence of any of the following:

1. Clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis:
 - a) Angiographic documentation of a complete occlusion (TIMI flow 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

⁶ 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.

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:

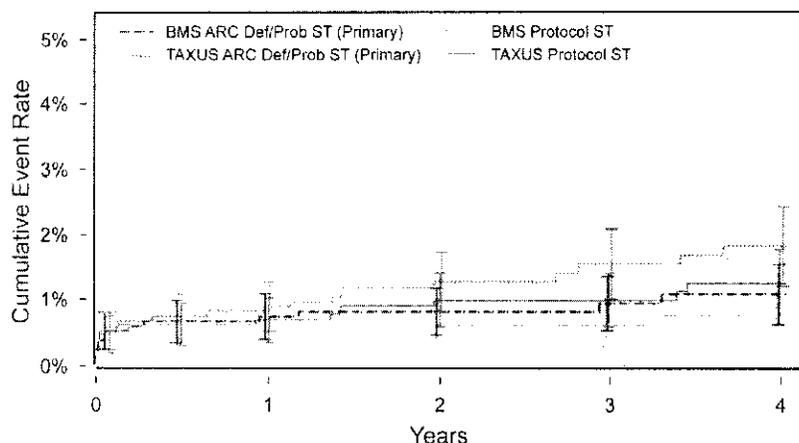
- **Definite stent thrombosis**
Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation.
- **Probable stent thrombosis**
Probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:
 - 1) Any unexplained 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 stent thrombosis**
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

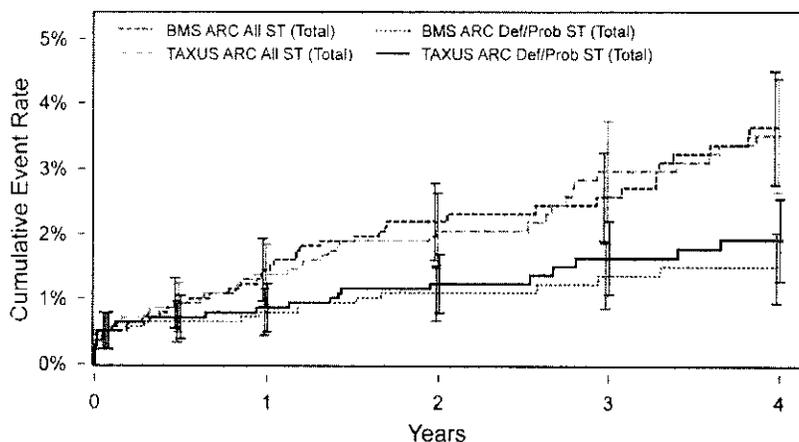
- Primary - Stent thrombosis after index procedure without any preceding target lesion revascularization
- Secondary - Stent thrombosis after index procedure with intervening target lesion revascularization
- Total - Primary plus secondary stent thromboses

The uniform ARC definitions are complex, and there is an ongoing debate as to whether it is more appropriate to use *Primary* (TLR-censored, to reveal the intrinsic behaviors of the drug-eluting stent [DES] and bare metal stent [BMS], rather than the known risks of brachytherapy) or *Total* (to capture even post-brachytherapy stent thromboses in BMS) when assessing stent thrombosis rates. While the broadest definitions are the most sensitive, they lack specificity. The largest differences in stent thrombosis estimates between the DES and BMS cohorts are thus seen using either the original (Protocol) or the ARC Definite+Probable Primary definitions. The addition of *Possible* or the inclusion of post-TLR (post-brachytherapy in the BMS arm) in the ARC *Total* definition may obscure any differences between TAXUS and BMS. In the interest of completeness, however, all definition variants are reported for the pooled TAXUS data and are displayed below (Figure 9.6.4). There is no statistical difference between the TAXUS and the control in cumulative stent thrombosis, according to any definition of stent thrombosis, and in any time window. However, for very late stent thrombosis (VLST, after 1 year), a small numerical excess can be seen with TAXUS versus BMS control that did not reach statistical significance using the protocol definition (p=0.06) or the Primary ARC Definite plus Probable definition (p=0.08).

