SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Drug-Eluting Coronary Stent System (NIQ)
Device Trade Name:	ION™ Paclitaxel-Eluting Coronary Stent System (Monorail and Over-the-Wire)
Applicant's Name and Address:	Boston Scientific Corporation One Boston Scientific Place Natick, MA 01760-1537
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P100023/S015
Date of FDA Notice of Approval:	February 22, 2012
Expedited:	Not applicable

The original PMA (P100023) was approved on April 22, 2011 and 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 ≤ 34 mm in length. The SSED to support the indication is available on the CDRH website and is incorporated by reference here: http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100023b.pdf

This supplement approval revises the indications statement to include patients undergoing primary angioplasty to treat acute ST-segment elevation myocardial infarction, true posterior myocardial infarction, or presumed new left bundle branch block with symptoms of acute myocardial infarction lasting > 20 minutes and < 12 hours in duration.

II. INDICATIONS FOR USE

The ION Stent System is indicated for improving luminal diameter:

- for the treatment of de novo lesions in native coronary arteries 2.25 mm to 4.00 mm in diameter in lesions ≤ 34 mm in length; or
- in patients undergoing primary angioplasty to treat acute ST-segment elevation myocardial infarction, true posterior myocardial infarction, or presumed new left bundle branch block with symptoms of acute myocardial infarction lasting > 20 minutes and < 12 hours in duration.

III. CONTRAINDICATIONS

Use of the ION Stent System is contraindicated in patients with:

- Known hypersensitivity to 316L stainless steel or platinum.
- Known hypersensitivity to paclitaxel or structurally-related compounds.
- Known hypersensitivity to the polymer or its individual components

Coronary Artery Stenting is contraindicated for use in:

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

IV. WARNING AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

The ION Paclitaxel-Eluting Coronary Stent System is a device / drug combination product comprised of two regulated components: a device (Element Coronary Stent System) and a drug product (a formulation of paclitaxel contained in a polymer coating). The components and characteristics of the ION Paclitaxel-Eluting Coronary Stent System are identical to the product approved in P100023. Please refer to the original device description for additional details. The characteristics of the ION Stent System are described in **Table 1**.

Table 1 ION Stent System Product Description

	ION Monorail Stent Delivery System	ION Over-the-Wire Stent Delivery System
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32, 38	
Available Stent Diameters (mm)	2.25*, 2.50*, 2.75, 3.00, 3.50, 4.00	
Stent Material	Platinum Chromium Alloy (PtCr)	
Stent Strut Thickness	0.0032 in (0.081 mm) for diameters 2.25 mm to 3.5 mm 0.0034 in (0.086 mm) for diameter 4.0 mm	
Drug Product	A conformal coating of a polymer carrier loaded with 1 μg/mm² paclitaxel applied to the stent with a maximum nominal drug content of 247 μg on the largest stent (4.00 x 38 mm).	
Delivery System		
Effective Length	144 cm	143 cm
Delivery System Y-Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 26 cm from tip. Designed for guidewire ≤ 0.014 in (0.36 mm)	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤ 0.014 in (0.36 mm)
Stent Delivery	A balloon, with two radiopaque balloon markers, nominally placed 0.385 mm (0.015 in) beyond the stent at each end.	
Balloon Inflation Pressure	Nominal Inflation Pressure: • Diameters 2.25 mm, 2.50 mm, 2.75 mm, 3.00 mm, 3.50 mm, 4.00 mm; 11 atm (1115 kPa)	
	Rated Burst Inflation Pressure: •Diameters 2.25 mm; 18 atm (1824 kPa) •Diameters 2.50 mm, 2.75 mm, 3.00 mm, 3.50 mm, 4.00 mm; 16 atm (1621 kPa)	
Catheter Shaft Outer Diameter	2.3 F (0.80 mm) proximal and 2.7 F (0.95 mm) distal.	3.4F (1.20 mm) proximal for 2.25 to 4.00 mm sizes 2.4F (0.85 mm) distal for 2.25 to 2.75 mm sizes 2.7F (0.95 mm) distal for 3.00 to 4.00 mm sizes
Guide Catheter Minimum Inner Diameter Requirement	≥ 0.056 in (1.42 mm) for 2.25 to 3.50 mm sizes. ≥ 0.058 in (1.47 mm) for 4.00 mm sizes.	≥ 0.066 in (1.68 mm)

*2.25 and 2.50 mm sizes are available in 8, 12, 16, 20, 24, 28, 32 mm lengths

VI. ALTERNATIVE PRACTICES OR PROCEDURES

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

VII. MARKETING HISTORY

ION Paclitaxel-Eluting Coronary Stent System is commercially available in the following countries. Note that ION is marketed as TAXUS Element outside the US, but the product is identical to ION. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

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

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) in alphabetical order, which may be associated with the use of a coronary stent in coronary arteries:

- Abrupt stent closure
- Acute myocardial infarction
- Allergic reaction to anticoagulants or antithrombotic therapy or contrast medium or stent materials
- Angina
- Arrhythmias, including ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Arteriovenous fistula
- Cardiac tamponade
- Cardiogenic shock/ pulmonary edema
- Death
- Dissection
- Emboli, distal (air, tissue, or thrombotic material, or material from device(s) used in the procedure)
- Heart failure
- Hematoma
- Hemorrhage, requiring transfusion
- Hypotension/hypertension
- Infection, local and/or systemic
- Ischemia, myocardial
- Pain at the access site
- Perforation or rupture of coronary artery
- Pericardial effusion
- Pseudoaneurysm, femoral
- Renal failure
- Respiratory failure
- Restenosis of stented segment
- Shock
- Stent embolization
- Stent migration
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident/TIA
- Total occlusion of coronary artery
- Vessel spasm
- Vessel trauma requiring surgical repair or reintervention

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

- Allergic/immunologic reaction to drug (paclitaxel or structurally-related compounds) or the polymer stent coating (or its individual components)
- Alopecia
- Anemia

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

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

IX. SUMMARY OF PRECLINICAL STUDIES

A series of non-clinical laboratory studies were performed to support the original approval – those related to the stent and the stent delivery system [i.e. the stent on either the Monorail (MR) or Over-The-Wire (OTW) stent delivery system (SDS)], the polymer substance [i.e., poly(styrene-b-isobutylene-b-styrene) (SIBS)], the drug substance (i.e., paclitaxel) and the finished combination product (i.e., ION™ Paclitaxel-Eluting Coronary Stent). No new nonclinical studies were needed to support the approval of this supplement.

