Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.

This device is supplied in sterile condition. All materials inside the sterile barrier pouch (the delivery system and stent, as well as the carrier tube and pouch liner) are sterile. The external surface of the sterile barrier pouch, as well as the product carton, should not be considered sterile.

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1 WARNING

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

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

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

DEVICE DESCRIPTION

2 ION Paclitaxel-Eluting Platinum Chromium Coronary Stent System

The ION Paclitaxel-Eluting Platinum Chromium Stent System (hereinafter referred to as ION Stent System) is a device/drug combination product comprised of two regulated components: a device (ION Stent System) and a drug product (a formulation of paclitaxel contained in a polymer coating). The characteristics of the ION Stent System are described in Table 2.1.

Table 2.1 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	
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	≥ 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

2.1 Device Component Description

The ION™ Stent is the paclitaxel-coated member of the platinum chromium (PtCr) Stent Series. The ION Stent System is available in four stent models each engineered for specific diameters to provide consistent stent-to-artery ratios across the range of reference vessel diameters indicated:

- Small Vessel (SV): 2.25 mm
- Small Workhorse (SWH): 2.50, 2.75 mm
- Workhorse (WH): 3.00, 3.50 mm
- Large Vessel (LV): 4.00 mm

CONTENTS for (1) ION Over-the-Wire Stent System

- One (1) ION Over-the-Wire Stent System

CONTENTS for (1) ION Monorail® Stent System

- One (1) ION Monorail Stent System
- Two (2) CLIPIT™ Coil clips

- One (1) Flushing needle with luer fitting

2.2 Drug Component Description

The stent component of the ION Stent System is a PtCr stent with a drug/polymer coating formulation consisting of paclitaxel (the active ingredient) and Translute™ Polymer carrier (the inactive ingredient). The drug/polymer coating formulation is identical to the drug/polymer coating formulation used in the following TAXUS products: TAXUS Express Paclitaxel-Eluting Stent and TAXUS Liberté Paclitaxel-Eluting Stent.

2.2.1 Paclitaxel

The active pharmaceutical ingredient in the ION 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-,6,12bbis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6, 9,10,11,12,12a,12bdodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester,[2a *R*-[2aα,4β,4aβ,6β,9α (α*R**,βS*),11α,12α, 12aα,12bα]]-. The chemical structure of paclitaxel is shown in Figure 2.1.

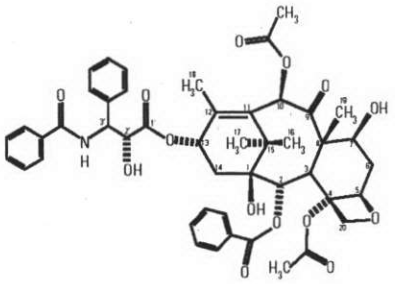
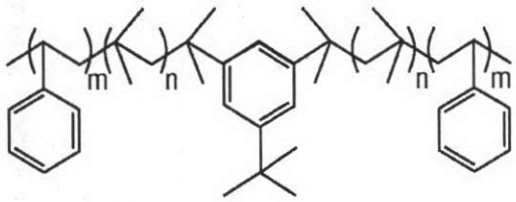


Figure 2.1 The Chemical Structure of Paclitaxel

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.

2.2.2 Translute Polymer Carrier

The only inactive ingredient in the ION Stent is SIBS [poly(styrene-b-isobutylene-b-styrene)], a tri-block copolymer (trade name: Translute), composed of polystyrene and polyisobutylene units. 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 paclitaxel and conformally applied to the stent. There is no primer or topcoat layer. The structural formula for the polymer is shown in Figure 2.2.



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

Figure 2.2 The Chemical Structure of Translute Polymer Carrier

2.2.3 Product Matrix and Paclitaxel Content

Table 2.2 ION Stent System Product Matrix and Paclitaxel Content

Product Code MR	Product Code OTW	Nominal Expanded Stent Inner Diameter (mm)	Nominal Unexpanded Stent Length	Nominal Paclitaxel Content (µg)
H74939024082	H74939023082	2.25	8	39
H74939024082	H74939023082	2.50	8	40
H74939024082	H74939023082	2.75	8	40
H74939024083	H74939023083	3.00	8	43
H74939024083	H74939023083	3.50	8	43
H74939024084	H74939023084	4.00	8	57
H74939024122	H74939023122	2.25	12	58
H74939024122	H74939023122	2.50	12	62
H74939024122	H74939023122	2.75	12	62
H74939024123	H74939023123	3.00	12	61
H74939024123	H74939023123	3.50	12	61
H74939024124	H74939023124	4.00	12	82
H74939024162	H74939023162	2.25	16	74
H74939024162	H74939023162	2.50	16	80
H74939024162	H74939023162	2.75	16	80
H74939024163	H74939023163	3.00	16	86
H74939024163	H74939023163	3.50	16	86

H74939024164	H74939023164	4.00	16	107
H74939024202	H74939023202	2.25	20	94
H74939024202	H74939023202	2.50	20	97
H74939024202	H74939023202	2.75	20	97
H74939024203	H74939023203	3.00	20	104
H74939024203	H74939023203	3.50	20	104
H74939024204	H74939023204	4.00	20	131
H74939024242	H74939023242	2.25	24	109
H74939024242	H74939023242	2.50	24	115
H74939024242	H74939023242	2.75	24	115
H74939024243	H74939023243	3.00	24	123
H74939024243	H74939023243	3.50	24	123
H74939024244	H74939023244	4.00	24	156
H74939024282	H74939023282	2.25	28	129
H74939024282	H74939023282	2.50	28	133
H74939024282	H74939023282	2.75	28	133
H74939024283	H74939023283	3.00	28	141
H74939024283	H74939023283	3.50	28	141
H74939024284	H74939023284	4.00	28	181
H74939024322	H74939023322	2.25	32	148
H74939024322	H74939023322	2.50	32	155
H74939024322	H74939023322	2.75	32	155
H74939024323	H74939023323	3.00	32	166
H74939024323	H74939023323	3.50	32	166
H74939024324	H74939023324	4.00	32	206
H74939024382	H74939023382	2.75	38	181
H74939024383	H74939023383	3.00	38	197
H74939024383	H74939023383	3.50	38	197
H74939024384	H74939023384	4.00	38	247

3 INTENDED USE/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 2.50 mm in diameter in lesions ≤ 28 mm in length;
- for the treatment of de novo lesions in native coronary arteries 2.75 mm to 4.00 mm in diameter in lesions ≤ 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.

4 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 (see Section 2.2.2., Translute Polymer Carrier for more information).

Coronary Artery Stenting is contraindicated for use in:

- Patients who cannot receive recommended antiplatelet and/or anticoagulant therapy (see Section 6.2 Pre- and Post-Procedure Antiplatelet Regimen for more information).
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery device.

5 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 stent thrombosis, vascular complications, and/or bleeding events.
- This product should not be used in patients who are not likely to comply with recommended antiplatelet therapy.

6 PRECAUTIONS

6.1 General Precautions

- Only physicians who have received adequate training should perform stent implantation.
- 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 6.1 System 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 the PERSEUS Clinical Program, which evaluated the ION Stent System, have been 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. In the clinical trials analyzed to date, evaluated on earlier generations of TAXUS Stents, the differences in the incidence of stent thrombosis observed with a paclitaxel-eluting stent compared to bare-metal stents have not been associated with an increased risk of cardiac death, myocardial infarction, or all-cause mortality. Additional data from longer-term follow-up in the PERSEUS clinical trials and in previous trials in the TAXUS program 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, may have an increased risk of adverse events, including stent thrombosis, stent embolization, myocardial infarction, or death.

6.2 Pre-and Post-Procedure Antiplatelet Regimen

In the PERSEUS Clinical Program, which evaluated the ION Stent System, clopidogrel or ticlopidine was administered pre-procedure and for a period of 6 months post procedure and for 12 months in patients who were not at high risk of bleeding. Aspirin was administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce the risk of thrombosis. See Section 10 Clinical Studies, for more specific information. In the HORIZONS AMI trial, clopidogrel or ticlopidine was to be administered pre-procedure and for a period of 6 months post-procedure, and recommended for 1 year or longer. Aspirin was to be administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely.

The optimal duration of antiplatelet therapy, specifically clopidogrel, is unknown after implantation of a DES and DES thrombosis may still occur despite continued therapy. Data from several studies suggest that a longer duration of antiplatelet therapy than was recommended post-procedurally in certain drug-eluting stent pivotal clinical trials (including TAXUS clinical trials which evaluated the earlier generation stents with the same drug/polymer coating formulation as the ION™ Stent System) may be beneficial. Provided herein are recent recommendations from the "2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention (PCI)" Section 6.2.1.

6.2.1 Oral Antiplatelet Therapy

For Elective PCI Procedures

Continuation of combination treatment with aspirin and a $P2Y_{12}$ inhibitor after PCI appears to reduce major adverse cardiac events. On the basis of randomized clinical trial protocols, secondary prevention measures, and expert consensus opinion, aspirin 81 mg daily should be given indefinitely after PCI. Likewise, a $P2Y_{12}$ inhibitor should be given daily for at least 12 months in patients who are not at high risk of bleeding. Full guidelines are provided at the following website:

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

For PCI in ST-Elevation MI (STEMI) Patients

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

1) A loading dose of a $P2Y_{12}$ inhibitor is recommended for STEMI patients for whom PCI is planned. Regimens should be one of the following:
   a) At least 300 to 600 mg of clopidogrel should be given as early as possible before or at the time of primary or nonprimary PCI.
   b) Prasugrel 60 mg should be given as soon as possible for primary PCI.
   c) For STEMI patients undergoing nonprimary PCI, the following regimens are recommended:
      (i) If the patient has received fibrinolytic therapy and has been given clopidogrel, clopidogrel should be continued as the thienopyridine of choice;
      (ii) If the patient has received fibrinolytic therapy without a thienopyridine, a loading dose of 300 to 600 mg of clopidogrel should be given as the thienopyridine of choice;
      (iii) if the patient did not receive fibrinolytic therapy, either a loading dose of 300 to 600 mg of clopidogrel should be given or, once the coronary anatomy is known and PCI is planned, a loading dose of 60 mg of prasugrel should be given promptly and no later than 1 hour after PCI.
2) The duration of $P2Y_{12}$ inhibitor therapy should be as follows:
   a) In patients receiving a stent (BMS or drug-eluting [DES]) during PCI for ACS, clopidogrel 75 mg, prasugrel 10 mg daily should be given for at least 12 months;
   b) If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by $P2Y_{12}$ receptor inhibitor therapy, earlier discontinuation should be considered.

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 which requires early discontinuation of antiplatelet therapy, the interventional cardiologist and patient should carefully consider whether a drug-eluting stent and its associated recommended antiplatelet therapy is the appropriate PCI choice. Following PCI, should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risk associated with premature discontinuation of antiplatelet therapy. Generally, it is recommended to postpone elective surgery for one year among those patients for whom surgery can be deferred, continuation of aspirin therapy should be considered during the perioperative period in high risk DES patients.

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

6.3 Use of Multiple Stents

In the PERSEUS Clinical Program, which evaluated the ION Stent System, the protocols specified that patients were to be treated with no more than one ION Stent, except in situations involving bailout stenting. The use of multiple drug-eluting stents will expose the patient to larger amounts of drug and polymer. In the HORIZONS AMI trial, lesions > 26 mm in length were to be treated with 2 (or more as required) overlapping study stents. Table 6.1 provides clinical outcomes on patients from the HORIZONS AMI trial who were treated with multiple overlapping study stents (528 patients in the TAXUS Express arm and 124 patients in the bare metal Express arm).

Table 6.1: Clinical Outcomes in HORIZON AMI Patients with Multiple Overlapping Study Stents

	1 Year		3 Year

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

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

When multiple overlapping stents are used resulting in stent-to stent contact, it is suggested that the stents be adequately overlapped to avoid the potential for gap restenosis. It is recommended that overlapping stents be of similar composition to minimize the likelihood of dissimilar metal corrosion.

Potential interactions of the ION Stent with other drug eluting or coated stents have not been evaluated in the PERSEUS Clinical Program.

6.4 Brachytherapy

The safety and effectiveness of the ION 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 an ION Stent have not been established. Both vascular brachytherapy and the ION Stent alter arterial remodeling. The synergy between these two treatments has not been determined.

6.5 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 ION Stent implantation have not been established.

6.6 Use in Special Populations

6.6.1 Pregnancy

Pregnancy "Category C". See Drug Information – Section 7.5, Pregnancy. There are no adequate or well-controlled studies in pregnant women or men intending to father children. ION 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 ION Stent in women who are of childbearing potential or in men intending to father children should be given careful consideration.

6.6.2 Lactation

See Drug Information – Section 7.6, 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.

6.6.3 Gender

See Clinical Information - Section 10, Clinical Studies.

6.6.4 Ethnicity

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

6.6.5 Pediatric Use

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

6.6.6 Geriatric Use

Clinical studies of the ION Stent did not have an upper age limit. In the PERSEUS Workhorse study, there were 402 patients in the ION Stent group who were age 65 or older, and 124 in the PERSEUS Small Vessel study. There were 22 ION Stent patients in the PERSEUS Workhorse study who were over 80 years of age, and 10 ION Stent patients in the PERSEUS Small Vessel study. There were no statistically significant differences in outcomes between patients under 65 and over 65 years of age in the ION Stent group.

6.7 Lesion/Vessel Characteristics

The safety and effectiveness of the ION Stent have not been established in the cerebral, carotid, or peripheral vasculature or the following coronary disease 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 34 mm or requiring more than one ION Stent.
- Patients with lesions located in the saphenous vein grafts, in the unprotected left main coronary artery, ostial lesions, or lesions located at a bifurcation.
- Patients with in-stent thrombosis.
- Patients with diffuse disease or poor flow distal to the identified lesions.
- Patients with tortuous vessels (> 60 degrees) in the region of the obstruction or proximal to the lesion.
- Patients with in-stent restenosis.
- Patients with moderate or severe calcification in the lesion or a chronic total occlusion.
- Patients with multi-vessel disease.

6.8 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 ION 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 7.3 Drug Interactions for more information.

6.9 Magnetic Resonance Imaging (MRI)

The ION Stent has been shown to be MR Conditional (poses no known hazards under specified conditions) through non-clinical testing of single and overlapped configurations up to 74 mm in overall length. The conditions are as follows:

- Field strengths of 1.5 and 3 Tesla
- Static magnetic field gradient < 9 T/m (extrapolated)
- Normal operational mode (maximum whole body averaged specific absorption rate (SAR) of lower than 2.0 W/kg) for a total active MR scan time (with RF exposure) of 15 minutes or less

The ION Stent should not migrate in this MRI environment. MR imaging within these conditions may be performed immediately following the implantation of the stent. This stent has not been evaluated to determine if it is MR Conditional beyond these conditions.

3.0 Tesla Temperature Information

Non-clinical testing of RF-induced heating was performed at 123 MHz in a 3.0 Tesla Magnetom Trio®, Siemens Medical Solutions MR system, software version Numaris/4, Syngo® MR A30. RF power was applied for 15 minutes and the measured conductivity of the phantom material was about 0.3 S/m. The phantom average SAR was calculated using calorimetry to be 2.2 W/kg. The maximal in-vitro temperature rise was calculated as 2.6°C for a measured stent length of 74 mm with the whole-body SAR scaled to 2.0 W/kg. The calculations did not include the cooling effects due to blood flow.

1.5 Tesla Temperature Information

Non-clinical testing of RF-induced heating was performed at 64 MHz in a 1.5 Tesla Intera® Philips Medical Systems, software version Release 10.6.2.0, 2006-03-10 whole body coil MR scanner. RF power was applied for 15 minutes and the measured conductivity of the phantom material was about 0.3 S/m. The phantom average SAR was calculated using calorimetry to be 2.1 W/kg. The maximal in-vitro temperature rise was calculated as 2.6°C for a measured stent length of 74 mm with the whole-body SAR scaled to 2.0 W/kg. The calculations did not include the cooling effects due to blood flow.

In vivo, local SAR depends on MR Field strength and may be different than the estimated whole body averaged SAR, due to body composition, stent position within the imaging field, and scanner used, thereby affecting the actual temperature rise.

Image Artifact Information

The calculated image artifact extends approximately 7 mm from the perimeter of the device diameter and 5 mm beyond each end of the length of the stent when scanned in non-clinical testing using a Spin Echo sequence. With a Gradient Echo sequence the calculated image artifact extends 5 mm beyond the perimeter of the diameter and 6 mm beyond each end of the length with both sequences partially shielding the lumen in a 3.0 Tesla Intera (Achieva Upgrade), Philips Medical Solutions, software version Release 2.5.3.0 2007-09-28 MR system with a transmit/receive head coil.