Figure 9.6.4: Stent thrombosis Rates for the TAXUS vs. BMS Pooled Analysis (TAXUS I, SR, IV, V de novo; N=2793) vs. BMS by Protocol and ARC Definitions



	4-yr cum	After 1 year [‡] BMS vs. TAXUS
ARC Definite/ Probable Primary [§]	C 1.1% (13) T 1.8% (21)	3 vs 9 (0.5%) Log-rank p=0.08
Protocol	C 0.8% (10) T 1.3% (16)	1 vs 6 (0.4%) Log-rank p=0.06



	4-yr cum	After 1 year [‡] BMS vs. TAXUS
ARC All, Total [†]	C 3.6% (41) T 3.5% (39)	21 vs 20 (-0.1%) Log-rank p=0.79
ARC Definite/ Probable Total	C 1.5% (18) T 1.9% (22)	7 vs 10 (0.3%) Log-rank p=0.45

		Protocol	ARC	ARC	ARC	Protocol	ARC	ARC	ARC
			Def/Prob Primary [§]	Def/Prob Total	All, Total [†]		Def/Prob Primary [§]	Def/Prob Total	All, Total [†]
			Year 1			Year 2			
TAXUS	# Entered	1398	1498	1343	1498	1337	1335	1335	1336
	# Events	10	12	12	19	4	5	5	9
BMS	# Entered	1395	1395	1350	1395	1342	1334	1332	1341
	# Events	9	10	11	20	0	1	4	10
			Year 3			Year 4			
TAXUS	# Entered	1217	1216	1288	1217	733	730	730	730
	# Events	0	2	3	7	2	2	2	4
BMS	# Entered	1238	1231	1293	1233	750	746	747	747
	# Events	0	1	2	3	1	1	1	8

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.

[†] P=NS

[‡] Includes definite, probable and possible. ARC definitions are provided in Section 9.5.1

[§] 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 definite/probable primary.

9.6.2 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), 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 9.7 ARRIVE Clinical Registry.

Table 9.6.2: Pooled TAXUS SR Clinical Results for Medically Treated Diabetic Patients (TAXUS I, II-SR, IV, and V de novo)

	9 months			4 years (latest available follow-up*)		
	TAXUS (N=356)	Control (N=359)	P-Value	TAXUS (N=356)	Control (N=359)	P-Value
EFFICACY						
TVR, Overall	8.7% (30)	16.2% (57)	0.002	26.0% (72)	32.0% (100)	0.0127
TLR, Overall	5.5% (19)	14.8% (52)	<0.0001	13.5% (40)	25.1% (81)	<0.0001
TLR, PCI	5.3% (18)	12.0% (42)	0.0013	12.9% (38)	19.6% (66)	0.0030
TLR, CABG	0.3% (1)	2.8% (10)	0.0067	0.6% (2)	6.7% (18)	0.0004
Non-TLR, Overall	4.3% (15)	2.3% (8)	0.1290	15.3% (40)	12.9% (34)	0.3648
Non-TLR, PCI	3.2% (11)	1.7% (6)	0.2072	9.7% (29)	11.3% (28)	0.7733
Non-TLR, CABG	1.2% (4)	0.6% (2)	0.4012	6.6% (13)	3.3% (8)	0.2242
SAFETY						
Total Death	2.0% (7)	2.2% (8)	0.8205	9.1% (25)	10.7% (28)	0.7819
Cardiac Death or MI	4.3% (15)	6.7% (24)	0.1516	10.1% (29)	9.6% (32)	0.7259
Cardiac Death	1.1% (4)	1.4% (5)	0.7594	4.4% (13)	3.4% (11)	0.6433
MI	3.4% (12)	5.3% (19)	0.2114	7.2% (20)	7.4% (24)	0.5761
Q-wave MI	0.3% (1)	0.6% (2)	0.5747	0.3% (1)	1.1% (3)	0.3362
Non-Q-wave MI	3.1% (11)	4.8% (17)	0.2600	7.0% (19)	6.2% (21)	0.7857
Stent Thrombosis	0.6% (2)	1.4% (5)	0.2668	1.2% (3)	1.4% (5)	0.5028

Ian-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.