X. SUMMARY OF CLINICAL STUDIES

A program of clinical studies (PERSEUS Workhorse and PERSEUS Small Vessel) was performed to support the original approval. Please refer to previous SSED for details. The HORIZONS AMI trial was performed to establish a reasonable assurance of safety and effectiveness for TAXUS Express2 Paclitaxel-Eluting Coronary Stent System for the proposed expanded indication under IDE G040188. Data from this clinical study were the basis for the PMA approval decision. The ION stent uses the same drug-polymer coating formulation as the TAXUS Express^2 stent. In addition, nonclinical studies of design attributes and the PERSEUS clinical studies in stable patients with coronary artery disease have established that the performance of the ION is similar. Given these supportive data, outcomes in patients with AMI would also be expected to be similar between these two stents, and therefore, the safety and effectiveness data from the HORIZONS AMI trial were considered applicable for the ION Paclitaxel-Eluting Coronary Stent System as well. A summary of the clinical study is presented below.

A. HORIZONS AMI Clinical Trial

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

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

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

Design

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

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

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

Table 2. HORIZONS AMI CLINICAL TRIAL OVERVIEW

	HORIZONS AMI (Indication Expansion)
Study Type	Prospective, multicenter, randomized, single-blind
Number of Patients (ITT)	Total: 3006 TAXUS: 2257 Control: 749
Dose Release Formulation	Slow Release (SR) (1 μg /mm2)
Lesion Criteria: Vessel Diameter (by visual estimate)	≥ 2.5 mm to ≤ 4.0 mm
Lesion Criteria: Lesion Length (by visual estimate)	< 100 mm
Product Used	TAXUS Express Paclitaxel-Eluting Coronary Stent System
Antiplatelet Therapy	Aspirin indefinitely and clopidogrel or ticlopidine for 6 months (1 year or longer recommended)
Follow-Up	30 days: clinical 6 months: clinical 12 month: clinical 13 month: angiographic/IVUS 2, 3 years: clinical

Abbreviations: ITT=intent-to-treat; IVUS=intravascular ultrasound

1. Clinical Inclusion and Exclusion Criteria

Primary Randomization – Inclusion Criteria:

1. The patient must be at least 18 years of age (there is no upper age limit).
2. Must have clinical symptoms consistent with AMI (e.g., angina or anginal equivalent) lasting >20 minutes but <12 hours in duration. If the symptom duration at the time of evaluation is <1 hour, to rule out unstable angina, the symptoms must be unresponsive to nitroglycerin (i.e. ongoing) prior to signing the informed consent. Patients with symptom onset within 12 hours, in whom the symptoms lasted >1 hour but subsequently resolved may still be enrolled if the ECG, at the time of the evaluation, shows definite ongoing ST segment elevation.
3. ECG criteria: ST-segment elevation of $\geq$ 1 mm in $\geq$ 2 contiguous leads, or (presumably new) left bundle branch block, or true posterior MI with ST depression of $\geq$ 1 mm in $\geq$ 2 contiguous anterior leads.
4. The patient or guardian agrees to the study protocol and the schedule of clinical and angiographic follow-up, and provides informed, written consent, as approved by the appropriate Institutional Review Board/Ethical Committee of the respective clinical site.

Primary Randomization – Exclusion Criteria:

1. The patient has a known hypersensitivity or contraindication to any of the following medications:
   - Heparin, pork or pork products
   - Both abciximab and eptifibatide
   - Aspirin
   - Both Clopidogrel and Ticlopidine
   - Bivalirudin
   - Paclitaxel or Taxol
   - The polymer components of the TAXUS Express DES stent (SIBS)
   - Stainless steel and/or
   - Contrast media (patients with documented sensitivity to contrast which can be effectively pre-medicated with steroids and diphenhydramine (e.g. rash) may be enrolled. Patients with true anaphylaxis to prior contrast media, however, should not be enrolled).
2. Prior administration of thrombolytic therapy, bivalirudin, GP IIb/IIIa inhibitors, low molecular weight heparin or fondaparinux for this admission. Patients receiving prior unfractionated heparin may be enrolled, and treated per randomization.
3. Current use of coumadin.
4. Systemic (intravenous) Paclitaxel or Taxol use within 12 months.
5. Female of childbearing potential, unless a recent pregnancy test is negative, who possibly plans to become pregnant any time after enrollment into this study.
6. History of bleeding diathesis or known coagulopathy (including heparin-induced thrombocytopenia), or will refuse blood transfusions.
7. History of intra-cerebral mass, aneurysm, arteriovenous malformation, or hemorrhagic stroke.
8. Stroke or transient ischemic attack within the past 6 months, or any permanent residual neurologic defect.
9. Gastrointestinal or genitourinary bleeding within the last 2 months, or major surgery within six weeks.

10. Recent history or known current platelet count <100,000 cells/mm3 or Hgb <10 g/dL (note: baseline labs did not have to be available prior to enrollment).
11. Extensive peripheral vascular disease, such that emergent angiography and intervention in the opinion of the investigator is likely to be difficult or complicated.
12. An elective surgical procedure is planned that would necessitate interruption of thienopyridines during the first six months post enrollment.
13. Non-cardiac co-morbid conditions are present with life expectancy <1 year or that may result in protocol non-compliance.
14. Patients who are actively participating in another drug or device investigational study, which have not completed the primary endpoint follow-up period.
15. Previous enrollment in this trial.
16. Patients who underwent coronary stent implantation within the past 30 days.

Secondary Randomization – Angiographic Inclusion Criteria:

1. At least one acute infarct artery target vessel is present in which:
   a. ALL hemodynamically significant lesions can be stented with study stents, and
   b. ALL such lesions have a visually estimated reference diameter ≥2.25 mm and ≤ 4.0 mm.
2. Expected ability to deliver the stent(s) to all culprit lesions (absence of excessive proximal tortuosity or severe calcification).
3. Expected ability to fully expand the stent(s) at all culprit lesions (absence of marked calcification).