Medical Registration

It is recommended that patients register the conditions under which the implant can be scanned safely with the MedicAlert Foundation (www.medicalert.org) or equivalent organization.

Magnetic Resonance Conditional

6.10 Stent Handling

(also see Section 14, Operational Instructions)

- For single use only. Do not resterilize or reuse this product. Note product "Use By" date. (See Warning - Section 1)
- The premounted ION 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 Operational Instructions - Section 14.3.3, Balloon Preparation). Do not use air or any gas medium to inflate the balloon.
- In the event the ION Stent is not deployed, do not use the product and contact your local Boston Scientific Representative for return information.

6.11 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 Operational Instructions - Section 14.3.3 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 6.12, 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 6.12, Stent System Removal).
- Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on product label (see Table 14.5.1. Typical **ION™ Stent System compliance**). Use of pressures higher than specified on product label may result in a ruptured balloon and potential intimal damage and dissection. The stent inner diameter should approximate 1.1 times the reference diameter of the vessel.
- Placement of the stent has the potential to compromise side branch patency.
- Implanting a stent may lead to dissection of the vessel distal and/or proximal to the stented portion, and may cause acute closure of the vessel requiring additional intervention (e.g. CABG, further dilation, placement of additional stents, or other).
- When treating multiple lesions, the distal lesion should be initially stented, followed by stenting of the more proximal lesion(s). Stenting in this order alleviates the need to cross the proximal stent in placement of the distal stent and reduces the chances of dislodging the proximal stent.

6.12 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 6.2 System Deflation Time Specifications). If greater than usual resistance is felt during delivery system 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 6.2 System Deflation Time Specifications (seconds)

<table>
<tr><th>Balloon Length/ Diameter</th><th>8 mm</th><th>12 mm</th><th>16 mm</th><th>20 mm</th><th>24 mm</th><th>28 mm</th><th>32 mm</th><th>38 mm</th></tr>
<tr><td>2.25 mm</td><td rowspan="5">≤ 16</td><td rowspan="5">≤ 16</td><td rowspan="2">≤ 16</td><td rowspan="2">N/A</td></tr>
<tr><td>2.50 mm</td></tr>
<tr><td>2.75 mm</td><td rowspan="3">≤ 21</td><td rowspan="3">≤ 30</td></tr>
<tr><td>3.00 mm</td></tr>
<tr><td>3.50 mm</td><td>≤ 21</td></tr>
<tr><td>4.00 mm</td><td></td><td></td></tr>
</table>

6.13 Post-Procedure

- Care must be exercised when crossing a newly deployed stent with any wire, catheter or ancillary device to avoid disrupting the stent placement, apposition, and/or coating.
- In the PERSEUS Clinical Program, which evaluated the ION Stent System, clopidogrel or ticlopidine was administered pre-procedure and for a period of 6 months post-procedure and for 12 months in patients who were not at high risk of bleeding. Aspirin was administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce the risk of thrombosis. See Section 10 – Clinical Studies, for more specific information.
- If the patient requires imaging, see Precautions – Section 6.9, Magnetic Resonance Imaging (MRI).

7 DRUG INFORMATION

7.1 Mechanism of Action

The mechanism (or mechanisms) by which an ION 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.

7.2 Pharmacokinetics

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

7.3 Drug Interactions

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

Formal drug interaction studies have not been conducted with the ION Stent. Consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place an ION 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 an ION Stent.

7.4 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 39 times the dose provided by the largest ION Stent coated with 247 µg paclitaxel adjusted for body surface area).

7.5 Pregnancy

Pregnancy Category C: There are no adequate and well controlled studies in pregnant women of paclitaxel or ION 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 39 and 236 times the dose provided by the largest ION Stent coated with 247 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 39 times the dose provided by the largest ION Stent coated

with 247 µg paclitaxel adjusted for body surface area). ION 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 ION Stent in women who are of childbearing potential should be given careful consideration.

7.6 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 an ION 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.

8 OVERVIEW OF CLINICAL STUDIES

The PERSEUS Clinical Trial Program[2] evaluates the ION Stent for the treatment of single, *de novo* atherosclerotic lesions in 2 parallel studies, PERSEUS Workhorse (WH) and PERSEUS Small Vessel (SV). The ION Stent uses the same drug-polymer coating formulation as the TAXUS Express stent. Given this similarity, the HORIZONS AMI trial, which evaluated the safety and effectiveness of the TAXUS Express stent in patients with ST-elevated myocardial infarction undergoing primary stenting, is also relevant and included below. This overview includes a summary of each trial design as well as data generated from each trial. Table 8.1 provides a summary of the PERSEUS (WH and SV) and HORIZONS AMI trial designs.

8.1 PERSEUS Workhorse

The PERSEUS Workhorse (WH) study is a prospective, randomized, controlled, single-blind, non-inferiority trial to evaluate the safety and efficacy of the 1 µg/mm^2 (loaded drug/stent surface area) ION Stent in the treatment of *de novo* coronary lesions. Subjects with *de novo* target lesion length ≤ 28 mm and target vessel diameter ≥ 2.75 mm to ≤ 4.0 mm were considered for enrollment. The trial employs a 3:1 randomization to the ION or the TAXUS Express Paclitaxel-Eluting Stent respectively. The TAXUS Express Stent is an earlier generation stent with the same drug/polymer coating formulation as the ION Stent System.

The primary endpoint is the rate of target lesion failure (TLF; including any ischemia-driven revascularization of the target lesion [TLR], myocardial infarction [MI; Q-wave and non–Q-wave] related to the target vessel, or cardiac death related to the target vessel) at 12 months post-index procedure, testing non-inferiority of the ION Stent relative to the TAXUS Express Paclitaxel-Eluting Stent control. In-segment percent diameter stenosis at 9 months post-index procedure as measured by quantitative coronary angiography (QCA) is the secondary endpoint.

Enrollment of 1264 subjects was planned; 1262 (942 ION Stent and 320 TAXUS Express Stent) were enrolled and randomized at 90 sites. A total of 330 subjects were randomly assigned to protocol-mandated 9-month angiographic follow-up (angiographic subset). The protocol mandated antiplatelet therapy compliance in accordance with the ACC/AHA/SCAI Guidelines for PCI.[3]

The study is now considered complete with regard to the 12-month primary endpoint. Additional follow-up is ongoing to 5 years.

8.2 PERSEUS Small Vessel

The PERSEUS Small Vessel (SV) study is a prospective, single-arm, superiority trial to evaluate the safety and efficacy of the 1 µg/mm^2 (loaded drug/stent surface area) 2.25 mm and 2.5 mm ION Stents in the treatment of *de novo* coronary lesions in small vessels. Subjects with *de novo* target lesion length ≤ 20 mm and target vessel diameter ≥ 2.25 mm to < 2.75 mm in a native coronary artery were considered for enrollment. The trial compares the ION Stent to a matched bare metal (Express Stent) historical control group comprised of subjects with reference vessel diameter (RVD) ≥ 2.25 to < 2.75 mm and lesion length ≤ 20 mm from the TAXUS V trial.

All subjects in PERSEUS SV were required to undergo a 9-month angiographic assessment. The primary endpoint is in-stent late loss by quantitative coronary angiography (QCA) on 9-month follow-up (ION Stent compared to bare metal Express Stent) and the secondary endpoint is TLF at 12 months (ION Stent compared to a performance goal based on TAXUS Express Stent results from the TAXUS IV and TAXUS V trials).

A total of 224 patients were enrolled at 28 sites. The control group consisted of 125 matched bare metal Express Stent subjects from the TAXUS V trial, including 108 with 9-month QCA follow-up. The protocol mandated antiplatelet therapy compliance in accordance with the ACC/AHA/SCAI Guidelines for PCI.[4]

The study is now considered complete with regard to the primary endpoint. Additional follow-up is ongoing to 5 years.

8.3 HORIZONS AMI

The HORIZONS AMI trial[4,5] is a randomized, single-blind trial in patients with ST segment elevation MI designed to compare: (1) the outcomes of anticoagulation with either unfractionated heparin plus routine GP IIb/IIIa inhibition or bivalirudin and bail-out GP IIb/IIIa inhibition, and (2) primary angioplasty with stent implantation with either a slow rate-release paclitaxel-eluting stent (TAXUS Express) or an otherwise identical uncoated bare metal stent (Express). A total of 3602 patients were consented and randomized (primary randomization) in a 1:1 fashion in the emergency room to anticoagulation with unfractionated heparin plus routine GP IIb/IIIa inhibition or bivalirudin and bail-out GP IIb/IIIa inhibition. Emergent coronary angiography with left ventriculography was performed after primary randomization, followed by triage to either percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery or medical management at physician discretion. After coronary angiography, a total of 3006 patients were triaged to PCI and randomized (secondary randomization) in a 3:1 fashion to either a TAXUS Express stent or an uncoated bare metal stent Express stent. Patients were enrolled at 123 study centers in U.S., Argentina, Europe, and Israel. The primary efficacy endpoint of the stent randomization was ischemic target lesion revascularization at 12 months and the primary safety endpoint was the composite rate of death, reinfarction, stent thrombosis or stroke (MACE) at 12 months. Secondary endpoints included the rate of analysis segment angiographic binary restenosis at 13 months in the 1,203 patient angiographic cohort, as well as ischemic target lesion revascularization, MACE and its components at clinical follow-up through 3 years. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 6 months (1 year or longer recommended). Follow-up through 3 years is complete.

Table 8.1. Comparison of Clinical Studies

	PERSEUS Workhorse	PERSEUS Small Vessel	HORIZONS AMI
Purpose	To evaluate the safety and effectiveness in workhorse lesions	To evaluate the safety and effectiveness in small vessel lesions	To evaluate the safety and effectiveness of patients with ST-elevated myocardial infarction undergoing primary stenting
Study Design	Prospective, multicenter, randomized, single-blind, non-inferiority to PES	Prospective, multicenter, single-arm, open-label superiority to BMS	Prospective, multicenter, randomized, single-blind, superiority to BMS (efficacy) and non-inferiority to BMS (safety)

[2] Allocco DJ, Cannon LA, Britt A, et al. A prospective evaluation of the safety and efficacy of the TAXUS Element paclitaxel-eluting coronary stent system for the treatment of de novo coronary artery lesions: Design and statistical methods of the TAXUS PERSEUS clinical program. *Trials*. 2010;11(1):1.

[3] King SB, 3rd, Smith SC, Jr., Hirshfeld JW, Jr., et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee. *Circulation* 2008;117:261-95.

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

[5] Mehran R, Brodie B, Cox DA, et al. The Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial: study design and rationale. Am Heart J. 2008 Jul;156(1):44-56.

Primary Endpoint	12-month TLF	9-month in-stent late loss	Efficacy: Ischemic TLR Safety: Composite MACE (death, reinfarction, stroke or stent thrombosis)
Number of Subjects (ITT)	Total: 1264 planned; 1262 enrolled and randomized ION™ Stent: 942 TAXUS Express Stent: 320	Total: 224 ION Stent: 224 BMS Control Group: 125	Total: 3006 TAXUS: 2257 BMS Control: 749
Polymer	Translute™ Polymer		
PTx Dose Density	1 μg/mm^2		
Lesion Criteria: Vessel Diameter (by visual estimate)	≥ 2.75 mm to ≤ 4.00 mm	≥ 2.25 mm to < 2.75 mm	≥ 2.25 mm to ≤ 4.00 mm
Lesion Criteria: Lesion Length (by visual estimate)	≤ 28 mm	≤ 20 mm	< 100 mm
Number of stents	Single		Single or multiple
Stent Matrix	2.75-4.0 mm diameter 8, 12, 16, 20, 24, 28, 32 mm length	2.25-2.50 mm diameter 8, 12, 16, 20, 24 mm length	2.25-4.0 mm diameter 8, 12, 16, 20, 24, 28, and 32 mm length
Post-Procedure Antiplatelet Therapy	Clopidogrel or ticlopidine: at least 6 months, ideally for 12 months in patients who are not at high risk for bleeding. ASA: indefinitely		Aspirin indefinitely and clopidogrel or ticlopidine for 6 months (1 year or longer recommended)
Follow-Up	Clinical: 30 day, 9 month, 1 year, 18 month, annually 2-5 years Angiographic (330 subject subset): 9 month	Clinical: 30 day, 9 month, 1 year, 18 month, annually 2-5 years Angiographic (all): 9 month	Clinical: 30 day, 6 month, 1 year, 2 year, 3 year Angiographic / IVUS: 13 month
Abbreviations: ASA=aspirin; BMS=bare metal stent; ITT=intent-to-treat; PES=paclitaxel-eluting stent; PTx=paclitaxel; TLF=target lesion failure			

9 ADVERSE EVENTS

9.1 Observed Adverse Events

Observed adverse event experience comes from two studies which evaluated the ION Stent System: PERSEUS Workhorse and PERSEUS Small Vessel. Principal adverse events for these trials are shown in Table 9.1.1. Principal adverse event for the HORIZONS AMI trial are shown in Table 9.1.2

Table 9.1.1. PERSEUS Workhorse and PERSEUS Small Vessel Major Adverse Cardiac Events (MACE) and Stent Thrombosis From Post-Procedure to 1 Year Follow-Up

	PERSEUS Workhorse to 1 Year		PERSEUS Small Vessel to 1 Year	
	ION Stent (N=942)	TAXUS Express Stent[1] (N=320)	ION Stent (N=224)	Express Stent[2] (N=125)
In-Hospital MACE	1.9% (18/942)	2.5% (8/320)	0.0% (0/224)	1.6% (2/125)
30-Day MACE	2.2% (21/939)	3.1% (10/319)	0.9% (2/221)	2.4% (3/124)
9-Month MACE	5.6% (52/932)	6.3% (20/317)	7.8% (17/218)	14.6% (18/123)
Cardiac Death	0.3% (3/932)	0.3% (1/317)	0.9% (2/218)	0.8% (1/123)
MI	2.0% (19/932)	2.8% (9/317)	0.9% (2/218)	2.4% (3/123)
Q-Wave MI	0.4% (4/932)	0.0% (0/317)	0.5% (1/218)	0.0% (0/123)
Non-Q-Wave MI	1.6% (15/932)	2.8% (9/317)	0.5% (1/218)	2.4% (3/123)
TVR	4.0% (37/932)	4.4% (14/317)	6.9% (15/218)	12.2% (15/123)
TLR	2.6% (24/932)	3.5% (11/317)	3.7% (8/218)	10.6% (13/123)
Non-TLR	1.9% (18/932)	1.3% (4/317)	5.0% (11/218)	4.1% (5/123)

1-Year MACE	7.4% (68/922)	7.7% (24/313)	12.4% (27/218)	27.3% (33/121)
Cardiac Death	0.5% (5/922)	0.3% (1/313)	1.4% (3/218)	0.8% (1/121)
MI	2.2% (20/922)	2.9% (9/313)	0.9% (2/218)	2.5% (3/121)
Q-Wave MI	0.5% (5/922)	0.0% (0/313)	0.5% (1/218)	0.0% (0/121)
Non-Q-Wave MI	1.6% (15/922)	2.9% (9/313)	0.5% (1/218)	2.5% (3/121)
TVR	5.6% (52/922)	5.8% (18/313)	11.5% (25/218)	24.8% (30/121)
TLR	3.8% (35/922)	4.5% (14/313)	8.0% (13/218)	20.7% (25/121)
Non-TLR	2.5% (23/922)	1.9% (6/313)	7.8% (17/218)	7.4% (9/121)
1-Year ARC Stent Thrombosis				
Definite or Probable	0.4% (4/918)	0.3% (1/313)	0.5% (1/215)	0.8% (1/119)
Definite	0.3% (3/918)	0.3% (1/313)	0.5% (1/215)	0.8% (1/119)
Probable	0.1% (1/918)	0.0% (0/313)	0.0% (0/215)	0.0% (0/119)

Abbreviations: ARC=Academic Research Consortium; BMS=bare metal stent; DES=drug-eluting stent; MACE=major adverse cardiac events (cardiac death, Q- or non-Q-wave MI, TVR); MI=myocardial infarction; TLR=target lesion revascularization; TVR=target vessel revascularization.

[1] DES Control

[2] BMS Control

Table 9.1.2 : HORIZONS AMI Major Adverse Cardiac Events (MACE) From Post-Procedure to Latest Follow-Up

	HORIZONS AMI	
	TAXUS Express (N=2257)	**Bare Metal Express (N=749)**
30-Day		
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)
TL stent thrombosis	2.3% (50)	2.7% (20)
1-Year		
Net Adverse Clinical Events[1]	15.8% (355)	16.3%(121)
MACE 1[2]	10.6% (237)	12.4% (92)
MACE 2 (Safety MACE)[3]	8.1% (181)	8.0% (59)
2-Year		
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)
3-Year		
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)

Table 9.1.2 : HORIZONS AMI Major Adverse Cardiac Events (MACE) From Post-Procedure to Latest Follow-Up

	HORIZONS AMI	
	TAXUS Express (N=2257)	**Bare Metal Express (N=749)**
Major bleeding (non-CABG)	8.4% (188)	7.3% (54)
TL 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.