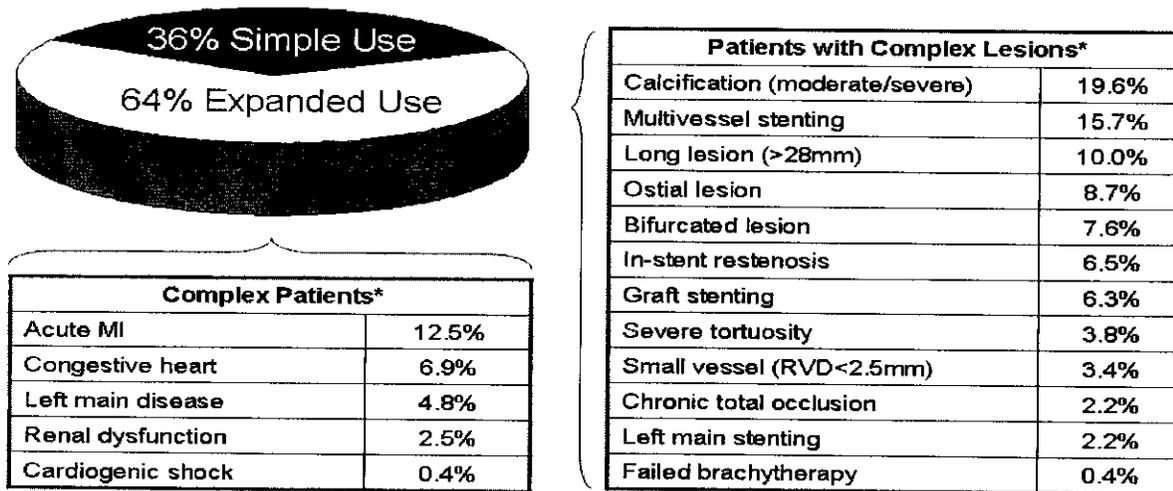
*There were a total of 356 TAXUS and 359 Control patients in the analysis, including 183 TAXUS and 173 Control from TAXUS V with only 2 year follow up data.

9.7 ARRIVE Clinical Registry

The TAXUS Clinical Trial program was complemented by the ARRIVE real-world registry program. The goals of this program are: (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 patients (2631/7307) had single vessel, single stent lesions that met the inclusion criteria of TAXUS IV, the pivotal trial for TAXUS approval (Figure 9.7.1). The remaining 64% of all patients from ARRIVE 1 and ARRIVE 2 (4676/7307) had more complex disease. Thus, 64% of ARRIVE patients represent an expanded use of the TAXUS stent not formally assessed within the pivotal dataset.

Figure 9.7.1: Lesion complexity in ARRIVE 1 and 2 combined (N=7307)



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

9.7.1 ARRIVE 1

ARRIVE 1 is a peri-approval FDA-mandated safety surveillance program designed to compile real-world use, safety, and clinical outcomes data for the TAXUS[®] Express^{2™} 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. Events were adjudicated by an independent CEC.

Patient follow-up out to 2 years has been completed in the entire patient population. The analysis population at 2 years includes 2487 patients with 3631 lesions, 2958 vessels, and 4068 stents. Baseline demographics and procedural characteristics (Table 9.6.1), as well as safety results (Table 9.7.2), 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 9.6.1). These results are also displayed below (Table 9.7.3).