Secondary Randomization – Angiographic Exclusion Criteria:

1. One or more hemodynamically significant lesion(s) is present in the infarct vessel (or side branches) which can only undergo balloon angioplasty or cannot be stented with a study stent, (i.e., do not meet the angiographic inclusion criteria for a study stent).

   Note: The only exception to this exclusion criterion is bifurcation lesions with main branch and ostial side branch involvement, which may be enrolled as long as the main branch is eligible to be treated with a study stent. The ostial side branch lesion should then be treated with balloon angioplasty, with bail-out stenting performed only for a sub-optimal result in the side branch (diameter stenosis >50% or dissection ≥ NHLBI type C refractory to prolonged (>2 minute) balloon inflations). Bifurcation lesions are otherwise excluded if the planned strategy definitely requires 2 stents (e.g., planned T-stenting, V-stenting, culotte stenting or crush).

2. The presence of a bifurcation lesion in the infarct vessel, which will definitely require the implantation of two stents for treatment.

   Note: A true bifurcation lesion qualifies for randomization if the operator believes he/she will be likely able to successfully approach the lesion with "provisional stenting", (i.e., the side branch ostial lesion is dilated first, and stented only for a sub-optimal result as defined above, after prolonged (>2 minute) balloon inflations).

3. Anticipated need for greater than 100mm of study stent length.
4. The infarct related artery is an unprotected left main segment.
5. Patients with significant multi-vessel disease or anatomical features otherwise unfavorable for angioplasty such that the patient will have a high likelihood of requiring bypass surgery prior to 30 days.
6. The culprit vessel or lesion cannot be identified.
7. Patient presenting with possible/probable stent thrombosis
8. Any patient in whom angiography demonstrates the infarct lesion to be at the site of a previously implanted stent (bare metal or drug-eluting)

2. Follow-up Schedule

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

3. Clinical Endpoints

- Primary Efficacy Endpoint: Ischemic target lesion revascularization
- Primary Safety Endpoint: The composite rate of death, reinfarction, stent thrombosis, or stroke (MACE)
- Major Secondary Endpoint: Analysis segment binary restenosis in the 13 month angiographic subset

All primary and major secondary endpoints were analyzed both on an intent-to-treat (ITT) basis (all patients analyzed as part of their assigned treatment group) and on a per protocol basis (patients analyzed as part of their assigned treatment group only if they actually received their assigned treatment). The principal analyses were by intention-to-treat.

The primary and major secondary endpoints were analyzed using risk differences and compared to the pre-specified non-inferiority margin. Kaplan-Meier curves and survival analyses were also constructed. Secondary efficacy and safety data were analyzed using descriptive statistics.

For principle statistical analyses, all endpoints were analyzed on a per patient basis.

B. Accountability of PMA Cohort

Refer to **Table 3** for primary endpoint patient disposition.

Table 3. Patient Disposition

	TAXUS DES N=2257	EXPRESS2 BMS N=749	Combined N=3006
Patients Enrolled (ITT Population)	100.0% (2257/2257)	100.0% (749/749)	100.0% (3006/3006)

Table 3. Patient Disposition

	TAXUS DES N=2257	EXPRESS2 BMS N=749	Combined N=3006
Completed 1 year follow-up[1]	96.9% (2186/2257)	95.5% (715/749)	96.5% (2901/3006)
Reason not completed:			
Lost to Follow-up	3.0% (68/2257)	4.0% (30/749)	3.3% (98/3006)
Patient/Physician withdrawal	0.9% (20/2257)	1.1% (8/749)	0.9% (28/3006)
Death	3.4% (76/2257)	3.5% (26/749)	3.4% (102/3006)
Patients qualified for PP analysis	95.1% (2146/2257)	96.0% (719/749)	95.3% (2865/3006)
Stented Patients	99.2% (2238/2257)	99.3% (744/749)	99.2% (2982/3006)

[1] Includes patients with 30 day, 6 month or 1 year follow-up or any follow-up visit post the follow-up window or any MACE event.

C. Study Population Demographics and Baseline Parameters

The baseline demographics and medical history are reported in **Table 4**.

Table 4. HORIZONS AMI Patient Demographics and Medical History (ITT Population)

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

IQR = interquartile range

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

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

[3] Left ventricular ejection fraction, visual assessment from the baseline contrast left ventriculogram.

D. Safety and Effectiveness Results

The primary and secondary endpoints of the trial were met and are reported in **Table 5** and **Table 6**. The clinical results of the trial are reported in **Table 7**. In **Figure 1**, the rates of ischemic TLR are illustrated for all patients and those patients who were not in the protocol required angiographic subset. **Figures 2-6** provide results of major clinical outcomes to 3 years. Angiographic and IVUS results are reported in **Table 8**.

Table 5. HORIZONS AMI Primary Endpoints

Ischemic TLR	TAXUS Express (N=2257)	Bare Metal Express (N=749)	Difference (95% CI)	Hazard Ratio (95% CI)	P-value[1]
1 Year	4.5% (98)	7.5% (54)	-3.0% (-5.1, -0.9)	0.59 (0.43, 0.83)	0.0018
Safety MACE2	**TAXUS Express (N=2257)**	**Bare Metal Express (N=749)**	**Difference (95%CI)**	**Hazard Ratio (95% CI)**	**P-value[3]**
1 Year	8.1% (181)	8.0% (59)	0.1% (-2.1, 2.4)	1.02 (0.76, 1.36)	0.0075

[1]1P-value for the test of superiority
[2] Safety MACE includes death, reinfarction, stroke or stent thrombosis.
[3] P-value for the test of non-inferiority

Table 6. HORIZONS AMI Secondary Endpoint

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

[1]P-value superiority

Adverse effects that occurred in the PMA clinical study

Observed adverse event experience comes from the HORIZONS AMI trial. Major clinical events for this study are shown in Table 6.