An angiographic core laboratory review of all available angiograms in the PERSEUS Clinical Trials revealed a total of 3 stent fractures - 2 ION stent fractures (Type 3[6]) that were seen on angiograms performed at 286 and 259 days post-stent implantation and 1 Taxus Express stent fracture (Type 4[4]) noted on an angiogram performed 861 days post-stent implantation. Only the fracture that occurred with the Taxus Express stent was associated with a major adverse cardiovascular event (a TLR).

9.2 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 anti-coagulant and/or antiplatelet therapy, contrast medium, or stent materials
- Angina
- Arrhythmias, including ventricular fibrillation and ventricular tachycardia
- Arteriovenous fistula
- Cardiac tamponade
- Cardiogenic shock/pulmonary edema
- Coronary aneurysm
- Death
- Dissection
- Emboli, distal (air, tissue or thrombotic material or material from devices(s) used in the procedure)
- Heart failure
- Hematoma
- Hemorrhage, required transfusion
- Hypotension/hypertension
- Infection, local or systemic
- Ischemia, myocardial
- Pain, access site
- Perforation or rupture of coronary artery
- Pericardial effusion
- Pseudoaneurysm, femoral
- Renal failure
- Respiratory failure
- Restenosis of stented segment
- Stent embolization or migration
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident /TIA
- Total occlusion of coronary artery
- Vessel spasm
- Vessel trauma requiring surgical repair or reintervention

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

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

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

10 CLINICAL STUDIES

[6] From Table 1 in Popma, JJ, Tiroch, K, Almonacid, A, Cohen, SA, Kandzari, DE, and Leon, MB. A Qualitative and Quantitative Angiographic Analysis of Stent Fracture Late Following Sirolimus-Eluting Stent Implantation. Am J Cardiol 103: 923–929, 2009.

10.1 PERSEUS Workhorse

Primary Objective: The primary objective of the PERSEUS WH study was to evaluate the safety and efficacy of the ION™ Paclitaxel-Eluting Platinum Chromium Coronary Stent System for the treatment of *de novo* atherosclerotic lesions of up to 28 mm in length (by visual estimate) in native coronary arteries of 2.75 mm to 4.0 mm diameter (by visual estimate) compared to the TAXUS Express Stent control. The TAXUS Express Stent is an earlier generation stent with the same drug/polymer coating formulation as the ION Stent System.

Design: PERSEUS Workhorse is a prospective, randomized, controlled, single-blind, non-inferiority trial which employs a 3:1 randomization to the ION or the TAXUS Express Paclitaxel-Eluting Stent respectively. Eligible patients were those ≥ 18 years old with documented stable angina pectoris, unstable angina pectoris, or documented silent ischemia and left ventricular ejection fraction (LVEF) ≥ 30%. *De novo* target lesions in a native coronary artery with diameter stenosis ≥ 50%, reference vessel diameter ≥ 2.75 mm to ≤ 4.0 mm, and cumulative lesion length ≤ 28 mm coverable by a single study stent were eligible. Multiple stenting was allowed for bail-out only. The protocol mandated antiplatelet therapy compliance in accordance with the ACC/AHA/SCAI Guidelines for PCI.[2]

The primary endpoint is the rate of target lesion failure (TLF; including any ischemia-driven revascularization of the target lesion [TLR], myocardial infarction [MI; Q-wave and non–Q-wave] related to the target vessel, or cardiac death related to the target vessel) at 12 months post-index procedure, testing non-inferiority of the ION Stent relative to the TAXUS Express Paclitaxel-Eluting Stent control. In-segment percent diameter stenosis at 9 months post-index procedure as measured by quantitative coronary angiography (QCA) is the secondary endpoint.

Enrollment of 1264 subjects was planned. A total of 1262 (942 ION Stent and 320 TAXUS Express Stent) were enrolled and randomized at 90 centers. Of the 1262 subjects included in the intent-to-treat analysis set, a total of 1235 subjects (922 ION Stent and 313 TAXUS Express Stent) were evaluable for the 12-month primary endpoint. A total of 330 subjects (256 ION Stent, 74 TAXUS Express Stent) were randomly assigned to protocol-mandated 9-month angiographic follow-up (angiographic subset). Angiographic assessments were performed for the area of the vessel within the stent margins (in-stent) and the areas immediately 5 mm proximal and distal from the stent margins (analysis segment).

Follow-up included clinical assessments at 30 days, 9, 12 and 18 months, and 2, 3, 4 and 5 years post index procedure. After the 12-month follow-up, the study population was reduced to a pre-specified cohort (Safety Population), which consists of all patients who received a study stent (ION Stent or TAXUS Express Stent). The study is now considered complete with regard to the 12-month primary endpoint.

Both the primary and secondary endpoints were analyzed under a Bayesian framework. Bayesian analyses can be interpreted in a more intuitive way than conventional frequentist analyses through the posterior distributions they produce. These posterior distributions give the probability that a parameter of interest (e.g. the difference in the rate of TLF across treatment groups) lies within a certain range, given the data observed. Therefore Bayesian methods can provide a posterior probability that the non-inferiority hypothesis is true given the data observed, whereas the frequentist P value provides the probability of observing data as or more extreme than that observed assuming the non-inferiority hypothesis is false.

Results: Results are presented below (Tables 10.1.1 - 10.1.6, Figure 10.1.1 and Figure 10.1.2).

Demographics: Patients were well-matched for baseline demographics. There were no significant differences between the randomized treatment groups with the exception of slightly lower age in the ION Stent group compared to the TAXUS Express Stent control (62.2±9.6 versus 63.5±9.5, P=0.03). Approximately 71% of patients in the ION Stent group and 69% of patients in the TAXUS Express Stent group were male. Approximately 93% of patients in both the ION and TAXUS Express Stent groups were Caucasian, and 25% were medically treated diabetics.

Baseline lesion characteristics: Reference vessel diameter was 2.78±0.48 mm and 2.75±0.47 mm in the ION Stent and TAXUS Express Stent groups, respectively, with baseline lesion length of 14.2±6.1 mm and 14.1±5.8 mm, respectively.

12-Month Clinical and 9-Month Angiographic Outcomes

Table 10.1.1. PERSEUS Workhorse Clinical Results

	1-year (ITT population)	
	ION Stent (N=942)	TAXUS Express Stent[1] (N=320)
EFFICACY		
TVR, Overall	5.6% (52/922)	5.8% (18/313)
TLR, Overall	3.8% (35/922)	4.5% (14/313)
TLR, PCI	3.6% (33/922)	4.2% (13/313)
TLR, CABG	0.3% (3/922)	0.6% (2/313)
Non-TLR, Overall	2.5% (23/922)	1.9% (6/313)
Non-TLR, PCI	2.3% (21/922)	1.6% (5/313)
Non-TLR, CABG	0.3% (3/922)	1.0% (3/313)
SAFETY		
Total Death	0.7% (6/922)	0.6% (2/314)
Cardiac Death or MI	2.5% (23/922)	2.9% (9/313)
Cardiac Death	0.5% (5/922)	0.3% (1/313)

MI	2.2% (20/922)	2.9% (9/313)
Q-wave MI	0.5% (5/922)	0.0% (0/313)
Non-Q-wave MI[2]	1.6% (15/922)	2.9% (9/313)
ARC Stent Thrombosis		
Definite or Probable	0.4% (4/918)	0.3% (1/313)
Definite	0.3% (3/918)	0.3% (1/313)
Probable	0.1% (1/918)	0.0% (0/313)

[1] DES Control
[2] Timing of non-Q-wave MI: 15/15 ION events and 8/9 TAXUS Express events occurred peri-procedurally.
This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass graft; DES=drug-eluting stent; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization;TVR=target vessel revascularization.

Primary Endpoint (12-Month TLF): The primary endpoint was met: There is a 99.96% Bayesian posterior probability that the ION Stent is non-inferior to TAXUS Express Stent (given the data observed), demonstrating non-inferiority of the ION Stent versus the TAXUS Express Stent.

Table 10.1.2. PERSEUS Workhorse Primary Endpoint

12-Month Target Lesion Failure (TLF)	ION Stent	TAXUS Express Stent	Difference			Posterior Probability of NI[3]
Per Protocol[1]	5.568% (0.0076)	6.138% (0.0136)	-0.570% (0.0155)	1.85%	4.1%	0.9996

[1] Primary analysis for assessing hypothesis of non-inferiority and study success criterion. For per protocol analyses, only ITT PERSEUS Workhorse trial subjects who had the randomly assigned study stent implanted in the target coronary artery were included.
[2] 1-Sided 95% posterior credible interval, based off the 95th percentile of the posterior distribution.
[3] Posterior probability that the difference in the rate of 12-month TLF between ION Stent and TAXUS Express Stent is less than the pre-specified margin of 4.1%, given the data.
12-Month TLF: the proportion of patients who experience a TLF up to 365 days post-procedure out of the population that have been followed for at least 335 days or who have experienced a TLF up to 365 days post-procedure.

Secondary Endpoint (9-Month %DS): The secondary endpoint was met: There is a 99.70% Bayesian posterior probability that the ION Stent is non-inferior to the TAXUS Express Stent (given the data observed), demonstrating non-inferiority of the ION Stent versus the TAXUS Express Stent.

Table 10.1.3. PERSEUS Workhorse Secondary Endpoint

Ln (9-Month In-Segment %DS)	ION Stent	TAXUS Express Stent	Difference			Posterior Probability of NI[3]
Per Protocol[1]	3.087 (0.0374)	3.117 (0.0736)	-0.0294 (0.08253)	0.1078	0.20	0.9970

[1] Primary analysis for assessing hypothesis of non-inferiority. For per protocol analyses, only ITT PERSEUS Workhorse trial subjects who had the randomly assigned study stent implanted in the target coronary artery were included.
[2] 1-Sided 95% posterior credible interval, based off the 95th percentile of the posterior distribution.
[3] Posterior probability that the difference in mean ln (9-month %DS) between the ION Stent and the TAXUS Express Stent is less than the pre-specified margin of 0.20, given the data.
The secondary endpoint is 9-month in-segment %DS. For the secondary endpoint, a natural log (ln) transformation was used to improve the normality of the distribution. Analyses are performed on the transformed data.

Table 10.1.4. PERSEUS Workhorse Angiographic Results

Angiographic Outcomes[1]	ION™ Stent (N=228)	TAXUS Express Stent[2] (N=61)
MLD (mm), In-stent		
Post-Procedure	2.68±0.39 (228)	2.54±0.36 (61)
9-Month	2.34±0.67 (228)	2.28±0.64 (61)
MLD (mm), Analysis Segment		
Post-Procedure	2.25±0.49 (228)	2.16±0.37 (61)
9-Month	2.08±0.63 (228)	2.00±0.56 (61)
Acute Gain (mm), In-stent	1.93±0.41 (228)	1.83±0.40 (61)
Acute Gain, Analysis Segment (mm)	1.51±0.48 (228)	1.45±0.40 (61)
% DS, In-stent		
Post-Procedure	4.1±10.13 (228)	5.64±8.05 (61)
9-Month	16.37±20.86 (228)	16.02±20.61 (61)
% DS, Analysis Segment		
Post-Procedure	20.21±9.71 (228)	19.87±7.57 (61)
9-Month	26.10±17.71 (228)	26.37±17.47 (61)
Late Loss, In-stent (mm)	0.34±0.55 (228)	0.26±0.52 (61)
Late Loss, Analysis Segment (mm)	0.17±0.48 (228)	0.16±0.45 (61)
Binary Restenosis		
In-stent restenosis	7.9% (18/228)	6.6% (4/61)
Analysis segment restenosis	8.8% (20/228)	9.8% (6/61)

[1] Includes all patients in the angiographic subset with paired lesion data.
[2] DES Control
Abbreviations: DES=drug-eluting stent; DS=diameter stenosis; MLD=minumum lumen diameter.

Table 10.1.5. PERSEUS Workhorse Stent Thrombosis

Intent-to-Treat Population	ION Stent (N=942)	TAXUS Express Stent[2] (N=320)
Protocol Defined Stent Thrombosis[1]		
Cumulative through 1 year	0.4% (4/918)	0.3% (1/313)
Acute ST (≤ 24 hrs)	0.2% (2/942)	0.3% (1/320)
Subacute ST (> 24 hrs and ≤ 30 days)	0.0% (0/939)	0.0% (0/319)
Late ST (> 30 days and ≤ 12 months)	0.2% (2/936)	0.0% (0/317)

ARC Definite & Probable Stent Thrombosis[2]		
Cumulative through 1 year	0.4% (4/918)	0.3% (1/313)
Acute ST (≤ 24 hrs)	0.2% (2/942)	0.3% (1/320)
Subacute ST (> 24 hrs and ≤ 30 days)	0.0% (0/939)	0.0% (0/319)
Late ST (> 30 days and ≤ 12 months)	0.2% (2/936)	0.0% (0/317)

To be included in the calculation of stent thrombosis (ST) 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).

[1]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.

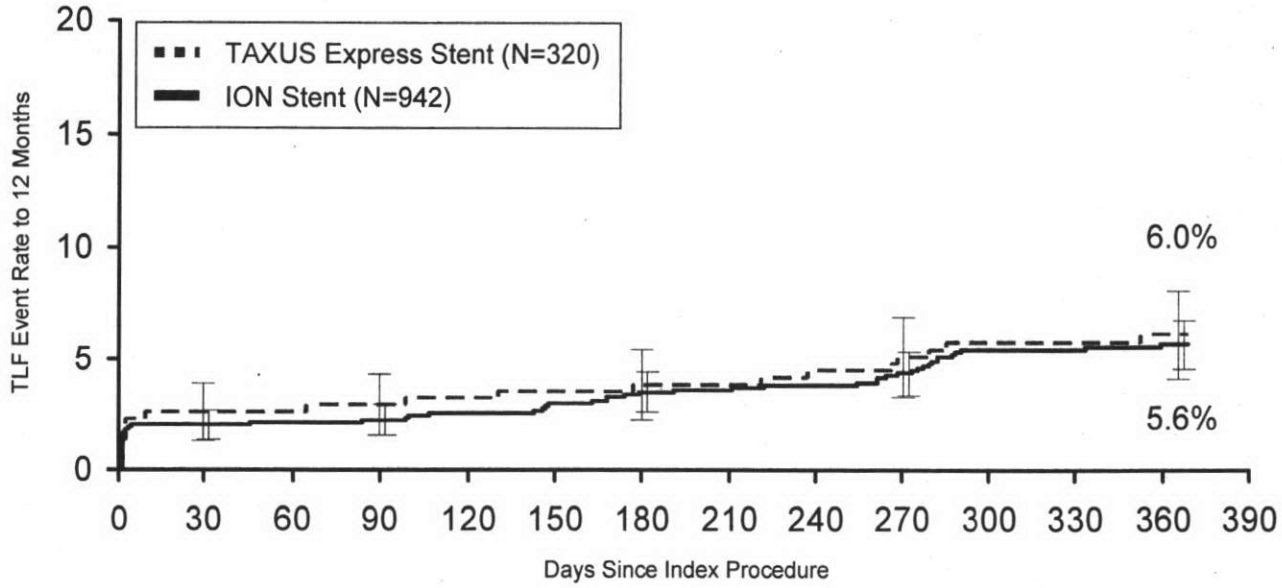
[2]Academic Research Consortium (ARC) stent thrombosis is defined as follows[7]:

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

[3]DES Control

Numbers are % (Count/Sample Size).

This trial was not sized to determine the rate of low frequency events with a pre-specified precision.