8/14/2018

Table 9.7.1: ARRIVE 1 - Baseline Demographics and Procedural Characteristics

Analysis Group: 2487 patients; 3631 lesions; 2958 vessels; 4068 stents

Patient Demographics		Procedural Characteristics	
		Vessels Treated	
Male	68.0% (1691/2487)	1	82.7% (2057/2487)
Age (yr)	63.7±11.5 (2487)	2	15.7% (391/2487)
Diabetes	30.4% (756/2487)	≥3	1.6% (39/2487)
Oral Medication Treated	24.5% (610/2487)	Target Vessels	
Insulin Treated	9.8% (243/2487)	RCA	33.2% (1204/3631)
Multi-vessel Disease	38.7% (962/2487)	LAD	35.6% (1292/3631)
Prior MI	36.8% (916/2487)	CX	24.6% (894/3631)
Prior PCI	36.1% (889/2465)	LM	1.8% (66/3631)
Prior CABG	20.8% (517/2483)	Graft	4.8% (174/3631)
Lesion Characteristics		Stenting	
Reference Vessel Diameter (mm)	3.0±0.4	Direct stenting (per lesion)	35.1% (1275/3630)
Lesion Length (mm)	16.1±9.3	TAXUS stents per patient	1.6±0.9
Lesion Type		Patients with >1 TAXUS stent	41.5%
A	13.4% (485/3627)	Stent length per patient (mm)	30.9±20.0
B1	34.5% (1251/3627)	Stent length per lesion (mm)	21.3±10.7
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 9.7.2: ARRIVE 1 Principal Safety Results Summary to 2 years,
All Patients, Binary Proportion Analysis**

Analysis Group: 2487 patients; 3631 lesions; 2958 vessels; 4068 stents	
	Event Rate
TAXUS-related cardiac event (Cardiac death, MI, TAXUS-related re-intervention)	9.9% (230/2319)
Cardiac death	1.3% (30/2319)
MI	2.4% (55/2319)
Q-wave MI	0.8% (19/2319)
Non Q-wave MI	1.5% (34/2319)
TAXUS-related re-intervention	8.2% (189/2319)
All Death [†]	6.0% (140/2319)

Numbers are % (Count/Sample Size).

[†] Includes non-stent-related deaths.

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

**Table 9.7.3: Stent Thrombosis by Time Interval in ARRIVE 1
Binary Proportion Analysis (N=2487)**

	Per protocol*	ARC Definite & Probable Primary [§]	ARC Definite & Probable Total [§]
0 days - 1 day	0.2% (4/2487)	0.2% (4/2487)	0.2% (4/2487)
2 days - 30 days	1.2% (29/2477)	1.2% (29/2477)	1.2% (29/2477)
31 days - 180 days	0.3% (7/2421)	0.2% (6/2421)	0.2% (6/2421)
181 days - 365 days	0.5% (13/2387)	0.6% (14/2387)	0.6% (14/2387)
366 days - 730 days	0.6% (14/2280)	0.6% (13/2280)	0.7% (16/2280)
0 days - 730 days	2.9% (67/2319)	2.8% (66/2319)	3.0% (69/2319)

* 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 9.6.1

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

9.7.2 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 is to occur 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 triggers an additional 12-month observation for subsequent events. Events are adjudicated by an independent CEC.

A total of 5,016 patients enrolled in the ARRIVE 2 registry. At this time, the 1-year follow-up has been completed in all patients. The analysis population at 1 year includes 4,820 patients with 6,774 lesions in 5,627 vessels who received 7,525 stents. Baseline demographics and procedural characteristics (Table 9.7.4), as well as safety results (Table 9.7.5), are listed below.

In addition to the protocol-specified (and CEC-adjudicated) definitions of stent thrombosis used to generate the results in Table 9.7.5 below, the FDA requested an additional retrospective assessment of all events using the proposed ARC definitions (see Section 9.6.1). These results are also presented (Table 9.7.6).

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Table 9.7.4: ARRIVE 2 - Baseline Demographics and Procedural Characteristics