Table 7. HORIZONS AMI Kaplan-Meier Estimates of Clinical Endpoints at 30 Day, 1, 2, and 3 Years (ITT Population)

	TAXUS Express (N=2257)	Bare Metal Express (N=749)
30 Day Clinical Endpoints		
Net Adverse Clinical Events[1]	10.3% (232)	9.0% (67)
MACE 1[2]	4.8% (109)	4.5% (34)
MACE 2 (Safety MACE)[3]	4.5% (102)	4.3% (32)
Death	2.1% (47)	1.9% (14)
- Cardiac	2.0% (44)	1.7% (13)
- Noncardiac	0.1% (3)	0.1% (1)
Reinfarction	1.7% (37)	2.2% (16)
- Q wave	1.2% (28)	1.6% (12)
- Non Q wave	0.4% (10)	0.5% (4)
Death or reinfarction	3.6% (80)	3.5% (26)
Ischemic TVR	2.3% (51)	2.6% (19)
Ischemic TLR	2.1% (46)	2.6% (19)
Stroke	0.5% (11)	0.5% (4)
Major bleeding (non-CABG)	7.1% (159)	5.6% (42)
Target Lesion stent thrombosis	2.3% (50)	2.7% (20)
1 Year Clinical Endpoints		
Net Adverse Clinical Events[1]	15.8% (355)	16.3%(121)
MACE 1[2]	10.6% (237)	12.4% (92)

Table 7. HORIZONS AMI Kaplan-Meier Estimates of Clinical Endpoints at 30 Day, 1, 2, and 3 Years (ITT Population)

	TAXUS Express (N=2257)	Bare Metal Express (N=749)
MACE 2 (Safety MACE)[3]	8.1% (181)	8.0% (59)
Death	3.5%(78)	3.5% (26)
- Cardiac	2.4%(54)	2.7% (20)
- Noncardiac	1.1%(24)	0.8% (6)
Reinfarction	3.7%(81)	4.5% (33)
- Q wave	2.0%(45)	1.9% (14)
- Non Q wave	1.8%(39)	2.6% (19)
Death or reinfarction	6.8%(152)	7.0% (52)
Ischemic TVR	5.9% (129)	8.8% (64)
Ischemic TLR	4.6% (101)	7.4% (54)
Stroke	1.0%(23)	0.7% (5)
Major bleeding (non-CABG)	7.7% (172)	6.6% (49)
Target Lesion stent thrombosis	3.1% (69)	3.4% (25)
2 Year Clinical Endpoints		
Net Adverse Clinical Events[1]	21.5% (480)	26.0% (191)
MACE 1[2]	16.8% (373)	22.2% (162)
MACE 2 (Safety MACE)[3]	11.0% (245)	11.2% (82)
Death	4.3% (96)	5.3% (39)
- Cardiac	2.7% (60)	3.3% (24)
- Noncardiac	1.7% (36)	2.1% (15)
Reinfarction	5.7% (123)	6.0% (43)
- Q wave	3.1% (67)	2.8% (20)
- Non Q wave	3.0% (64)	3.2% (23)
Death or reinfarction	9.4% (210)	9.8% (72)
Ischemic TVR	10.9% (236)	16.7% (119)
Ischemic TLR	8.3% (180)	14.2% (101)
Stroke	1.4% (30)	1.1% (8)
Major bleeding (non-CABG)	8.0% (178)	7.0% (52)
Target Lesion stent thrombosis	4.2% (91)	4.1% (30)
3 Year Clinical Endpoints		
Net Adverse Clinical Events[1]	24.5% (544)	28.0% (205)
MACE 1[2]	20.0% (441)	24.0% (175)
MACE 2 (Safety MACE)[3]	13.6% (300)	12.9% (94)
Death	5.6% (123)	6.6% (48)
- Cardiac	3.2% (71)	3.8% (28)
- Noncardiac	2.4% (52)	2.9% (20)
Reinfarction	7.0% (150)	6.6% (47)
- Q wave	3.5% (75)	2.8% (20)
- Non Q wave	4.0% (84)	3.8% (27)
Death or reinfarction	11.8% (260)	11.5% (84)
Ischemic TVR	12.4% (265)	17.6% (125)
Ischemic TLR	9.4% (202)	15.1% (107)
Stroke	1.6% (35)	1.4% (10)
Major bleeding (non-CABG)	8.4% (188)	7.3% (54)
Target Lesion stent thrombosis	4.8% (103)	4.3% (31)

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

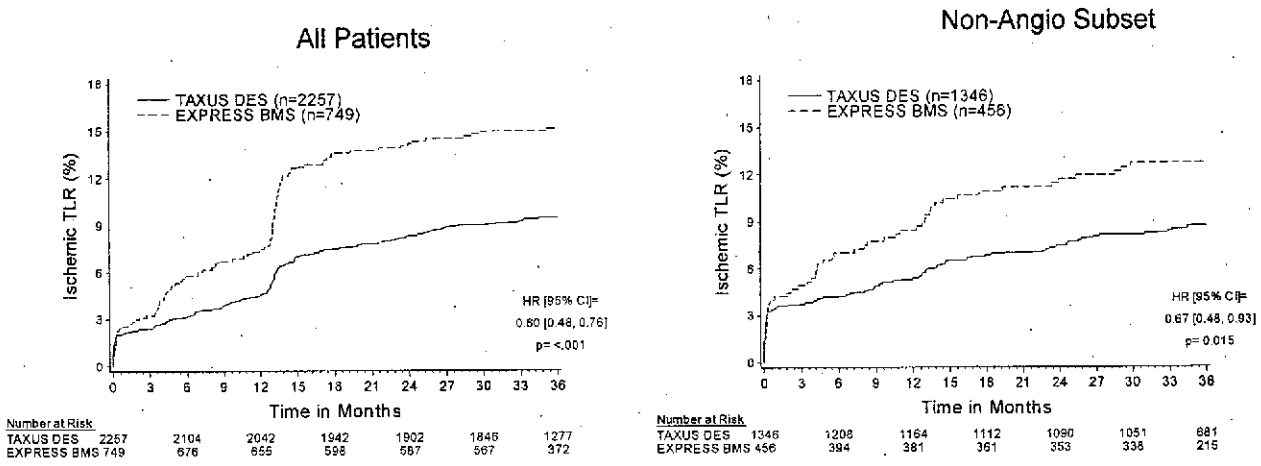

Figure 1. HORIZONS AMI Cumulative Rates of Ischemic Target Lesion Revascularization to 3 Years For All Patients and Patients Not in the Protocol Required Angiographic Subset