TAXUS Express Stent:	320	311	310	309	308	307	306				305		301
ION Stent:	942	921	918	914	913	910	905				900		887

	Event Rate	Event Free
ION Stent	5.6%	94.4%
TAXUS Express Stent DES Control	6.0%	94.0%

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

Figure 10.1.1. PERSEUS Workhorse Cumulative Rate of Target Lesion Failure to 12 Months, Intent-to-Treat, Event Rate ± 1.5 SE, All Patients (N=1262)

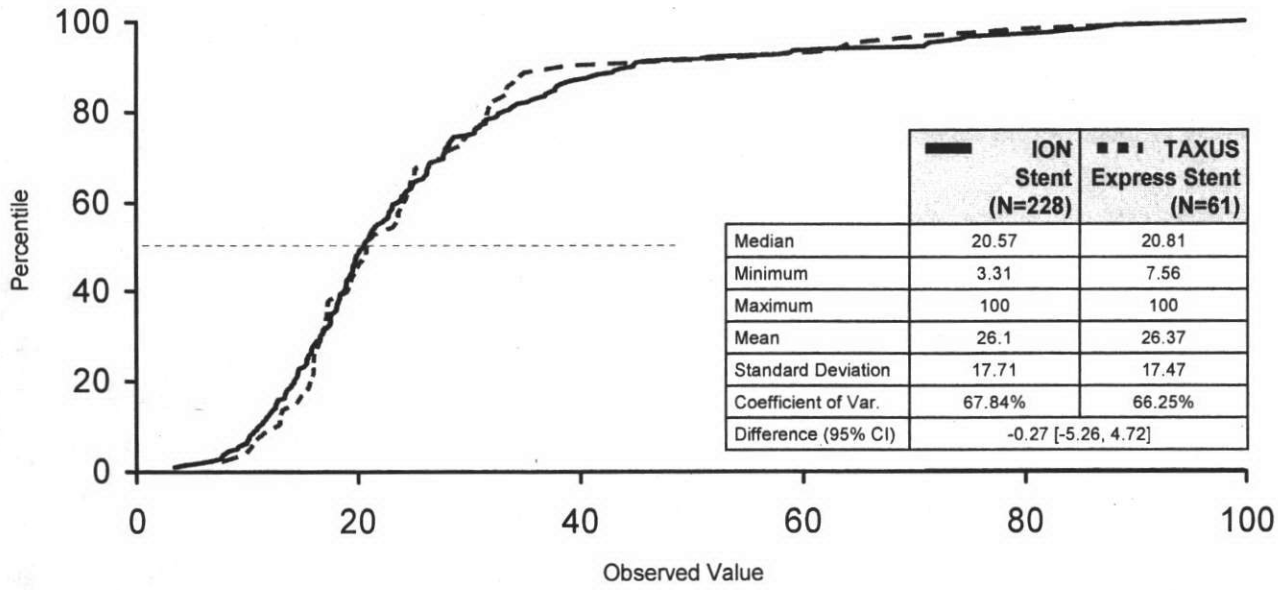


Figure 10.1.2. PERSEUS Workhorse Cumulative Frequency Distribution of 9-Month In-Segment Percent Diameter Stenosis by QCA, Intent-to-Treat, All Angiographic Subset Patients (N=330)

Results in patients with and without diabetes: Patients with diabetes mellitus represent a high-risk group for adverse events following percutaneous coronary intervention. Table 10.1.6 shows 1-year outcomes in patients with and without medically treated diabetes (defined as treatment with oral hypoglycemic agents or insulin at enrollment). While the PERSEUS WH study randomization was stratified for diabetic status, this trial was not adequately powered to study safety or effectiveness of the TAXUS Express Stent versus the ION Stent in patients with or without diabetes and was not designed to specifically support an approval for use in diabetic patients. These exploratory analyses suggest that in patients treated with the ION Stent, 1-year TLR rates were 4.9% in diabetic and 3.4% in non-diabetic patients.

Table 10.1.6. PERSEUS Workhorse Clinical Results in Patients with and Without Medically Treated Diabetes

	1-year (ITT Population)	
	ION™ Stent Patients With Medically Treated Diabetes (N=232)	ION Stent Patients Without Medically Treated Diabetes (N=710)
EFFICACY		
TVR, Overall	7.6% (17/223)	5.0% (35/699)
TLR, Overall	4.9% (11/223)	3.4% (24/699)
TLR, PCI	4.5% (10/223)	3.3% (23/699)
TLR, CABG	0.4% (1/223)	0.3% (2/699)
Non-TLR, Overall	3.6% (8/223)	2.1% (15/699)
Non-TLR, PCI	2.7% (6/223)	2.1% (15/699)
Non-TLR, CABG	0.9% (2/223)	0.1% (1/699)
SAFETY		

	1-year (ITT Population)	
	ION™ Stent Patients With Medically Treated Diabetes (N=232)	ION Stent Patients Without Medically Treated Diabetes (N=710)
Total Death	1.4% (3/222)	0.4% (3/700)
Cardiac Death or MI	3.1% (7/223)	2.3% (16/699)
Cardiac Death	1.3% (3/223)	0.3% (2/699)
MI	2.2% (5/223)	2.1% (15/699)
Q-wave MI	0.9% (2/223)	0.4% (3/699)
Non-Q-wave MI	1.3% (3/223)	1.7% (12/699)
ARC Stent Thrombosis		
Definite or Probable	0.5% (1/220)	0.4% (3/698)
Definite	0.0% (0/220)	0.4% (3/698)
Probable	0.5% (1/220)	0.0% (0/698)

This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass graft; DES=drug-eluting stent; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization; TVR=target vessel revascularization.

In the PERSEUS Workhorse ITT population, of the 942 subjects randomized to ION, 667 subjects were male (70.8%) and 275 subjects were female (29.2%). The proportions in the TAXUS Express group were similar (68.8% male, 31.2% female). In comparison, the prevalence of coronary artery disease (CAD) is estimated at 9.2 million in males and 8.4 million in females for adults age 20 and older in the United States (i.e., the CAD population is estimated to be 52.2% males and 47.7% females). The disproportionate enrollment distribution in this trial may be partly attributable to gender differences in symptoms and pathophysiology[8], which may lead to under-diagnosis and referral of female patients with CAD. The gender proportions enrolled in this trial are similar to other drug-eluting stent trials; a meta-analysis of paclitaxel-eluting stent clinical trials reported an overall gender distribution of 71.8% male and 28.2% female.

To evaluate for possible sex-based differences in outcome of treatment with the ION Stent, sex/gender-specific analyses were performed on safety and effectiveness endpoints. The results suggest that the general conclusions of the overall study regarding both safety and effectiveness can be generalized for males and females.

The PERSEUS WH study was not powered to study safety or effectiveness of the ION Stent versus the TAXUS Express Stent in sex-specific subgroups. PERSEUS WH primary and secondary endpoint data were assessed for differences between male and female subgroups, as well as for any interaction between treatment group and gender. These post hoc analyses suggest that in patients treated with the ION stent, 12-month TLF rates were 7.0% in females and 5.1% in males, and 9-month %DS was 26.95±18.62 in females and 25.71±17.32 in males. Numerical differences were observed in the treatment effect (i.e., the difference between the ION Stent and TAXUS Express Stent), as shown in **Table 10.1.7** below. No significant treatment-by-gender interaction effect was observed for the primary endpoint of 12-month TLF (P=0.5485). A marginally significant treatment-by-gender interaction effect was observed for the secondary endpoint of 9-month in-segment %DS under the natural log transformation (P=0.0628). However, this analysis is limited by the small sample size; fifteen female TAXUS Express patients have available 9-month in-segment %DS data, and the mean %DS for those patients was markedly low. Considering the small sample size and the lack of observed interaction effect for the primary endpoint of 12-month TLF, there does not appear to be a clinically significant treatment-by-gender interaction in the PERSEUS WH trial. This suggests that the overall conclusions of this trial regarding both safety and effectiveness of the ION Stent can be generalized for males and females.

Table 10.1.7. PERSEUS Workhorse Primary and Secondary Endpoint Results by Gender, Intent-to-Treat, All Patients (N=887)

	TAXUS Express	ION Stent	Relative Risk [95% CI]	Difference [95% CI]	P value	Interaction p-Value
12-month TLF (Primary Endpoint)						
	(N=220)	**(N=667)**				0.5485
Male	4.7% (10/214)	5.1% (33/650)	1.09 [0.54, 2.17]	0.4% [-2.9%, 3.7%]	0.8136	
	(N=100)	**(N=275)**				

[8] Shaw LJ, Bairey Merz CN, Pepine CJ, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. J Am Coll Cardiol. 2006; 47(3):S4-S20.

	TAXUS Express	ION Stent	Relative Risk [95% CI]	Difference [95% CI]	P value	Interaction p-Value
Female	9.1% (9/99)	7.0% (19/272)	0.77 [0.36, 1.64]	-2.1% [-8.5%, 4.3%]	0.4971	
9-month Percent Diameter Stenosis in-Segment (Secondary Endpoint)						
	(N=53)	**(N=180)**				
Male	28.57±19.16 (46) (7.56, 100.00)	25.71±17.32 (156) (3.31, 100.00)	NA	-2.86 [-8.70, 2.97]	0.3373	0.0628
	(N=21)	**(N=76)**				
Female	19.60±7.91 (15) (9.71, 31.66)	26.95±18.62 (72) (4.22, 95.29)	NA	7.34 [-2.29, 16.97]	0.1389	

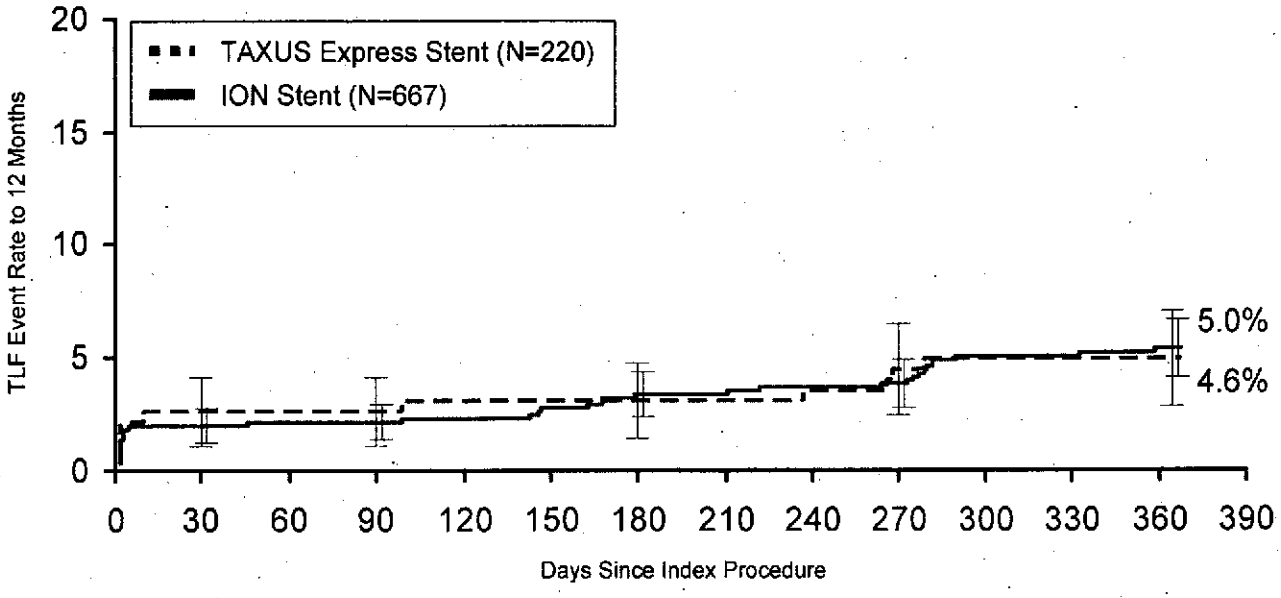
Table 10.1.8 shows PERSEUS Workhorse12-month clinical results in male and female patients.

Table 10.1.8. PERSEUS Workhorse 12-Month Clinical Endpoints, All ION™ Male and Female Patients, Intent-to-Treat, (N=942)

Endpoint	ION Male Stent Patients (N=667)	ION Female Stent Patients (N=275)
EFFICACY		
TVR, Overall	5.7% (37/650)	5.5% (15/272)
TLR, Overall	3.4% (22/650)	4.8% (13/272)
TLR, PCI	3.2% (21/650)	4.4% (12/272)
TLR, CABG	0.3% (2/650)	0.4% (1/272)
Non-TLR, Overall	2.8% (18/650)	1.8% (5/272)
Non-TLR, PCI	2.5% (16/650)	1.8% (5/272)
Non-TLR, CABG	0.5% (3/650)	0.0% (0/272)
SAFETY		
Total Death	0.8% (5/650)	0.4% (1/272)
Cardiac Death or MI	2.3% (15/650)	2.9% (8/272)
Cardiac Death	0.6% (4/650)	0.4% (1/272)
MI	2.0% (13/650)	2.6% (7/272)
Q-wave MI	0.5% (3/650)	0.7% (2/272)
Non-Q-wave MI	1.5% (10/650)	1.8% (5/272)
ARC Stent Thrombosis		
Definite or Probable	0.6% (4/647)	0.0% (0/271)
Definite	0.5% (3/647)	0.0% (0/271)

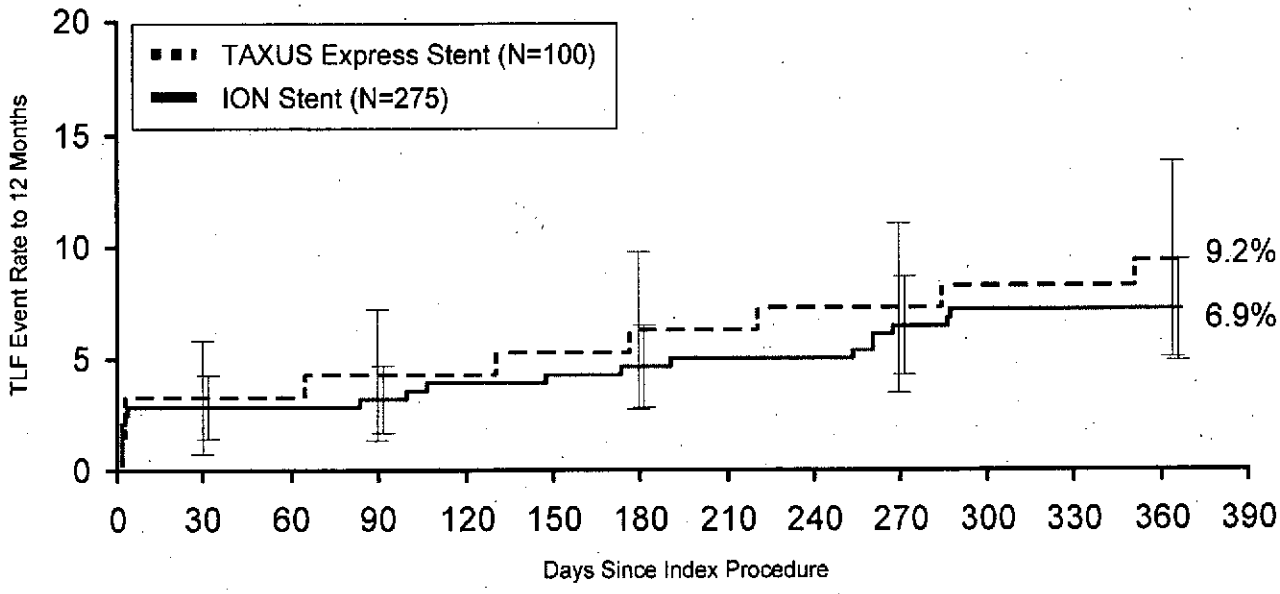
Endpoint	ION Male Stent Patients (N=667)	ION Female Stent Patients (N=275)
Probable	0.2% (1/647)	0.0% (0/271)

Figures 10.1.3 and **10.1.4** show the cumulative TLF rate through 12-months for males and females, respectively. This post-hoc analysis suggests that within each sex-specific subgroup, non-inferiority of ION to TAXUS Express for this endpoint is maintained at all follow-up time-points (30d, 90d, 180d, 270d, 360d).



TAXUS Express Stent:	220	214	213	212	212	211	211		211	208
ION Stent:	667	653	650	647	647	646	642		638	631

Figure 10.1.3. PERSEUS Workhorse Cumulative Rate of Target Lesion Failure to 12 Month, All Male Patients, Intent-to-Treat, Event Rate ± 1.5 SE (N=887)



TAXUS Express Stent:	100	97	97	97	96	96	95		94	93
ION Stent:	275	268	268	267	266	264	263		262	256

Figure 10.1.4. PERSEUS Workhorse Cumulative Rate of Target Lesion Failure to 12 Month, All Female Patients, Intent-to-Treat, Event Rate ± 1.5 SE (N=375)

10.2 PERSEUS Small Vessel Clinical Trial

Primary Objective: The primary objective of the PERSEUS SV study was to evaluate the safety and efficacy of the ION Paclitaxel-Eluting Platinum Chromium Coronary Stent System for the treatment of *de novo* atherosclerotic lesions of ≤ 20 mm in length in native coronary arteries with visual RVD of ≥ 2.25 mm to < 2.75 mm diameter.