Analysis Group: 4820 patients, 6774 lesions, 5627 vessels, 7525 stents

Patient Demographics		Procedural Characteristics	
		Vessels Treated	
Male	67.0% (3230/4820)	1	84.5% (4072/4820)
Age (yr)	64.6±11.8 (4820)	2	14.4% (693/4820)
Diabetes	32.1% (1549/4820)	≥3	1.1% (55/4820)
Oral Medication Treated		Target Vessels	
Insulin Treated	22.1% (1063/4820)	RCA	33.3% (2258/6774)
Multi-vessel Disease	10.4% (503/4820)	LAD	35.3% (2390/6774)
Prior MI	35.5% (1710/4820)	CX	24.2% (1640/6774)
Prior PCI	35.7% (1723/4820)	LM	1.4% (97/6774)
Prior CABG	36.9% (1757/4765)	Graft	5.7% (389/6774)
Lesion Characteristics		Stenting	
Reference Vessel Diameter (mm)	3.0±0.5 (6774)	Direct stenting (per lesion)	41.1% (2786/6774)
Lesion Length (mm)	15.5±9.2 (6774)	TAXUS stents per patient	1.6±0.9 (4820)
Lesion Type		Stent length per lesion (mm)	20.9±11.1 (6673)
A	13.8% (932/6773)		
B1	36.7% (2485/6773)		
B2	31.2% (2111/6773)		
C	18.4% (1245/6773)		

Numbers are % (Count/Sample Size), n, or Mean±SD.

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

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

Table 9.7.5: ARRIVE 2 Principal Effectiveness Summary to 1 Year

Overall: 4820 patients; 6774 lesions; 5627 vessels, 7525 Stents	
	Event Rate
TAXUS-related cardiac event (Cardiac death, MI, TAXUS-related re-intervention)	6.1% (278/4569)
Cardiac death	1.0% (44/4569)
MI [‡]	1.5% (69/4569)
Q-wave MI (only)	0.5% (23/4569)
Non Q-wave MI (only)	1.0% (44/4569)
TAXUS-related re-intervention	4.8% (219/4569)
All Death [†]	3.3% (150/4569)

Numbers are % (Count/Sample Size).

[‡] One additional patient had a Q-wave and a non Q-wave MI.

[†] Includes non-stent-related deaths.

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

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**Table 9.7.6: Stent Thrombosis by Time Interval in ARRIVE 2
Binary Proportion Analysis (N=4820)**

	Per protocol*	ARC Definite & Probable Primary [§]	ARC Definite & Probable Total [§]
0 days -1 day	0.2% (12/4820)	0.3% (13/4820)	0.3% (13/4820)
2 days - 30 days	0.5% (26/4797)	0.6% (28/4797)	0.6% (28/4797)
31 days - 180 days	0.3% (15/4706)	0.3% (15/4706)	0.3% (16/4706)
181 days – 365 days	0.3% (15/4595)	0.2% (11/4595)	0.3% (13/4595)
0 days – 365 days	1.5% (68/4569)	1.5% (67/4570)	1.5% (70/4570)

* 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 9.5.1

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

9.8 Subgroup analysis of the ARRIVE registries

A subgroup analysis was conducted on the ARRIVE 1 and ARRIVE 2 patients. Results for pooled ARRIVE 1 and ARRIVE 2 from 0-1 year are presented in Table 9.8.1, ARRIVE 1 from 0-1 and 1-2 years are presented in Tables 9.8.2 and 9.8.3, and ARRIVE 2 from 0-1 year are presented in Table 9.8.4.

Table 9.8.1: Subgroup Outcomes in Pooled ARRIVE 1 and 2 (0-1 year), Binary Proportion Analysis