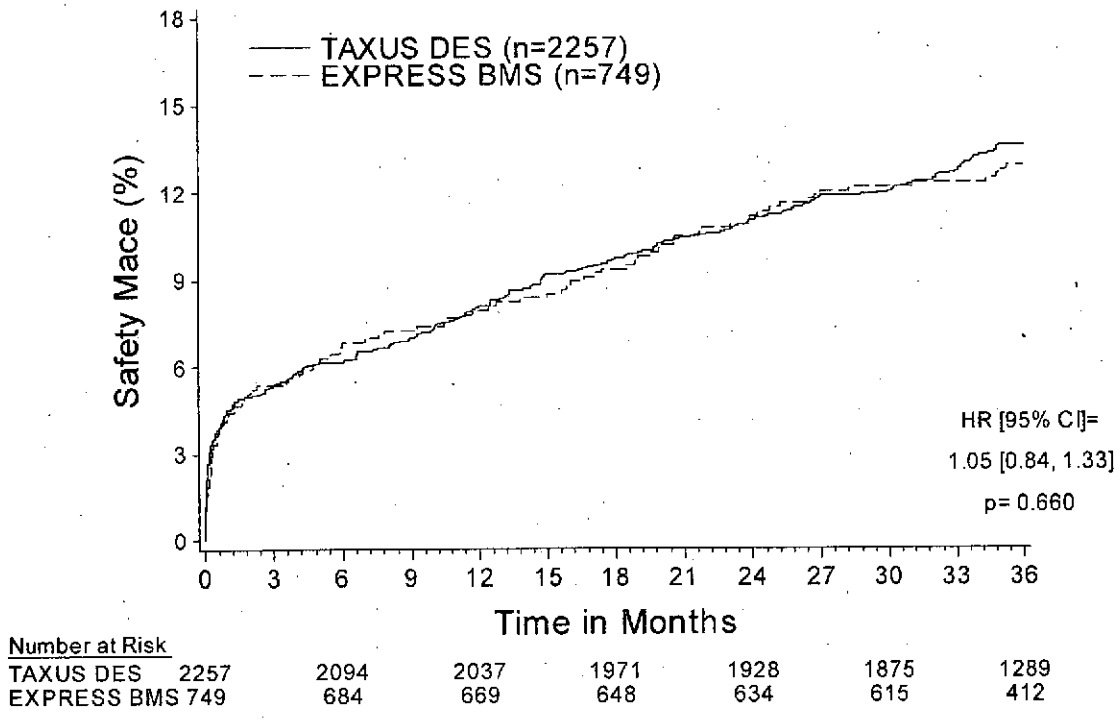

Figure 2. HORIZONS AMI Cumulative Rates of Safety MACE (Death, Reinfarction, Stent Thrombosis or Stroke) to 3 Years