Design: PERSEUS Small Vessel is a prospective, single-arm, superiority trial that compares the ION Stent to a matched bare metal (Express Stent) historical control group comprised of subjects with reference vessel diameter (RVD) ≥ 2.25 mm to < 2.75 mm and lesion length ≤ 20 mm garnered from the TAXUS V trial. Eligible patients were those ≥ 18 years old with documented stable angina pectoris, unstable angina pectoris, or documented silent ischemia and left ventricular ejection fraction (LVEF) ≥ 30%. *De novo* target lesions in a native coronary artery with diameter stenosis ≥ 50%, reference vessel diameter ≥ 2.25 mm to < 2.75 mm, and cumulative lesion length ≤ 20 mm coverable by a single study stent were eligible. Multiple stenting was allowed for bail-out only. The protocol mandated antiplatelet therapy compliance in accordance with the ACC/AHA/SCAI Guidelines for PCI.[4]

The primary endpoint is in-stent late loss by QCA on 9-month follow-up (ION Stent compared to bare metal Express Stent) and the secondary endpoint is target lesion failure (TLF; including any ischemia-driven revascularization of the target lesion [TLR], myocardial infarction [MI; Q-wave and non–Q-wave] related to the target vessel, or cardiac death related to the target vessel) at 12 months (ION Stent compared to a performance goal based on TAXUS Express Stent results from the TAXUS IV and TAXUS V trials). (The TAXUS Express Stent is an earlier generation stent with the same drug/polymer coating formulation as the ION Stent System.) The study success criteria are met when both the primary and secondary endpoints are met, that is, when mean in-stent late loss at 9 months post-index procedure for the ION Stent group is shown to be superior to that of the historical control and the 12-month TLF rate for the ION Stent group is shown to be less than the 19.5% performance goal, which is based on TAXUS Express Stent results in lesion-matched patients in TAXUS IV and TAXUS V.

Enrollment of 224 subjects was planned. A total of 224 subjects were enrolled at 28 centers. Of the 224 subjects included in the intent-to-treat analysis set, a total of 197 subjects were evaluable for the 9-month primary endpoint of in-stent late loss. The control group consisted of 125 matched bare metal Express subjects from the TAXUS V trial, including 108 with 9-month QCA follow-up.

Follow-up included clinical assessments at 30 days, 9, 12 and 18 months, and 2, 3, 4 and 5 years post index procedure. All 224 enrolled subjects were required to undergo protocol-mandated 9-month angiographic follow-up. Angiographic assessments were performed for the area of the vessel within the stent margins (in-stent) and the areas immediately 5 mm proximal and distal from the stent margins (analysis segment). After the 12-month follow-up, the study population was reduced to a pre-specified cohort (Safety Population), which consists of all subjects who received a study stent (ION Stent). The study is now considered complete with regard to the 9-month primary and 12-month secondary endpoints.

Results: Results are presented below (Tables 10.2.1 - 10.2.6 and Figure 10.2.1).

Demographics: The ION Stent group had a higher rate of prior congestive heart failure (8.1% versus 2.4%), previous smoking (48.6% versus 36.8%) and higher baseline ejection fraction (57.9±9.4 versus 55.0±9.2) as compared with the historical BMS control group. The ION Stent group had lower rates of baseline unstable angina (20.1% versus 29.6%) and current smoking (13.6% versus 22.2%).

Baseline lesion characteristics: Differences in the ION Stent group compared to the historical BMS control group included shorter lesion length (11.7±5.1 versus 12.9±5.1), lower incidence of ACC/AHA Type B2/C lesions (58.0% versus 77.6%), and lower incidence of tortuosity (8.9% versus 18.4%). However, baseline RVD and MLD were lower in ION Stent subjects than in the BMS historical control (2.08±0.28 versus 2.19±0.35 for RVD and 0.55±0.23 versus 0.62±0.24 for MLD, respectively). These differences were not expected to affect outcomes variables, as propensity score adjustments showed no change in the outcome or conclusion of the trial.

12-Month Clinical and 9-Month Angiographic Results

Table 10.2.1 PERSEUS Small Vessel Clinical Results

	1 year (ITT population)	
	ION Stent (N=224)	Historical Control Express BMS (N=125)
EFFICACY		
TVR, Overall	11.5% (25/218)	24.8% (30/121)
TLR, Overall	6.0% (13/218)	20.7% (25/121)
TLR, PCI	5.5% (12/218)	19.0% (23/121)
TLR, CABG	0.5% (1/218)	1.7% (2/121)
Non-TLR, Overall	7.8% (17/218)	7.4% (9/121)
Non-TLR, PCI	7.3% (16/218)	6.6% (8/121)
Non-TLR, CABG	0.5% (1/218)	0.8% (1/121)
SAFETY		
Total Death	1.4% (3/218)	1.7% (2/121)
Cardiac Death or MI	2.3% (5/218)	3.3% (4/121)
Cardiac Death	1.4% (3/218)	0.8% (1/121)
MI	0.9% (2/218)	2.5% (3/121)
Q-wave MI	0.5% (1/218)	0.0% (0/121)

Non-Q-wave MI[1]	0.5% (1/218)	2.5% (3/121)
ARC Stent Thrombosis		
Definite or Probable	0.5% (1/215)	0.8% (1/119)
Definite	0.5% (1/215)	0.8% (1/119)
Probable	0.0% (0/215)	0.0% (0/119)

[1] Non-Q-wave MI timing: Events occurred at day 218 post-procedure in the ION Stent group and at days 0, 8, and 187 post-procedure in the historical BMS control group.
Abbreviations: ARC=Academic Research Consortium; BMS=bare metal stent; CABG=coronary artery bypass graft; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization;TVR=target vessel revascularization.
This trial was not sized to determine the rate of low frequency events with a pre-specified precision.

Table 10.2.2. PERSEUS Small Vessel Primary Endpoint

9-Month In-stent Late Loss	ION Stent (N=224)	Historical Control Express BMS (N=125)	Difference [95% CI]	*P* Value
Intent-to-Treat[1]	0.38±0.51 (197) (-0.38, 2.28)	0.80±0.53 (108) (-0.15, 2.10)	-0.42 [-0.54, -0.30]	< 0.0001
Propensity score adjusted	0.37	0.81	-0.45[-0.59, -0.31]	< 0.0001

[1] Primary analysis set for assessing hypothesis of superiority and study success criterion.

Table 10.2.3. PERSEUS Small Vessel Secondary Endpoint

12-Month TLF	Performance Goal	ION Stent (N=224)	Upper 95% Confidence Limit	*P* Value
Intent-to-Treat[1]	19.5%	7.34% (16/218)	10.80%	< 0.0001

[1] Primary analysis set for assessing hypothesis of superiority and study success criterion.

Table 10.2.4. PERSEUS Small Vessel Angiographic Results

Angiographic Outcomes[1]	ION™ Stent (N=197)	Historical Control Express BMS (N=108)
MLD (mm), In-stent		
Post-Procedure	2.11±0.21 (197)	2.09±0.30 (108)
9-Month	1.73±0.53 (197)	1.29±0.55 (108)
MLD (mm), Analysis Segment		
Post-Procedure	1.70±0.29 (197)	1.76±0.38 (108)
9-Month	1.50±0.48 (197)	1.22±0.50 (108)
Acute Gain (mm), In-stent	1.57±0.27 (197)	1.47±0.33 (108)
Acute Gain, Analysis Segment (mm)	1.16±0.30 (197)	1.14±0.39 (108)
% DS, In-stent		
Post-Procedure	0.31±10.76 (197)	6.63±10.97 (108)

9-Month	18.48±23.31 (197)	40.72±23.64 (108)
% DS, Analysis Segment		
Post-Procedure	20.12±9.42 (197)	22.34±10.69 (108)
9-Month	29.82±19.82 (197)	43.85±21.44 (108)
Late Loss, In-stent (mm)	0.38±0.51 (197)	0.80±0.53 (108)
Late Loss, Analysis Segment (mm)	0.21±0.41 (197)	0.53±0.52 (108)
Binary Restenosis		
In-stent restenosis	11.7% (23/197)	34.3% (37/108)
Analysis segment restenosis	13.7% (27/197)	38.0% (41/108)

[1] Includes all patients with paired lesion data.
Abbreviations: BMS=bare metal stent; DS=diameter stenosis; MLD=minumum lumen diameter.

Table 10.2.5. PERSEUS Small Vessel Stent Thrombosis

Intent-to-Treat Population	ION Stent (N=224)	Historical Control Express BMS (N=125)
Protocol Defined Stent Thrombosis		
Cumulative through 1 year	0.5% (1/215)	0.8% (1/119)
Acute ST (≤ 24 hrs)	0.0% (0/224)	0.0% (0/125)
Subacute ST (> 24 hrs and ≤ 30 days)	0.0% (0/221)	0.8% (1/125)
Late ST (> 30 days and ≤ 12 months)	0.5% (1/217)	0.0% (0/124)
ARC Definite & Probable Stent Thrombosis		
Cumulative through 1 year	0.5% (1/215)	0.8% (1/119)
Acute ST (≤ 24 hrs)	0.0% (0/224)	0.0% (0/125)
Subacute ST (> 24 hrs and ≤ 30 days)	0.0% (0/221)	0.8% (1/125)
Late ST (> 30 days and ≤ 12 months)	0.5% (1/217)	0.0% (0/124)

See definitions provided with Table 10.1.5
Numbers are % (Count/Sample Size).
This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
Abbreviations: BMS=bare metal stents; ST=stent thrombosis.

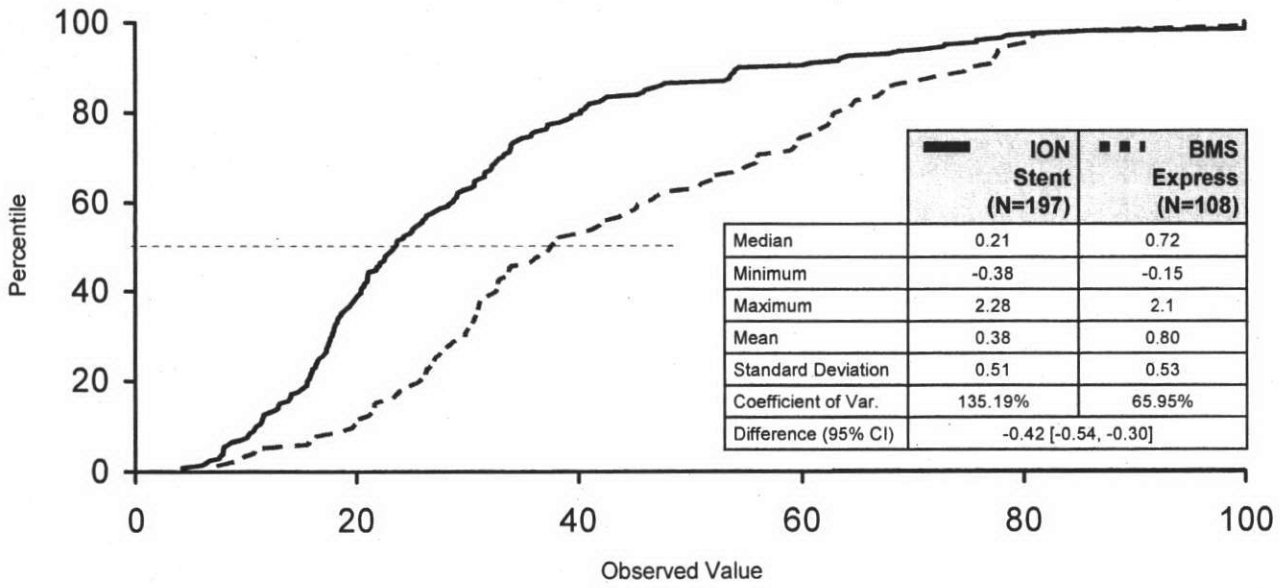


Figure 10.2.1. PERSEUS Small Vessel Cumulative Frequency Distribution of 9-Month In-Stent Late Loss by QCA, Intent-to-Treat, All Angiographic Subset Patients (N=349)

Results in patients with and without diabetes: Table 10.2.6 shows 1-year outcomes in patients with and without medically treated diabetes (defined as treatment with oral hypoglycemic agents or insulin at enrollment). The PERSEUS SV study was not stratified for diabetic status, was not adequately powered to study safety or effectiveness of the BMS Express Stent versus the ION Stent in patients with or without diabetes, and was not designed to specifically support an approval for use in diabetic patients. These exploratory analyses suggest that in patients treated with the ION Stent, 1-year TLR rates were 6.2% in diabetic and 5.8% in non-diabetic patients, and lower compared to the historical BMS Express control.

Table 10.2.6. PERSEUS Small Vessel Clinical Results in Patients with and Without Medically Treated Diabetes

	1-year (ITT Population)	
	ION Stent Patients With Medically Treated Diabetes (N=82)	ION Stent Patients Without Medically Treated Diabetes (N=142)
EFFICACY		
TVR, Overall	9.9% (8/81)	12.4% (17/137)
TLR, Overall	6.2% (5/81)	5.8% (8/137)
TLR, PCI	6.2% (5/81)	5.1% (7/137)
TLR, CABG	0.0% (0/81)	0.7% (1/137)
Non-TLR, Overall	6.2% (5/81)	8.8% (12/137)
Non-TLR, PCI	6.2% (5/81)	8.0% (11/137)
Non-TLR, CABG	0.0% (0/81)	0.7% (1/137)
SAFETY		
Total Death	2.5% (2/81)	0.7% (1/137)
Cardiac Death or MI	3.7% (3/81)	1.5% (2/137)
Cardiac Death	2.5% (2/81)	0.7% (1/137)
MI	1.2% (1/81)	0.7% (1/137)
Q-wave MI	1.2% (1/81)	0.0% (0/137)

	1-year (ITT Population)	
	ION Stent Patients With Medically Treated Diabetes (N=82)	ION Stent Patients Without Medically Treated Diabetes (N=142)
Non-Q-wave MI	0.0% (0/81)	0.7% (1/137)
ARC Stent Thrombosis		
Definite or Probable	1.3% (1/79)	0.0% (0/136)
Definite	1.3% (1/79)	0.0% (0/136)
Probable	0.0% (0/79)	0.0% (0/136)

Abbreviations: ARC=Academic Research Consortium; BMS=bare metal stent; CABG=coronary artery bypass graft; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization;TVR=target vessel revascularization.

This trial was not sized to determine the rate of low frequency events with a pre-specified precision.

In the PERSEUS Small Vessel ITT population, of the 224 registry subjects, 143 subjects were male (63.8%) and 81 subjects were female (36.2%). The proportions in the BMS Express historical control group were similar (60.8% male, 39.2% female). In comparison, the prevalence of coronary artery disease (CAD) is estimated at 9.2 million in males and 8.4 million in females for adults age 20 and older in the United States (i.e., the CAD population is estimated to be 52.2% males and 47.7% females). The disproportionate enrollment distribution in this trial may be partly attributable to gender differences in symptoms and pathophysiology[7], which may lead to under-diagnosis and referral of female patients with CAD. The gender proportions enrolled in this trial are somewhat more representative of the disease prevalence than the Workhorse trial (70.8% male; 29.2% female) and other drug-eluting stent trials. This may be due in part to the smaller average reference vessel diameter in female patients[9].

To evaluate for possible sex-based differences in outcome of treatment with the ION Stent when used in small vessels, sex/gender-specific analyses were performed on safety and effectiveness endpoints. The results suggest that the general conclusions of the overall study regarding both safety and effectiveness can be generalized for males and females.

The PERSEUS SV study was not powered to study safety or effectiveness of the ION Stent in sex-specific subgroups. PERSEUS SV primary and secondary endpoint data were assessed for differences between male and female subgroups, as well as for any interaction between treatment group and gender. These post hoc analyses suggest that in patients treated with the ION stent in small vessels, 9-month in-segment late loss was 0.41±0.48 in females and 0.36±0.52 in males, and 12-month TLF was 5.0% in females and 8.7% in males. In the BMS Express historical control group, rates of 12-month TLF were also numerically higher in males (25.2%) than females (16.8%). These observations are limited by the small sample size available for these analyses. Treatment effect (i.e., superiority of ION Stent to historical control BMS) was demonstrated for both males and females, as shown in **Table 10.2.7** below. No significant treatment-by-gender interaction effect was observed for the primary endpoint of 9-month in-stent late loss (P=0.7255) or 12-month TLF (P=0.9246). This suggests that the overall conclusions of this trial regarding both safety and effectiveness of the ION Stent in small vessels can be generalized for males and females.