	ARRIVE 1 & 2 Overall n=7307	"TAXUS IV-like" [§] n=2536	Long lesions (≥28 mm) n=952	Small vessels (RVD ≤2.5 mm) n=2243	Multivessel Stenting n=1148	Multiple Stents Per Patient n=2877	Bifurcated Lesions n=558	AMI n=917	All Diabetics n=2305	Insulin Treated Diabetics n=746	Non-Insulin Treated Diabetics n=1559
Efficacy											
TAXUS-related re-intervention	5.1% (355/6979)	3.0% (72/2437)	8.5% (77/905)	6.1% (130/2128)	7.7% (85/1097)	7.0% (193/2740)	8.9% (47/527)	4.2% (36/856)	4.6% (100/2191)	5.5% (38/691)	4.1% (62/1500)
Safety											
All death*	3.5% (242/6979)	3.0% (72/2437)	4.2% (38/906)	3.6% (76/2132)	4.2% (46/1097)	3.6% (99/2740)	5.3% (28/527)	3.7% (32/856)	5.1% (112/2191)	5.8% (40/691)	4.8% (72/1500)
Cardiac death	1.0% (71/6979)	0.7% (16/2437)	1.4% (13/906)	1.1% (24/2132)	1.9% (21/1097)	1.4% (38/2740)	2.3% (12/527)	0.9% (8/856)	1.6% (36/2191)	2.3% (16/691)	1.3% (20/1500)
MI	1.6% (113/6979)	0.9% (22/2437)	4.0% (36/906)	2.3% (48/2132)	3.1% (34/1097)	2.5% (68/2740)	2.3% (12/527)	1.6% (14/856)	1.8% (40/2191)	2.9% (20/691)	1.3% (20/1500)
Q-wave	0.6% (41/6979)	0.4% (9/2437)	1.9% (17/906)	0.8% (17/2132)	1.4% (15/1097)	1.1% (29/2740)	0.6% (3/527)	0.1% (1/856)	0.6% (14/2191)	0.9% (6/691)	0.5% (8/1500)
Stent thrombosis											
Per Protocol [†]	1.7% (121/6979)	0.8% (19/2437)	3.5% (32/905)	2.2% (46/2128)	2.7% (30/1097)	2.7% (73/2740)	3.0% (16/527)	2.5% (21/856)	2.0% (43/2191)	3.0% (21/691)	1.5% (22/1500)
Definite & Probable Total [‡]	1.8% (123/6980)	0.8% (19/2437)	3.8% (34/906)	2.3% (49/2133)	2.9% (32/1097)	2.7% (75/2740)	3.0% (16/527)	2.7% (23/857)	2.1% (46/2192)	3.5% (24/691)	1.5% (22/1501)

* Includes non-stent-related deaths.

§ All patients who are not defined as complex. Complex patients are defined as all patients with at least one of the following: acute myocardial infarction, left main disease, graft stenting, chronic total occlusion, in-stent restenosis, failed brachytherapy, bifurcation lesion, ostial lesion, severe tortuosity, multiple stents, multivessel stenting, reference vessel diameter (RVD) <2.5 mm or >3.5 mm, lesion length >26 mm.

† 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 9.6.1

Patients from two ARRIVE 1 sites and two ARRIVE 2 sites are excluded from analysis due to GCP non-compliance.

Table 9.8.2: Subgroup Outcomes in ARRIVE 1 (0-1 years), Binary Proportion Analysis

	ARRIVE Overall n=2487	"TAXUS IV-like" [§] n=837	Long lesions (≥28 mm) n=351	Small vessels (RVD ≤2.5 mm) n=743	Multivessel Stenting n=431	Multiple Stents Per Patient n=1032	Bifurcated Lesions n=201	AMI n=254	All Diabetics n=756	Insulin Treated Diabetics n=243	Non-Insulin Treated Diabetics n=513
Efficacy											
TAXUS-related re-intervention	5.6% (136/2410)	3.5% (28/806)	8.8% (30/341)	6.6% (47/716)	7.9% (33/419)	7.9% (79/997)	7.6% (15/197)	5.4% (13/242)	5.8% (42/729)	8.7% (20/231)	4.4% (22/498)
Safety											
All death*	3.8% (92/2410)	3.1% (25/806)	5.3% (18/341)	4.1% (29/716)	3.8% (16/419)	3.6% (36/997)	5.6% (11/197)	3.3% (8/242)	5.5% (40/729)	6.1% (14/231)	5.2% (26/498)
Cardiac death	1.1% (27/2410)	0.5% (4/806)	1.2% (4/341)	1.4% (10/716)	1.9% (8/419)	1.4% (14/997)	2.0% (4/197)	0.8% (2/242)	1.9% (14/729)	3.5% (8/231)	1.2% (6/498)
MI	1.8% (44/2410)	1.0% (8/806)	5.0% (17/341)	2.7% (19/716)	3.3% (14/419)	3.0% (30/997)	1.0% (2/197)	2.1% (5/242)	2.7% (20/729)	5.6% (13/231)	1.4% (7/498)
Q-wave	0.7% (16/2410)	0.2% (2/806)	2.3% (8/341)	1.0% (7/716)	1.7% (7/419)	1.4% (14/997)	0.5% (1/197)	0.4% (1/242)	0.7% (5/729)	1.7% (4/231)	0.2% (1/498)
Stent thrombosis											
Per Protocol [†]	2.2% (53/2410)	1.1% (9/806)	4.1% (14/341)	2.8% (20/716)	3.8% (16/419)	3.6% (36/997)	3.6% (7/197)	2.9% (7/242)	3.0% (22/729)	6.1% (14/231)	1.6% (8/498)
Definite & Probable Total [‡]	2.2% (53/2410)	1.1% (9/806)	4.7% (16/341)	2.9% (21/716)	3.8% (16/419)	3.8% (38/997)	3.6% (7/197)	3.7% (9/242)	3.2% (23/729)	7.4% (17/231)	1.2% (6/498)