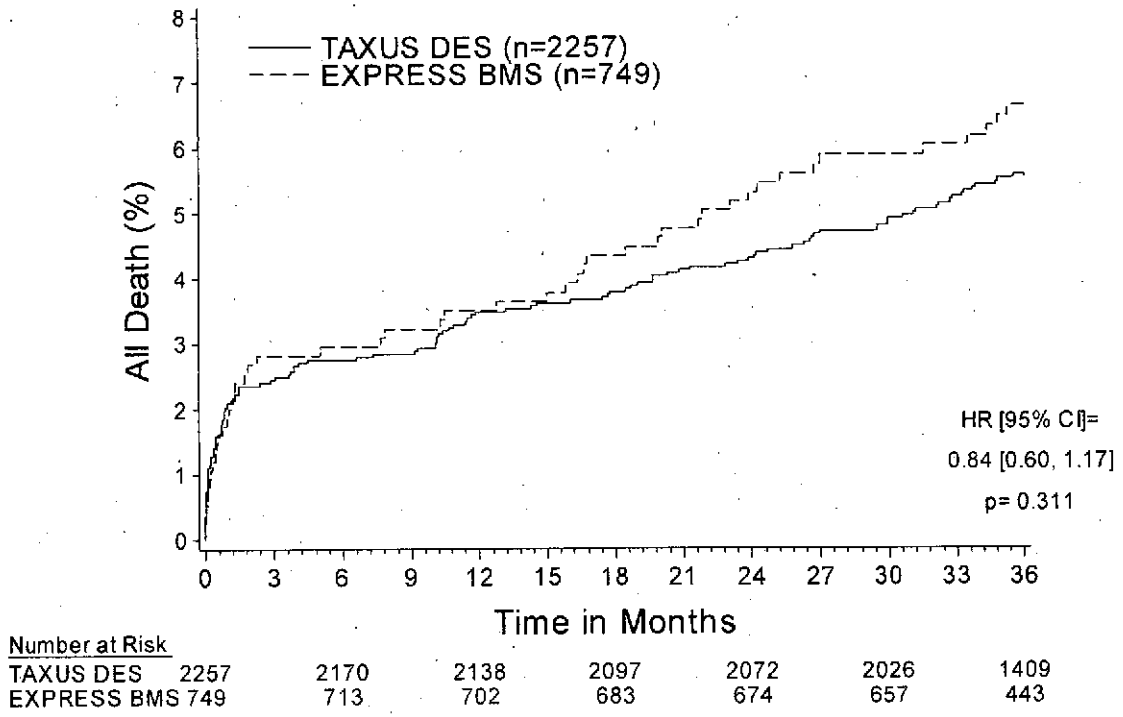

Figure 3. HORIZONS AMI Cumulative Rates of All Death to 3 Years

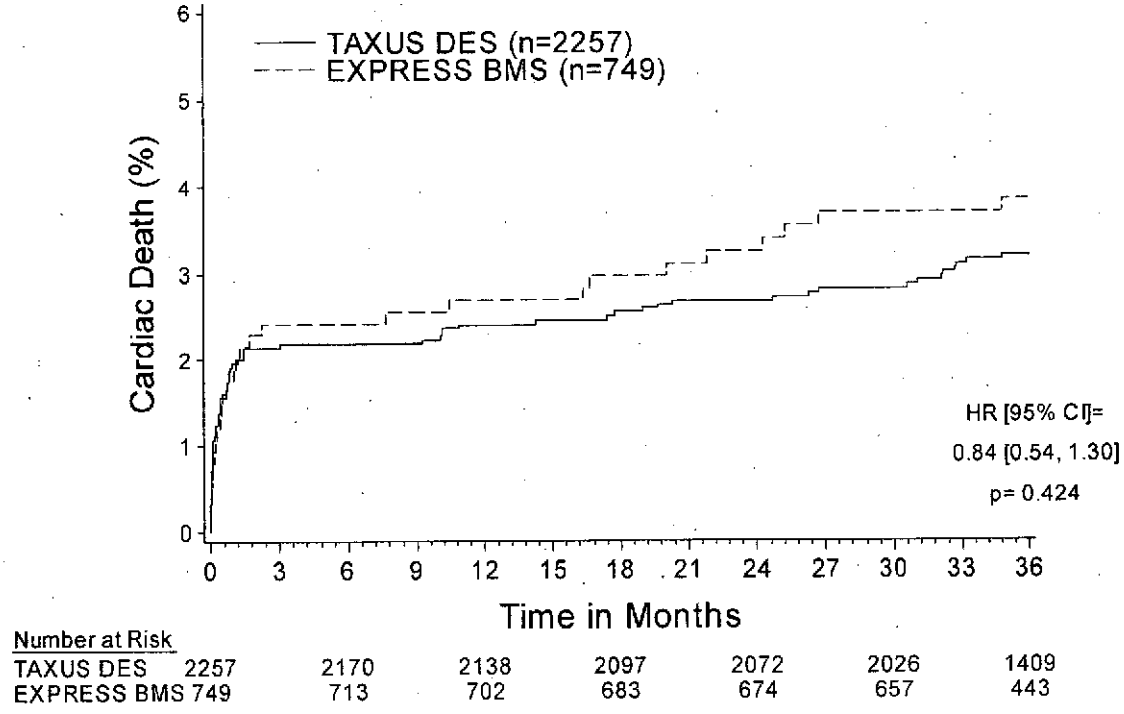

Figure 4. HORIZONS AMI Cumulative Rates of Cardiac Death to 3 Years

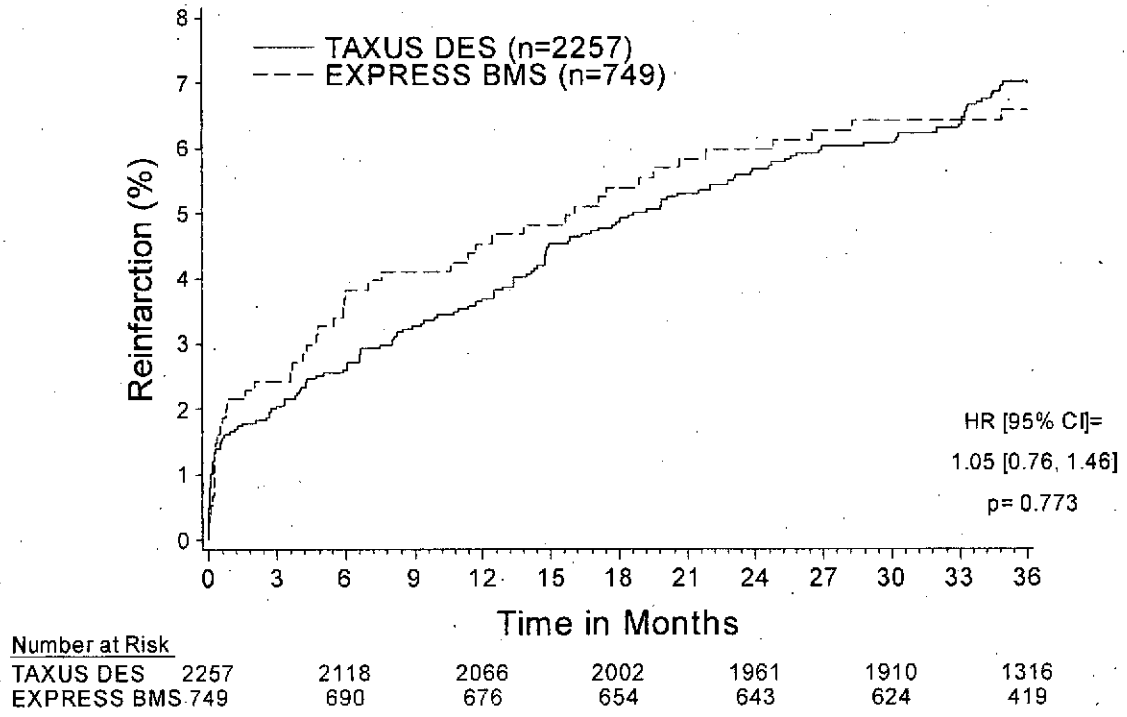

Figure 5. HORIZONS AMI Cumulative Rates of Reinfarction to 3 Years

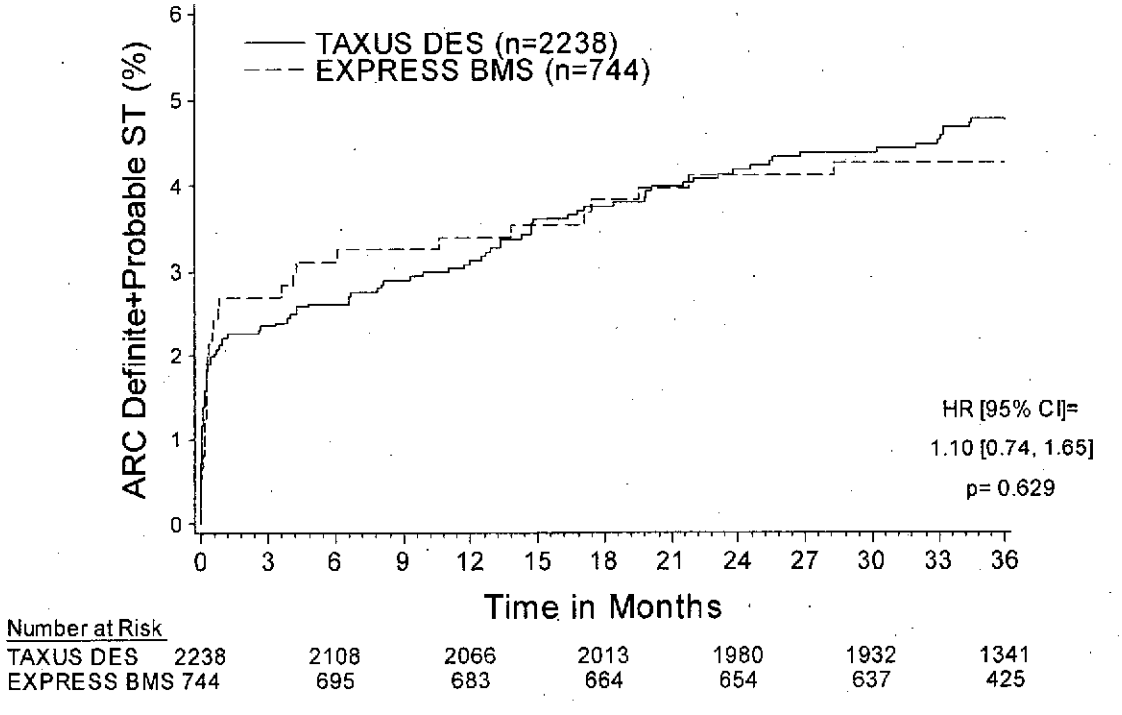

Figure 6. HORIZONS AMI Cumulative Rates of ARC Definite and Probable Stent Thrombosis to 3 Years

Table 8. HORIZONS AMI 13 Month Angiographic and IVUS Results)

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

QCA = quantitative coronary angiography, RVD = reference vessel diameter, MLD = minimal lumen diameter, %DS = percent diameter stenosis, IQR = interquartile range, SD = standard deviation
Follow-up QCA results on stented lesions only (per lesion)

Subgroup Analyses

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

In the HORIZONS AMI population, of patients randomized to TAXUS Express DES 1738/2257 (77%) subjects were male and 519/2257 (23%) subjects were female. The proportions in the Express BMS group were similar (76% male, 24% female). According to the Nationwide Inpatient Sample (a large database of inpatient admissions from 1988 to 2004), men had almost 2 times the age-adjusted STEMI rate as women (men 62.4%, women 37.6%)[1]. The gender proportions enrolled in this trial are similar to other trials in the STEMI population[2,3].

In subjects treated with TAXUS Express DES, 12-month TLR rates were 6.8% in females and 3.9% in males and Safety MACE rates were 10.1% in females and 7.5% in males. In subjects treated with Express BMS, 12-month TLR rates were 12.1% in females and 6.0% in males and Safety MACE rates were 12.3% in females and 6.6% in males (**Table 9**). Primary and secondary endpoint outcomes data stratified by gender are shown in **Tables 9** and **10**. HORIZONS AMI clinical results at 30 Days, 1 Year, 2 Year and 3 Year in male and female patients are reported in Table 11. Within the female group, cardiac death was numerically higher through 30 days in those treated with TAXUS Express versus bare metal Express, but the numerical difference between groups narrowed over time. Other trials of interventional treatment for AMI have shown female sex to be associated with higher mortality rates compared to men,[4,5] but differences appear to be largely explained by baseline risk factors such as BSA and angiographic disease severity. Rates of reinfarction and stent thrombosis in females were numerically lower in