Table 10.2.7. PERSEUS Small Vessel Primary and Secondary Endpoint Results, by Gender, Intent-to-Treat, All Patients (N=219)

	Historical Control BMS	ION Stent	Relative Risk [95% CI]	Difference [95% CI]	P value	Interaction p-Value
9-month Late Loss In-Stent (Primary Endpoint)						
	(N=76)	**(N=143)**				0.7255
Male	0.80±0.54 (70) (-0.15, 2.08)	0.36±0.52 (127) (-0.38, 2.28)	NA	-0.44 [-0.59, -0.28]	<.0001	
	(N=49)	**(N=81)**				
Female	0.80±0.50 (38) (-0.09, 2.10)	0.41±0.48 (70) (-0.34, 1.59)	NA	-0.39 [-0.59, -0.20]	0.0001	
12-month TLF (Secondary Endpoint)						
	(N=76)	**(N=143)**				0.9246
Male	25.7% (19/74)	8.7% (12/138)	0.34 [0.17, 0.66]	-17.0% [-28.0%, -6.0%]	0.0009	
	(N=49)	**(N=81)**				

[9] Lansky AJ, Costa RA, Mooney M, et al. Gender-based outcomes after paclitaxel-eluting stent implantation in patients with coronary artery disease. J Am Coll Cardiol. 2005; 45(8):1180-1185.

	Historical Control BMS	ION Stent	Relative Risk [95% CI]	Difference [95% CI]	P value	Interaction p-Value
Female	17.0% (8/47)	5.0% (4/80)	0.29 [0.09, 0.92]	-12.0% [NA]	0.0549	

Table 10.2.8. shows PERSEUS Small Vessel 12-month clinical results in male and female patients.

Table 10.2.8. PERSEUS Small Vessel 12-Month Clinical Endpoints, All ION Male and Female Patients, Intent-to-Treat, (N=224)

Endpoint	ION Male Stent Patients (N=143)	ION Female Stent Patients (N=81)
EFFICACY		
TVR, Overall	13.8% (19/138)	7.5% (6/80)
TLR, Overall	7.2% (10/138)	3.8% (3/80)
TLR, PCI	6.5% (9/138)	3.8% (3/80)
TLR, CABG	0.7% (1/138)	0.0% (0/80)
Non-TLR, Overall	9.4% (13/138)	5.0% (4/80)
Non-TLR, PCI	8.7% (12/138)	5.0% (4/80)
Non-TLR, CABG	0.7% (1/138)	0.0% (0/80)
SAFETY		
Total Death	1.4% (2/138)	1.3% (1/80)
Cardiac Death or MI	2.9% (4/138)	1.3% (1/80)
Cardiac Death	1.4% (2/138)	1.3% (1/80)
MI	1.4% (2/138)	0.0% (0/80)
Q-wave MI	0.7% (1/138)	0.0% (0/80)
Non-Q-wave MI	0.7% (1/138)	0.0% (0/80)
ARC Stent Thrombosis		
Definite or Probable	0.7% (1/136)	0.0% (0/79)
Definite	0.7% (1/136)	0.0% (0/79)
Probable	0.0% (0/136)	0.0% (0/79)

In the PERSEUS SV Trial, the study success criterion for 12-month TLF was met for both sexes (greater than performance goal of 19.5%). **Figures 10.2.2** and **10.2.3** show the cumulative TLF rate through 12-months for males and females, respectively. This post-hoc analysis suggests that within each sex-specific subgroup, the ION group had lower TLF rates than the BMS Express historical control group at all follow-up time-points (30d, 90d, 180d, 270d, 360d), although confidence intervals are wide and overlap at earlier time points.

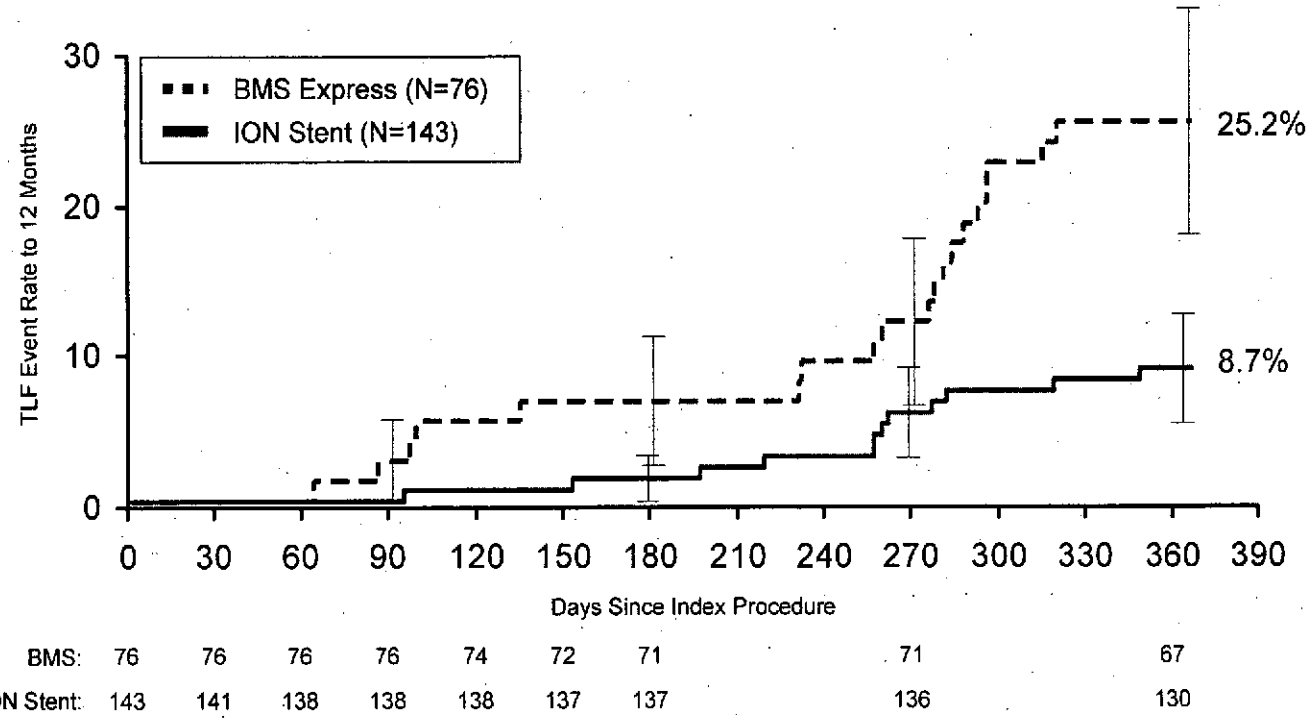


Figure 10.2.2. PERSEUS Small Vessel Cumulative Rate of Target Lesion Failure to 12 Month, All Male Patients, Intent-to-Treat, Event Rate ± 1.5 SE (N=219)

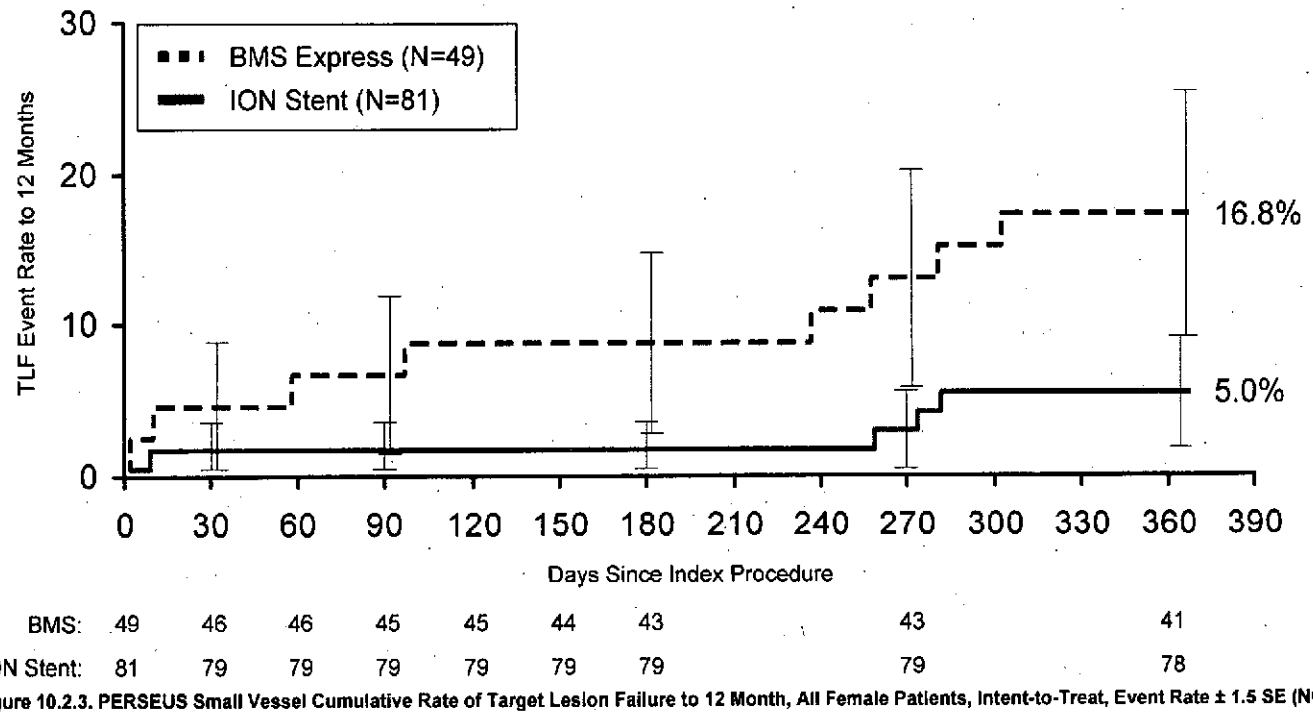


Figure 10.2.3. PERSEUS Small Vessel Cumulative Rate of Target Lesion Failure to 12 Month, All Female Patients, Intent-to-Treat, Event Rate ± 1.5 SE (N=130)

10.3 HORIZONS AMI

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 ≥ 1mm in ≥ 2 contiguous leads, or presumed new LBBB, or true posterior MI with ST depression of ≥ 1mm in ≥ 2 contiguous anterior leads. A total of 3602 patients were randomized (primary randomization) in a 1:1 fashion in the emergency room to anticoagulation with unfractionated heparin plus routine GP IIb/IIIa inhibition or bivalirudin and bail-out GP IIb/IIIa

inhibition.

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

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

Clinical follow-up was performed at 30 days (± 1 week), 6 months (± 2 weeks), 1 year (± 2 weeks) and 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).

Results: The baseline demographics and medical history are reported in Table 10.3.1. The primary and secondary endpoints of the trial were met and are reported in Table 10.3.2 and Table 10.3.3. The clinical results of the trial are reported in Table 10.3.4. In Figure 10.3.1, the rates of ischemic TLR are illustrated for all patients and those patients who were not in the protocol-required angiographic subset. Figures 10.3.2, 10.3.3, 10.3.4, 10.3.5, and 10.3.6 provide results of major clinical outcomes to 3 years. Angiographic and IVUS results are reported in Table 10.3.5.

Table 10.3.1: 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.

Table 10.3.2: 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 MACE[2]	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] P-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 10.3.3: 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

Table 10.3.4: HORIZONS AMI Kaplan-Meier Estimates of Clinical Endpoints at 30 Day, 1, 2, and 3 Years (ITT Population)

	TAXUS Express (N=2257)	Bare Metal Express (N=749)
30 Day Clinical Endpoints	10.3% (232)	9.0% (67)
Net Adverse Clinical Events[1]	4.8% (109)	4.5% (34)
MACE 1[2]	4.5% (102)	4.3% (32)
MACE 2 (Safety MACE)[3]	2.1% (47)	1.9% (14)
Death	2.0% (44)	1.7% (13)
- Cardiac	0.1% (3)	0.1% (1)
- Noncardiac	1.7% (37)	2.2% (16)
Reinfarction	1.2% (28)	1.6% (12)
- Q wave	0.4% (10)	0.5% (4)
- Non Q wave	3.6% (80)	3.5% (26)
Death or reinfarction	2.3% (51)	2.6% (19)

Ischemic TVR	2.1% (46)	2.6% (19)
Ischemic TLR	0.5% (11)	0.5% (4)
Stroke	7.1% (159)	5.6% (42)
Major bleeding (non-CABG)	2.3% (50)	2.7% (20)
Target Lesion stent thrombosis	10.3% (232)	9.0% (67)
1 Year Clinical Endpoints		
Net Adverse Clinical Events[1]	15.8% (355)	16.3%(121)
MACE 1[2]	10.6% (237)	12.4% (92)
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.

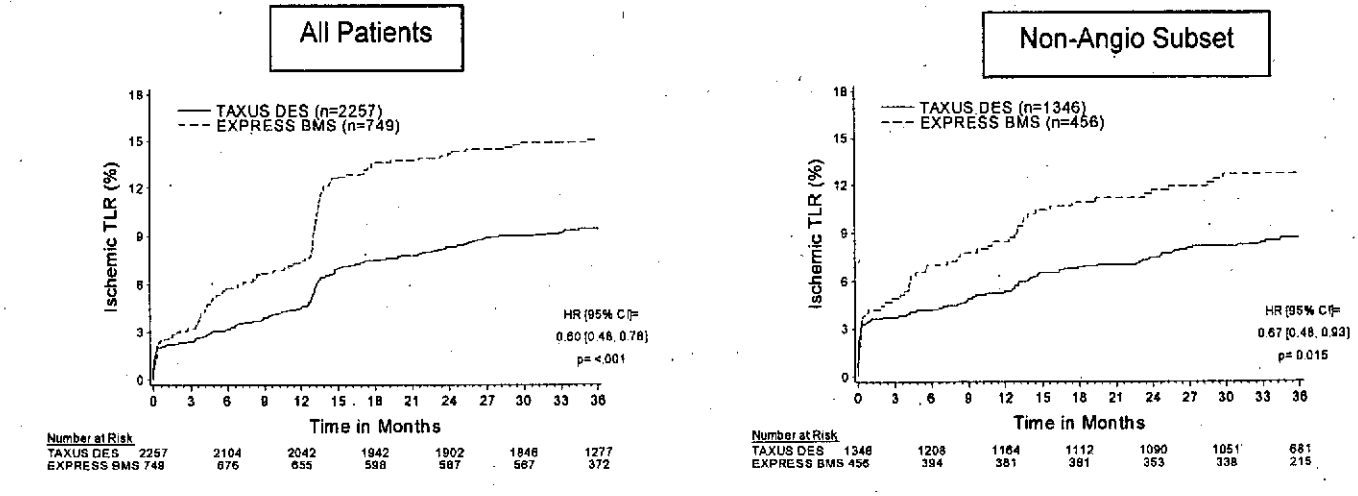
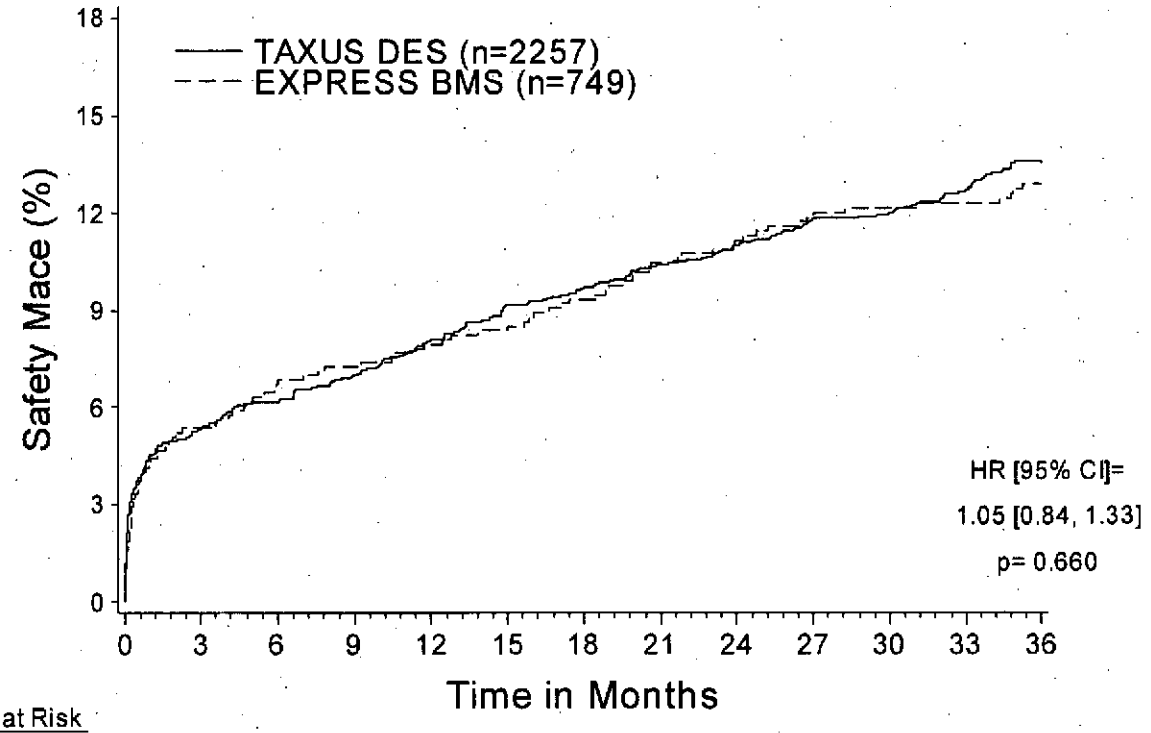