* Includes non-stent-related deaths.

[§] All patients who are not defined as complex. Complex patients are defined as all patients with at least one of the following: acute myocardial infarction, left main disease, graft stenting, chronic total occlusion, in-stent restenosis, failed brachytherapy, bifurcation lesion, ostial lesion, severe tortuosity, multiple stents, multivessel stenting, reference vessel diameter (RVD) <2.5 mm or >3.5 mm, lesion length >26 mm.

[†] 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 9.6.1

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

Table 9.8.3: Subgroup Outcomes in ARRIVE 1 (1-2 years), Binary Proportion Analysis

	ARRIVE Overall n=2487	"TAXUS IV-like" ^s n=837	Long lesions (≥28 mm) n=351	Small vessels (RVD ≤2.5 mm) n=743	Multivessel Stenting n=431	Multiple Stents Per Patient n=1032	Bifurcated Lesions n=201	AMI n=254	All Diabetics n=756	Insulin Treated Diabetics n=243	Non- Insulin Treated Diabetics n=513
Efficacy											
TAXUS-related re-intervention	2.3% (53/2280)	1.8% (14/765)	3.1% (10/321)	2.7% (18/675)	3.3% (13/389)	2.7% (26/946)	3.8% (7/183)	1.8% (4/224)	2.8% (19/678)	4.7% (10/212)	1.9% (9/466)
Safety											
All death*	2.1% (48/2280)	1.4% (11/765)	2.5% (8/321)	2.1% (14/675)	1.8% (7/389)	1.9% (18/946)	1.6% (3/183)	3.1% (7/224)	2.9% (20/678)	2.4% (5/212)	3.2% (15/466)
Cardiac death	0.1% (3/2280)	0.0% (0/765)	0.0% (0/321)	0.1% (1/675)	0.3% (1/389)	0.1% (1/946)	0.0% (0/183)	0.9% (2/224)	0.1% (1/678)	0.0% (0/212)	0.2% (1/466)
MI	0.5% (11/2280)	0.7% (5/765)	0.3% (1/321)	0.4% (3/675)	0.5% (2/389)	0.3% (3/946)	0.0% (0/183)	0.4% (1/224)	0.4% (3/678)	0.9% (2/212)	0.2% (1/466)
Q-wave	0.2% (5/2280)	0.1% (1/765)	0.3% (1/321)	0.1% (1/675)	0.0% (0/389)	0.2% (2/946)	0.0% (0/183)	0.4% (1/224)	0.0% (0/678)	0.0% (0/212)	0.0% (0/466)
Stent thrombosis											
Per Protocol [†]	0.6% (14/2280)	0.7% (5/765)	1.6% (5/321)	0.6% (4/675)	0.8% (3/389)	0.7% (7/946)	0.5% (1/183)	0.4% (1/224)	0.7% (5/678)	1.4% (3/212)	0.4% (2/466)
Definite & Probable Total [‡]	0.7% (16/2280)	0.7% (5/765)	1.6% (5/321)	0.7% (5/675)	1.0% (4/389)	0.7% (7/946)	0.5% (1/183)	0.9% (2/224)	0.9% (6/678)	1.4% (3/212)	0.6% (3/466)

* Includes non-stent-related deaths.