TAXUS Express DES versus bare metal Express at 30 days and through 3 years. Formal interaction testing revealed no difference (at a significance level of p=0.15) between males and females in treatment effect at any time point, suggesting the conclusions of the overall study can be generalized for males and females.

Table 9: HORIZONS AMI Primary Endpoints by Gender

1 Year Ischemic TLR	TAXUS Express (N=2257)	Bare Metal Express (N=749)
Male (N=2307)	(N=1738)	(N=569)
	3.9% (66)	6.0% (33)
Female (N=699)	(N=519)	(N=180)
	6.8% (34)	12.1% (21)
Safety MACE[1]	**TAXUS Express (N=2257)**	**Bare Metal Express (N=749)**
Male (N=2307)	(N=1738)	(N=569)
	7.5% (129)	6.6% (37)
Female (N=699)	(N=519)	(N=180)
	10.1% (52)	12.3% (22)

[1] Safety MACE includes death, reinfarction, stroke or stent thrombosis

Table 10: HORIZONS AMI Secondary Endpoint by Gender

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

Table 11: HORIZONS AMI Clinical Endpoints, All TAXUS Express Male and Female Patients at 30 Days, 1 Year, 2 Year and 3 Year (Stent ITT Population)

Endpoint	TAXUS Express Male Patients (N=1738)	TAXUS Express Female Patients (N=519)	Bare Metal Express Male Patients (N=569)	Bare Metal Express Female Patients (N=180)
30 Day				
Net Adverse Clinical Events[1]	8.6% (149)	16.2% (84)	7.2% (41)	16.1% (29)
MACE 1[2]	4.1% (71)	7.4% (38)	3.5% (20)	7.8% (14)
MACE 2 (Safety MACE)[3]	3.9% (68)	6.6% (34)	3.2% (18)	7.8% (14)
Death	1.5% (26)	4.1% (21)	1.6% (9)	2.8% (5)
- Cardiac	1.4% (24)	3.9% (20)	1.6% (9)	2.2% (4)
- Noncardiac	0.1% (2)	0.2% (1)	0.0% (0)	0.6% (1)
Reinfarction	1.6% (27)	2.0% (10)	1.6% (9)	3.9% (7)
- Q wave	1.2% (21)	1.4% (7)	1.2% (7)	2.8% (5)
- Non Q wave	0.4% (7)	0.6% (3)	0.4% (2)	1.1% (2)
Death or reinfarction	2.9% (51)	5.6% (29)	2.8% (16)	5.6% (10)
Ischemic TVR	2.0% (35)	3.5% (18)	2.1% (12)	3.9% (7)
Ischemic TLR	1.8% (32)	3.1% (16)	2.1% (12)	3.9% (7)
Stroke	0.6% (10)	0.2% (1)	0.2% (1)	1.7% (3)

Table 11: HORIZONS AMI Clinical Endpoints, All TAXUS Express Male and Female Patients at 30 Days, 1 Year, 2 Year and 3 Year (Stent ITT Population)