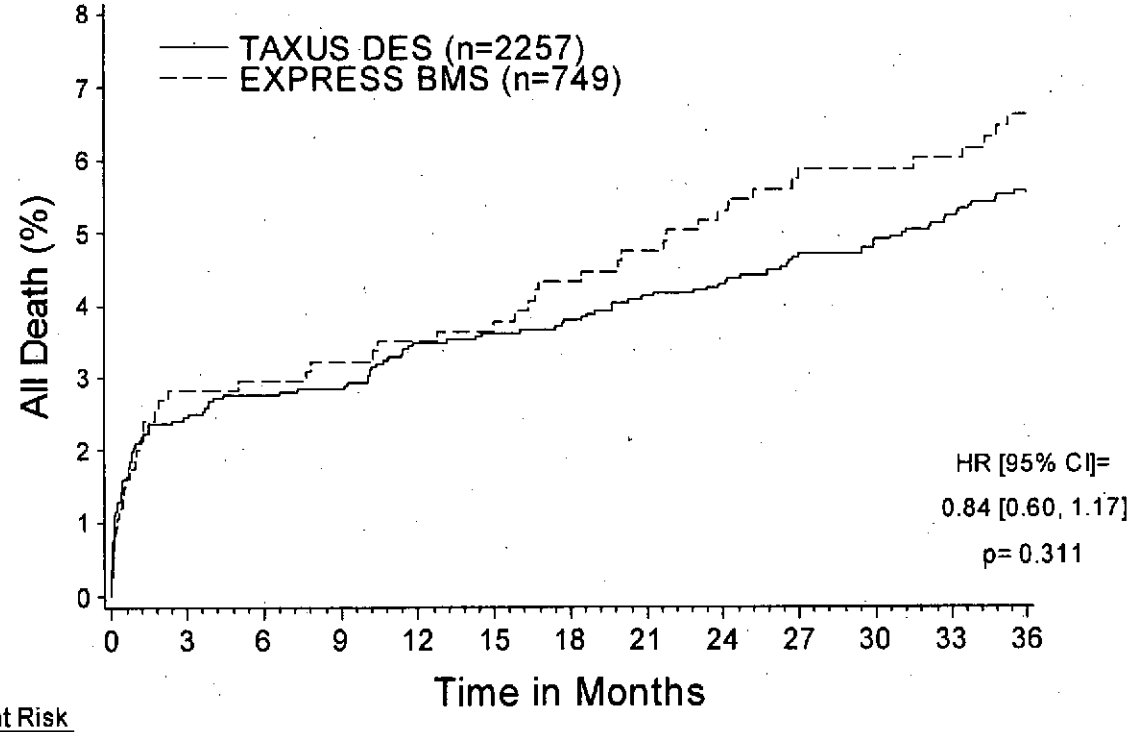
Figure 10.3.1: HORIZONS AMI Cumulative Rates of Ischemic Target Lesion Revascularization to 3 Years For All Patients and Patients Not in the Protocol Required Angiographic Subset



Number at Risk

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

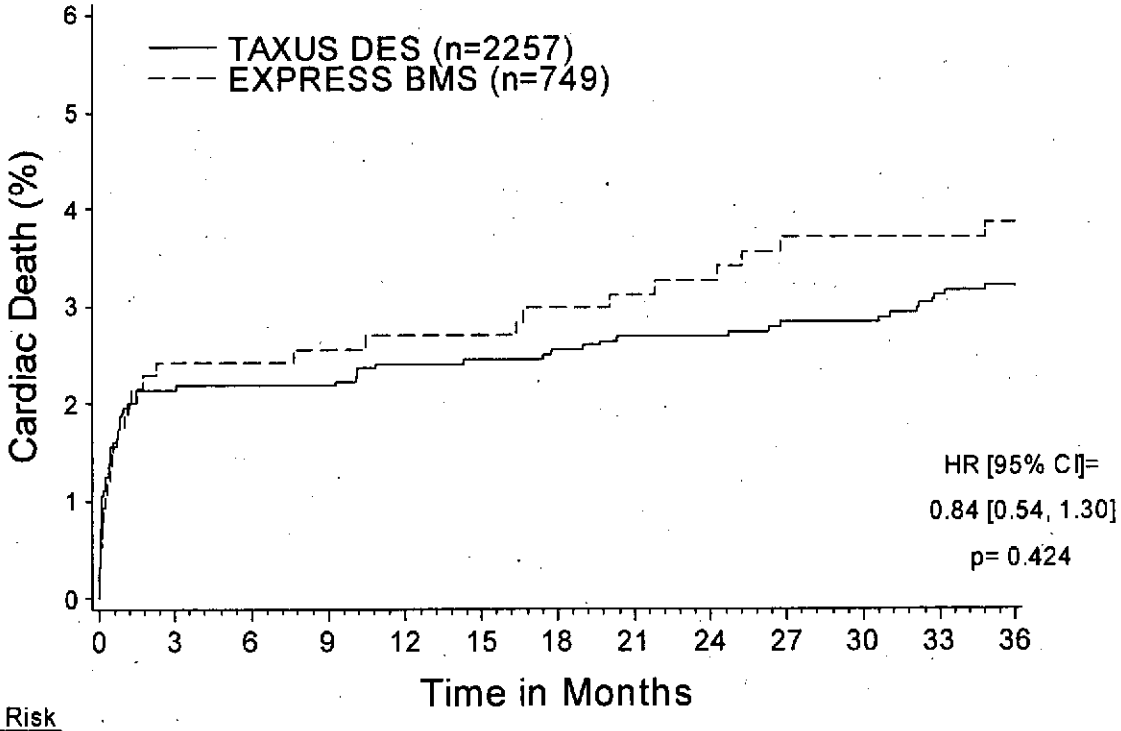
Figure 10.3.2: HORIZONS AMI Cumulative Rates of Safety MACE (Death, Reinfarction, Stent Thrombosis or Stroke) to 3 Years



Number at Risk

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

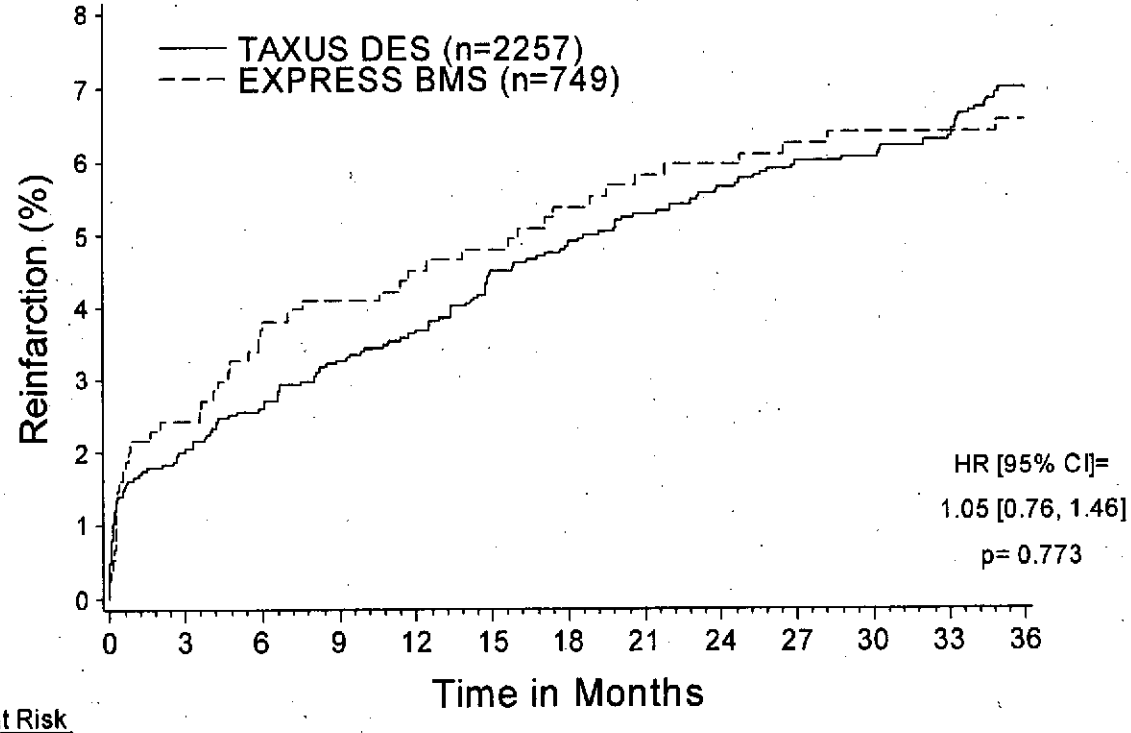
Figure 10.3.3: HORIZONS AMI Cumulative Rates of All Death to 3 Years



Number at Risk

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

Figure 10.3.4: HORIZONS AMI Cumulative Rates of Cardiac Death to 3 Years



Number at Risk

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

Figure 10.3.5: HORIZONS AMI Cumulative Rates of Reinfarction to 3 Years

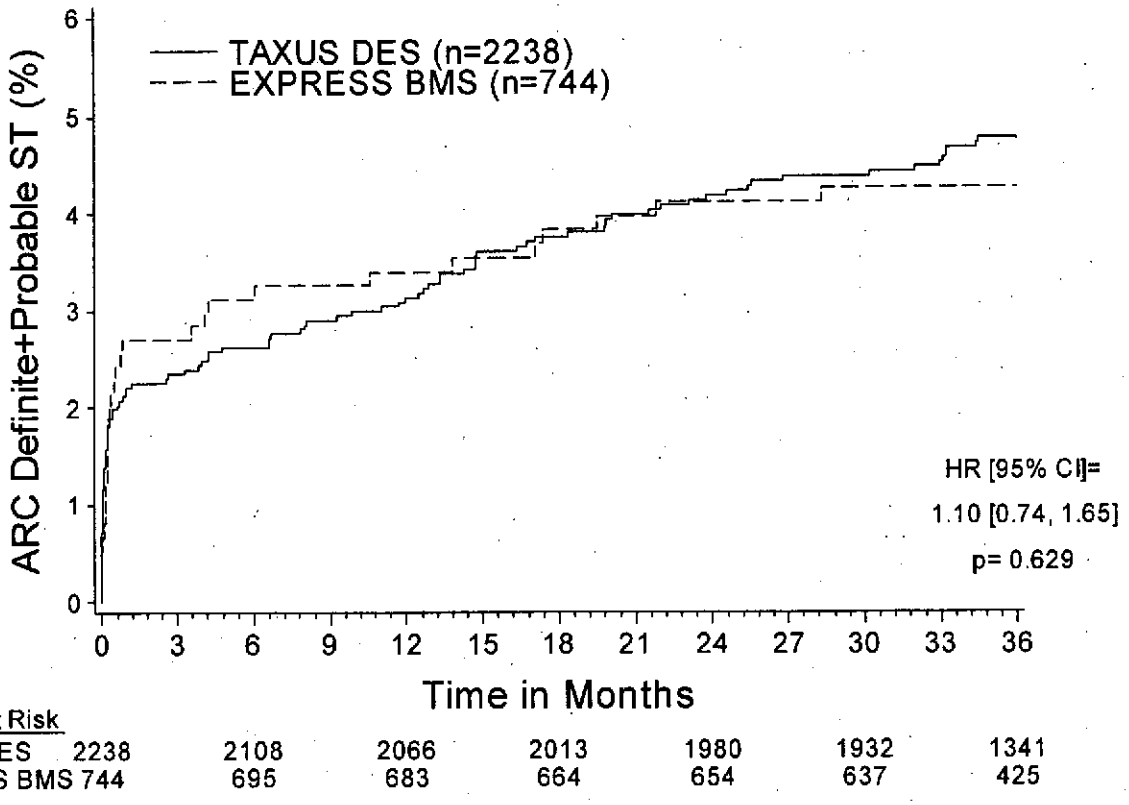


Figure 10.3.6: HORIZONS AMI Cumulative Rates of ARC Definite and Probable Stent Thrombosis to 3 Years

Table 10.3.5: HORIZONS AMI 13 Month Angiographic and IVUS Results)

QCA	TAXUS Express (N=910 Patients / 1081 Lesions)	Bare Metal Express (N=293 Patients / 332 lesions)
Follow-up MLD in-stent (mm)	2.36 ± 0.75 (1062)	1.98 ± 0.82 (328)
Follow-up MLD in-segment (mm)	2.09 ± 0.68 (1062)	1.84 ± 0.76 (328)
Follow-up %DS in-stent	18.7 ± 22.8 (1062)	32.6 ± 24.9 (328)
Follow-up %DS in-segment	28.8 ± 19.6 (1062)	37.4 ± 22.0 (328)
Late Loss in-stent (mm)	0.41 ± 0.64 (1062)	0.82 ± 0.70 (328)
Late Loss in-segment (mm)	0.30 ± 0.56 (1062)	0.59 ± 0.64 (328)
Binary restenosis, in-stent	8.2% (87/1062)	21.0% (69/328)
Binary restenosis, in-segment	9.6% (102/1062)	23.2% (76/328)
IVUS	**TAXUS Express (N=196 pts / 219 lesions)**	**Bare Metal Express (N=62 pts / 67 lesions)**
Neointimal Volume (mm^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)

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

In the HORIZONS-AMI population, of patients randomized to TAXUS Express DES 1738/2257 (77%) subjects were male and 519/2257 (23%) subjects were female. The proportions in the Express BMS group were similar (76% male, 24% female). According to the Nationwide Inpatient Sample (a large database of inpatient admissions from 1988 to 2004), men had almost 2 times the age-adjusted STEMI rate as women (men 62.4%, women 37.6%)[10]. The gender proportions enrolled in this trial are similar to other trials in the STEMI population[11,12]]

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 10.3.6). Primary and secondary endpoint outcomes data stratified by gender are shown in tables 10.6.6 and 10.6.7. HORIZONS AMI clinical results at 30 Days,

[10] Movahed M, Ramaraj R, Hashemzadeh, M, et. al. Rate of Acute ST-Elevation Myocardial Infarction in the United States from 1988 to 2004 (from the Nationwide Inpatient Sample), Am J Cardiol. 2009;104:5-8
[11] GUSTO Investigators, An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction, N Engl J Med; 1993; 329, 673-82.
[12] Lansky AJ, Pietras C, Costa RA, et. al. Gender Differences in Outcomes After Primary Angioplasty Versus Primary Stenting With and Without Abciximab for Acute Myocardial Infarction: Results of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Trial; Circulation; 2005: 111:1611-18.

1 Year, 2 Year and 3 Year in male and female patients are reported in Table 10.3.8. Within the female group, cardiac death was numerically higher through 30 days in those treated with TAXUS Express versus bare metal Express, but the numerical difference between groups narrowed over time. Other trials of interventional treatment for AMI have shown female sex to be associated with higher mortality rates compared to men,[13,14] 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 10.3.6: 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 10.3.7: 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 10.3.8: HORIZONS AMI Clinical Endpoints, All TAXUS Express Male and Female Patients at 30 Day, 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)
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)

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

[14] Berger JS, Elliott L, Gallup, et al. Sex Differences in Mortality Following Acute Coronary Syndrome; *JAMA*. 2009;302(8):874-882

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)
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.