^s All patients who are not defined as complex. Complex patients are defined as all patients with at least one of the following: acute myocardial infarction, left main disease, graft stenting, chronic total occlusion, in-stent restenosis, failed brachytherapy, bifurcation lesion, ostial lesion, severe tortuosity, multiple stents, multivessel stenting, reference vessel diameter (RVD) <2.5 mm or >3.5 mm, lesion length >26 mm.

[†] 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 9.6.1

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

Table 9.8.4: Subgroup Outcomes in ARRIVE 2 (0-1 years), Binary Proportion Analysis

	ARRIVE2 Overall n=4820	"TAXUS IV-like" [§] n=1699	Long lesions (≥28 mm) n=601	Small vessels (RVD ≤2.5 mm) n=1500	Multivessel Stenting n=717	Multiple Stents Per Patient n=1845	Bifurcated Lesions n=357	AMI n=663	All Diabetics n=1549	Insulin Treated Diabetics n=503	Non-Insulin Treated Diabetics n=1046
Efficacy											
TAXUS-related re-intervention	4.8% (219/4569)	2.7% (44/1631)	8.3% (47/564)	5.9% (83/1412)	7.7% (52/678)	6.5% (114/1743)	9.7% (32/330)	3.7% (23/614)	4.0% (58/1462)	3.9% (18/460)	4.0% (40/1002)
Safety											
All death*	3.3% (150/4569)	2.9% (47/1631)	3.5% (20/565)	3.3% (47/1416)	4.4% (30/678)	3.6% (63/1743)	5.2% (17/330)	3.9% (24/614)	4.9% (72/1462)	5.7% (26/460)	4.6% (46/1002)
Cardiac death	1.0% (44/4569)	0.7% (12/1631)	1.6% (9/565)	1.0% (14/1416)	1.9% (13/678)	1.4% (24/1743)	2.4% (8/330)	1.0% (6/614)	1.5% (22/1462)	1.7% (8/460)	1.4% (14/1002)
MI	1.5% (69/4569)	0.9% (14/1631)	3.4% (19/565)	2.0% (28/1416)	2.9% (20/678)	2.2% (38/1743)	3.0% (10/330)	1.5% (9/614)	1.4% (20/1462)	1.5% (7/460)	1.3% (13/1002)
Q-wave	0.5% (25/4569)	0.4% (7/1631)	1.6% (9/565)	0.7% (10/1416)	1.2% (8/678)	0.9% (15/1743)	0.6% (2/330)	0.0% (0/614)	0.6% (9/1462)	0.4% (2/460)	0.7% (7/1002)
Stent thrombosis											
Per Protocol [†]	1.5% (68/4569)	0.6% (10/1631)	3.2% (18/564)	1.8% (26/1412)	2.1% (14/678)	2.1% (37/1743)	2.7% (9/330)	2.3% (14/614)	1.4% (21/1462)	1.5% (7/460)	1.4% (14/1002)
Definite & Probable Total [‡]	1.5% (70/4570)	0.6% (10/1631)	3.2% (18/565)	2.0% (28/1417)	2.4% (16/678)	2.1% (37/1743)	2.7% (9/330)	2.3% (14/615)	1.6% (23/1463)	1.5% (7/460)	1.6% (16/1003)

* Includes non-stent-related deaths.

[§] All patients who are not defined as complex. Complex patients are defined as all patients with at least one of the following: acute myocardial infarction, left main disease, graft stenting, chronic total occlusion, in-stent restenosis, failed brachytherapy, bifurcation lesion, ostial lesion, severe tortuosity, multiple stents, multivessel stenting, reference vessel diameter (RVD) <2.5 mm or >3.5 mm, lesion length >26 mm.

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

3. angiographically confirmed - thrombus detected in any stent placed in the target vessel(s), or
4. 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 9.6.1

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