Endpoint	TAXUS Express Male Patients (N=1738)	TAXUS Express Female Patients (N=519)	Bare Metal Express Male Patients (N=569)	Bare Metal Express Female Patients (N=180)
Major bleeding (non-CABG)	6.1% (105)	10.7% (55)	4.6% (26)	10.6% (19)
Target Lesion stent thrombosis	2.0% (35)	2.8% (14)	2.1% (12)	4.5% (8)
1 Year				
Net Adverse Clinical Events[1]	13.3% (231)	23.7% (122)	13.7% (77)	24.5% (44)
MACE 1[2]	9.3% (161)	14.8% (76)	10.4% (58)	19.0% (34)
MACE 2 (Safety MACE)[3]	7.5% (129)	10.1% (52)	6.6% (37)	12.3% (22)
Death	2.9% (50)	5.4% (28)	2.8% (16)	5.6% (10)
- Cardiac	1.8% (32)	4.3% (22)	2.3% (13)	3.9% (7)
- Noncardiac	1.1% (18)	1.2% (6)	0.5% (3)	1.8% (3)
Reinfarction	3.6% (62)	3.8% (19)	3.8% (21)	6.8% (12)
- Q wave	2.1% (36)	1.8% (9)	1.6% (9)	2.8% (5)
- Non Q wave	1.7% (28)	2.2% (11)	2.2% (12)	4.0% (7)
Death or reinfarction	6.2% (108)	8.6% (44)	6.0% (34)	10.0% (18)
Ischemic TVR	5.0% (85)	8.9% (44)	7.2% (40)	13.8% (24)
Ischemic TLR	3.9% (66)	6.8% (34)	6.0% (33)	12.1% (21)
Stroke	0.9% (16)	1.4% (7)	0.4% (2)	1.7% (3)
Major bleeding (non-CABG)	6.4% (110)	12.0% (61)	5.0% (28)	11.7% (21)
Target Lesion stent thrombosis	3.1% (52)	3.4% (17)	2.9% (16)	5.1% (9)
2 Year				
Net Adverse Clinical Events[1]	19.4% (333)	28.7% (147)	24.5% (135)	30.7% (55)
MACE 1[2]	15.9% (271)	20.0% (102)	21.4% (117)	24.7 (44)
MACE 2 (Safety MACE)[3]	10.5% (179)	12.9% (58)	10.5% (58)	13.4% (24)
Death	3.7% (63)	6.5% (33)	5.1% (28)	6.2% (11)
- Cardiac	2.2% (38)	4.3% (22)	2.9% (16)	4.5% (8)
- Noncardiac	1.5% (25)	2.3% (11)	2.3% (12)	1.8% (3)
Reinfarction	5.8% (96)	5.5% (27)	5.3% (29)	8.0% (14)
- Q wave	3.3% (55)	2.4% (12)	2.6% (14)	2.4% (6)
- Non Q wave	2.8% (46)	3.7% (18)	2.8% (15)	4.6% (8)
Death or reinfarction	9.0% (153)	11.2% (57)	9.4% (52)	11.2% (20)
Ischemic TVR	10.4% (173)	12.9% (63)	16.0% (86)	18.5% (32)
Ischemic TLR	7.7% (128)	10.2% (50)	13.6% (73)	16.2% (28)
Stroke	1.3% (22)	1.6% (8)	1.0% (5)	1.7% (3)
Major bleeding (non-CABG)	6.5% (113)	12.4% (63)	5.4% (30)	12.3% (22)
Target Lesion stent thrombosis	4.1% (69)	4.2% (21)	3.6% (20)	5.7% (10)
3 Year				
Net Adverse Clinical Events[1]	22.3% (381)	31.9% (163)	26.7% (148)	31.9% (57)
MACE 1[2]	18.9% (321)	23.7% (120)	23.4% (129)	25.9% (46)

Table 11: HORIZONS AMI Clinical Endpoints, All TAXUS Express Male and Female Patients at 30 Days, 1 Year, 2 Year and 3 Year (Stent ITT Population)

Endpoint	TAXUS Express Male Patients (N=1738)	TAXUS Express Female Patients (N=519)	Bare Metal Express Male Patients (N=569)	Bare Metal Express Female Patients (N=180)
MACE 2 (Safety MACE)[3]	12.9% (220)	15.8% (80)	12.5% (69)	14.0% (25)
Death	5.0% (85)	7.5% (38)	6.4% (35)	7.4% (13)
- Cardiac	2.8% (47)	4.7% (24)	3.6% (20)	4.5% (8)
- Noncardiac	2.3% (38)	2.9% (14)	2.8% (15)	3.0% (5)
Reinfarction	6.9% (115)	7.2% (35)	6.1% (33)	8.0% (14)
- Q wave	3.7% (62)	2.6% (13)	2.6% (14)	3.4% (6)
- Non Q wave	3.6% (59)	5.3% (25)	3.6% (19)	4.6% (8)
Death or reinfarction	11.2% (190)	13.8% (70)	11.4% (63)	11.8% (21)
Ischemic TVR	11.7% (194)	14.6% (71)	17.1% (92)	19.2% (33)
Ischemic TLR	8.7% (145)	11.7% (57)	14.5% (78)	16.9% (29)
Stroke	1.6% (26)	1.9% (9)	1.3% (7)	1.7% (3)
Major bleeding (non-CABG)	7.0% (120)	13.4% (68)	5.7% (32)	12.3% (22)
Target Lesion stent thrombosis	4.6% (77)	5.3% (26)	3.8% (21)	5.7% (10)

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

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

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

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA supplement approval as described above. The HORIZONS AMI trial showed that in STEMI patients, compared to an otherwise identical Express BMS, the TAXUS Express results in a similar rate of the composite of death, reinfarction, stroke or stent thrombosis at 1 year. Given the similarities between the ION Stent and the TAXUS Express^2 stent and available supportive nonclinical and clinical data (see Section X. above), the safety decision based on the HORIZONS AMI trial was considered applicable.

B. Effectiveness Conclusions

The HORIZONS AMI trial showed that in STEMI patients, compared to an otherwise identical Express BMS, the TAXUS Express results in reduced rates of ischemia-driven target lesion revascularization at 1 year and a lower rate of analysis segment binary angiographic restenosis at 13 months. Given the similarities between the ION Stent and the TAXUS Express^2 stent and available supportive nonclinical and clinical data (see Section X. above), the effectiveness decision based on the HORIZONS AMI trial was considered applicable.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIII. CDRH DECISION

CDRH issued an approval order on February 22, 2012

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

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