10.4 Sex-Specific Information from Pooled Analysis

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

To evaluate for sex-specific differences in long-term outcomes after percutaneous coronary intervention with the paclitaxel-eluting coronary stent, Boston Scientific conducted a retrospective pooled analysis of patients enrolled in five randomized trials (TAXUS I, II SR, IV, V *de novo*, and TAXUS ATLAS Workhorse), and two 'real world' registries (ARRIVE 1 and 2). Of the 2,271 patients pooled from the randomized trials, 665 (29.3%) were women. The proportion of women included in these studies is similar to that reported in literature.[17,18]

Despite significantly more adverse baseline risk factors in women (which was also observed in the TAXUS stent program, see Table 10.4.1), recent randomized trials of drug-eluting stents have demonstrated comparable safety and effectiveness outcomes in men and women[19,20]. As shown in Table 10.4.2 and Figure 10.4.1, clinical event rates were generally similar between men and women. Information on bleeding is not available, as these data were not collected in the randomized trials. Overall, the influence of gender on long-term drug-eluting stent outcomes has not been fully elucidated.[20]

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

Table 10.4.1: Baseline Clinical and Lesion Characteristics for Patients Receiving PES[1] in Randomized Trials

Variable	Women (N=665)	Men (N=1606)	P value
Age, (yr)	64.9±11.1 (665)	61.4±10.7 (1606)	<0.001
Weight (lbs)	171.3±37.1 (397)	200.8±38.4 (970)	<0.001
Cardiac History			
Stable Angina	55.1% (365/663)	57.8% (929/1606)	0.22
Unstable Angina	37.4% (248/663)	31.5% (496/1577)	0.006
Silent Ischemia	10.1% (67/665)	12.5% (201/1602)	0.10
Congestive Heart Failure	7.7% (51/664)	3.9% (63/1605)	<0.001
Previous Myocardial Infarction	25.8% (171/663)	31.8% (501/1577)	0.005

[15] Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart Disease and Stroke Statistics—2010 Update. A Report From the American Heart Association. Circulation. 2010;121(7):e46-e215.
[16] Berenguer A, Mainar V, Bordes P, Valencia J, Gomez S, Lozano T.. Incidence and predictors of restenosis after sirolimus-eluting stent implantation in high-risk patients. Am Heart J 2005;150:536-42.
[17] Seth A, Serruys PW, Lansky A, et al. A pooled gender based analysis comparing the Xience V everolimus-eluting stent and the TAXUS paclitaxel-eluting stent in male and female patients with coronary artery disease, results of the SPIRIT II and SPIRIT III studies: two-year analysis. EuroIntervention 2010;5:788-27.
[18] Women and Heart Disease Fact Sheet, Women's Heart Foundation, www.womensheart.org
[19] Lansky AJ, Costa RA, Mooney M, et al. Gender-based outcomes after paclitaxel-eluting stent implantation in patients with coronary artery disease. J am Coll Cardiol 2005;45;1180-5.
[20] Mikhail GW, Gerber RT, Cox DA, et al. Influence of Gender on Long-Term Outcomes after Percutaneous Coronary Intervention with the Paclitaxel-Eluting Coronary Stent: Results of the 'TAXUS Woman' Analysis. J Am Coll Cardiol Intv, 2010;3:1250-9.).

Table 10.4.1: Baseline Clinical and Lesion Characteristics for Patients Receiving PES[1] in Randomized Trials

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

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

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

Table 10.4.2: Clinical Outcomes at 5 Years for Patients Receiving PES in Randomized Trials

Variable	Male (N=1606)	Female (N= 665)	
TVR, Overall	19.8% (291/1470)	20.8% (124/595)	
TLR, Overall	11.9% (175/1470)	12.4% (74/595)	
TLR, PCI	10.5% (155/1470)	11.8% (70/595)	
TLR, CABG	1.6% (23/1470)	1.0% (6/595)	
Non-TLR	10.2% (150/1470)	11.4% (68/595)	
Non-TLR, PCI	7.8% (114/1470)	8.7% (52/595)	
Non-TLR, CABG	2.8% (41/1470)	3.0% (18/595)	
Total Death	9.1% (134/1470)	10.4% (62/595)	
Cardiac Death or MI	11.3% (166/1470)	12.3% (73/595)	
Cardiac Death	4.6% (68/1470)	5.0% (30/595)	
MI	7.4% (109/1470)	8.7% (52/595)	
Q-wave MI	1.8% (27/1470)	1.2% (7/595)	
Non-Q-wave MI	5.8% (85/1470)	7.6% (45/595)	
ARC Stent Thrombosis Definite or Probable	2.9% (40/1360)	2.0% (11/541)	
Definite	2.1% (29/1360)	1.1% (6/541)	
Probable	1.0% (13/1360)	0.9% (5/541)	

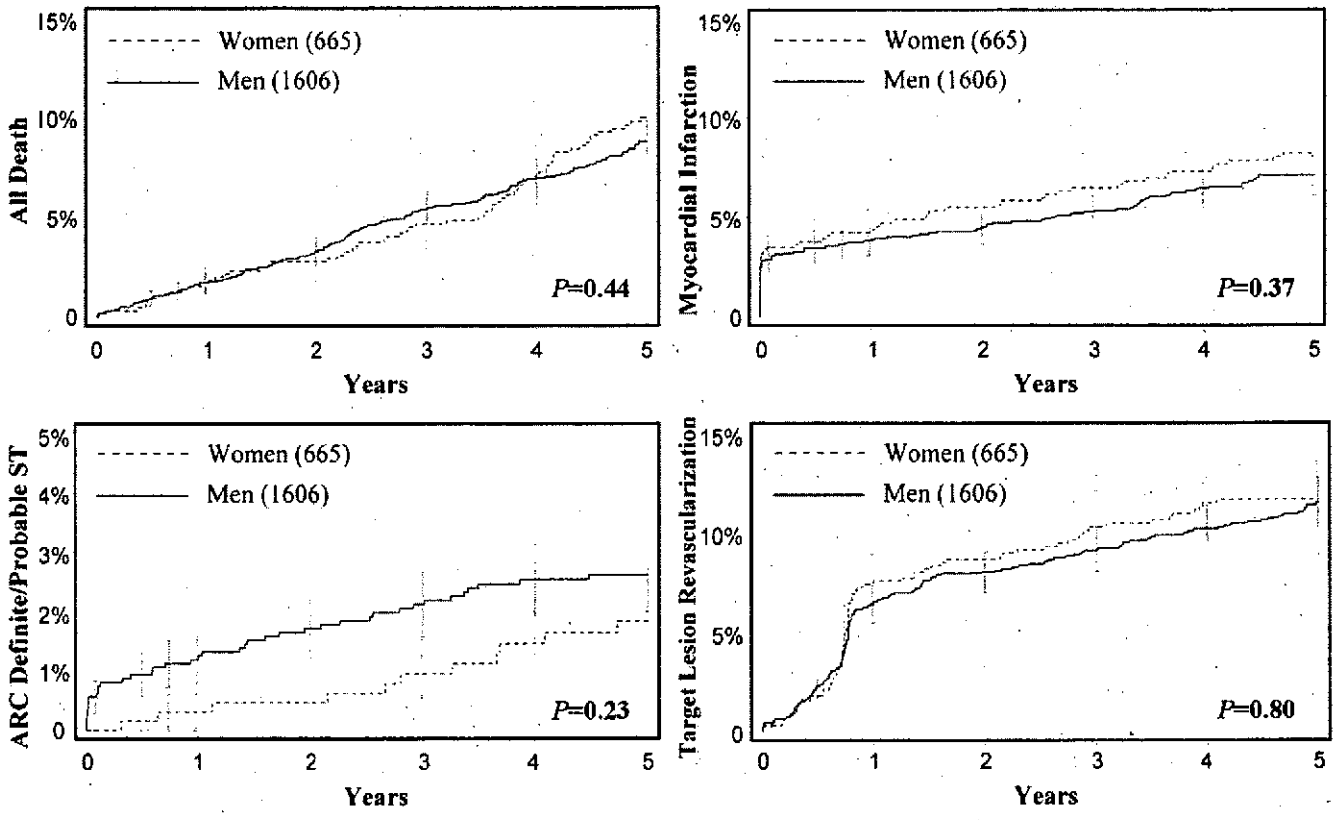


Figure 10.4.1: Kaplan-Meier Estimates of 5-year Cumulative Rates of Clinical Outcomes for Women versus Men for Patients Receiving Paclitaxel-eluting Stents in the Randomized Trials

11 INDIVIDUALIZATION OF TREATMENT

See also Precautions - Section 6.6, Use in Special Populations and Section 6.7, Lesion/Vessel Characteristics.

The risks and benefits should be carefully considered for each patient before use of the ION Stent System. Patient selection factors to be assessed should include a judgment regarding risk of prolonged antiplatelet therapy. For Elective PCI Procedures, based on randomized clinical trial protocols, a $P2Y_{12}$ inhibitor should be given for at least 6 months after paclitaxel-eluting stent (PES) implantation and ideally up to 12 months in patients who are not at high risk of bleeding. For PCI in ST-elevated MI Patients, a $P2Y_{12}$ inhibitor should be given for at least 12 months; however if the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by $P2Y_{12}$ inhibitor therapy, earlier discontinuation should be considered. Aspirin should be administered concomitantly with the $P2Y_{12}$ inhibitor and then continued indefinitely. Stenting is generally avoided in those patients at heightened risk of bleeding (e.g. those patients with recently active gastritis or peptic ulcer disease) in which anticoagulation therapy would be contraindicated.

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

12 PATIENT COUNSELING INFORMATION

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

- Discuss the risks associated with stent placement.
- Discuss the risks associated with a paclitaxel-eluting stent.
- Discuss the risks/benefits issues for this particular patient.
- Discuss alteration to current lifestyle immediately following the procedure and over the long term.
- A Patient Information Guide (included in the package or available on-line) which includes both product information and a stent implant card.
- An Angioplasty and Stent Education Guide (available on-line or by request) which includes information on coronary artery disease, the implant procedure and frequently asked questions.

13 HOW SUPPLIED

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

Handling and Storage: Protect from light. Do not remove from carton or foil pouch until ready for use. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

The foil pouch is not a sterile barrier.

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

14 OPERATIONAL INSTRUCTIONS

14.1 Inspection Prior to Use

Check foil pouch for "Use By" date. Do not use the product after the "Use By" date.

Carefully inspect the foil pouch and the sterile package before opening.

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

Note: At any time during use of the Monorail® Stent System, if the proximal shaft (hypotube) has been bent or kinked, do not continue to use the catheter.

14.2 Materials Required

(not included in Stent System package)

Quantity	Material
1	Appropriate guide catheter (see Table 2.1, ION™ Stent System Product Description).
2-3	20 ml (cc) syringe
1,000u / 500cc	Normal heparinized sterile saline
1	≤ 0.014 in (0.36 mm) guidewire
1	Rotating hemostatic valve
	Diluted contrast medium 1:1 with normal heparinized sterile saline
1	Inflation device
1	Torque device
1	Pre-deployment dilation catheter
1	Three-way stopcock
1	Appropriate arterial sheath

14.3 Preparation

14.3.1 Packaging Removal

Step Action

1. Open the outer box to reveal the foil pouch and carefully inspect the foil pouch for damage.
2. Carefully open the foil pouch by tearing along the tear strip as indicated on the foil pouch to access the sterile barrier package containing the stent delivery system.
3. Carefully inspect the sterile barrier package for damage.
4. Carefully peel open the sterile barrier using aseptic techniques and extract the stent delivery system.
5. Carefully remove the delivery system from its protective tubing for preparation of the delivery system. When using a Monorail system, do not bend or kink hypotube during removal.
6. Remove the product mandrel and stent protector by grasping the catheter just proximal to the stent (or just proximal to the balloon bond site), and with the other hand, grasp the stent protector and gently remove distally.

Note: If unusual resistance is felt during product mandrel and stent protector removal, do not use this product and replace with another.

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7. Examine the device for any damage. If it is suspected that the sterility or performance of the device has been compromised, the device should not be used.
8. A Monorail Catheter may be coiled once and secured using the CLIPIT™ Coil Clips provided in the catheter package. Only the proximal shaft should be inserted into the CLIPIT device; the clip is not intended for the distal end of the catheter.

Note: Care should be taken not to kink or bend the shaft upon application or removal of the CLIPIT Coil Clip.

14.3.2 Guidewire Lumen Flush

Step Action

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

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

14.3.3 Balloon Preparation

Step Action

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

9. Open stopcock to stent system.
10. Leave on neutral.

14.3.4 Delivery Procedure

Step Action

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

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

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7. Advance the stent system over the guidewire to target lesion under direct fluoroscopic visualization. Utilize the proximal and distal radiopaque balloon markers as a reference point. If the position of the stent is not optimal, it should be carefully repositioned or removed (See also Precautions - 6.12, Stent System Removal). The inside edges of the marker bands indicate both the stent edges and balloon shoulders. Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion segment of the vessel.

Note: If unusual resistance is felt at any time during lesion access before stent implantation, the stent system and the guide catheter should be removed as a single unit. (See also Precautions - 6.12, Stent System Removal).

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

14.3.5 Deployment Procedure

Step Action

1. Inflate the delivery system expanding the stent to a minimum pressure of 11 atm (1115 kPa). Higher pressure may be necessary to optimize stent apposition to the arterial wall. Accepted practice generally targets an initial deployment pressure that would achieve a stent inner diameter of about 1.1 times the reference vessel diameter (see Table 14.5.1). Balloon pressure must not exceed rated burst pressure of 18 atm (1824 kPa) for the 2.25 mm stents and 16 atm (1621 kPa) for the 2.50-4.00 mm stent sizes. (see Table 14.5.1).
2. Maintain inflation pressure for 15-30 seconds for full expansion of the stent.
3. Deflate balloon by pulling negative pressure on inflation device until balloon is fully deflated, see Table 6.1 System Deflation Time Specifications.
4. Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall contact should be verified through routine angiography or intravascular ultrasound (IVUS).
5. If stent sizing/apposition requires optimization, readvance the stent system balloon, or another high-pressure, balloon catheter of the appropriate size, to the stented area using standard angioplasty techniques.
6. Inflate the balloon to the desired pressure while observing under fluoroscopy. Deflate the balloon (refer to product labeling and/or Table 14.5.1 for proper stent inflation pressure).
7. If more than one ION Stent is needed to cover the lesion and balloon treated area, it is suggested that, to avoid the potential for gap restenosis, the stents be adequately overlapped. To ensure that there are no gaps between stents, the balloon marker bands of the second ION Stent should be positioned inside of the deployed stent prior to expansion.
8. Reconfirm stent position and angiographic result. Repeat inflations until optimal stent deployment is achieved.

14.3.6 Removal Procedure

Step Action

1. Ensure balloon is fully deflated before delivery system withdrawal.
2. Fully open rotating hemostatic valve.
3. While maintaining guidewire position and negative pressure on inflation device, withdraw delivery system.
4. Monorail catheters may be coiled once and secured using the CLIPIT Coil Clip (see Operational Instructions – Section 14.3.1, Packaging Removal).
5. Repeat angiography to assess the stented area. If an adequate expansion has not been obtained, exchange back to the original stent delivery catheter or exchange to another balloon catheter of appropriate balloon diameter to achieve proper stent apposition to the vessel wall.

14.4 Post-Deployment Dilatation of Stented Segments

Precaution: Do not dilate the stent beyond the limits tabulated below.

Nominal Stent Diameter (ID)	Dilatation Limits (ID)
2.25 mm	2.75 mm
2.50 mm - 2.75 mm	3.50 mm
3.00 mm - 3.50 mm	4.25 mm
4.00 mm	5.75 mm

All efforts should be taken to assure that the stent is not under-dilated. If the deployed stent size is still inadequate with respect to vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent. The stent may be expanded using a low profile and high pressure balloon catheter. If this is

required, the stented segment should be recrossed carefully with a prolapsed guidewire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

Note: **In line with Precaution 6.13 Post-Procedure:** Care must be exercised when crossing a newly deployed stent with any wire, catheter or ancillary device to avoid disrupting the stent placement, apposition, geometry, and/or coating.

14.5 In Vitro Information

Table 14.5.1 Typical ION™ Stent System compliance

Pressure Atm (kPa)		2.25 mm Stent I.D. (mm)	2.50 mm Stent I.D. (mm)	2.75 mm Stent I.D. (mm)	3.00 mm Stent I.D. (mm)	3.50 mm Stent I.D. (mm)	4.00 mm Stent I.D. (mm)
8.0 (811)		NA	2.32	2.58	2.84	3.26	3.71
9.0 (912)		2.11	2.38	2.65	2.92	3.35	3.80
10.0 (1013)		2.16	2.45	2.72	3.00	3.44	3.89
11.0 (1115)	Nominal	2.22	2.51	2.78	3.07	3.52	3.98
12.0 (1216)		2.27	2.59	2.86	3.13	3.61	4.07
13.0 (1317)		2.32	2.64	2.91	3.18	3.67	4.13
14.0 (1419)		2.37	2.69	2.96	3.22	3.72	4.19
15.0 (1520)		2.41	2.73	3.00	3.26	3.77	4.24
16.0* (1621)		2.46	2.77	3.04	3.29	3.81	4.29
17.0 (1723)		2.49	NA	NA	NA	NA	NA
18.0* (1824)		2.53	NA	NA	NA	NA	NA

* RATED BURST PRESSURE. DO NOT EXCEED.
Note: The Stent I.D. values listed are actual average stent inner diameters at the specific balloon inflation pressures obtained during in vitro testing at 37°C.

15 WARRANTY

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