SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Iliac Stent

Device Trade Name: Assurant® Cobalt Iliac Balloon-Expandable Stent System

Applicant's Name and Address: Medtronic Vascular
3576 Unocal Place
Santa Rosa, CA 95403

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P110011

Date of FDA Notice of Approval: October 26, 2011

Expedited: Not Applicable

II. INDICATIONS FOR USE

The Assurant® Cobalt Iliac Balloon-Expandable Stent System is indicated for improving iliac luminal diameter in patients with de novo and restenotic lesions in the common and external iliac arteries, with reference vessel diameters between 6 mm and 10 mm and lesion lengths up to 61 mm. The stent is intended as a permanent implant.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Assurant Cobalt Iliac Balloon-Expandable Stent System labeling.

V. DEVICE DESCRIPTION

The Assurant Cobalt Iliac Balloon-Expandable Stent System consists of a balloon delivery system catheter and a premounted balloon-expandable stent.

The Assurant Cobalt stent is made from a cobalt-chromium alloy (MP35N). The stent

delivery system has two radiopaque markers at the proximal and distal end of the balloon to aid in the placement of the stent. The stent is delivered to the intended lesion site, expanded by inflation, and remains as a permanent vessel scaffolding implant. An inflatable balloon on the stent delivery system allows for deployment of the stent. Upon deployment, the stent imparts an outward radial force on the arterial lumen to establish patency.

The Assurant Cobalt stent is available in 6 mm to 10 mm diameters and 20 mm to 60 mm lengths (Table 1). The Assurant Cobalt delivery system is available in 2 catheter lengths: 80 cm and 130 cm, and is compatible with a 6 Fr (0.086 in) sheath and a 0.035 in (0.89 mm) guidewire.

Table 1: Assurant Cobalt Iliac Balloon-Expandable Stent System Product Information

Stent Diameter	Product Length					
	80 cm				130 cm	
	Stent Length				Stent Length	
	20 mm	30 mm	40 mm	60 mm	20 mm	30 mm
6.0 mm	✓	✓	✓	✓	✓	✓
7.0 mm	✓	✓	✓	✓	✓	✓
8.0 mm	✓	✓	✓	✓	✓	✓
9.0 mm	Not Offered	✓	✓	✓	Not Offered	✓
10.0 mm		✓	✓	✓		✓

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative practices and procedures for treatment of Peripheral Vascular Disease (PVD) include percutaneous transluminal angioplasty (PTA), bypass surgery, stenting with another stent for which there is an approved indication, exercise therapy, and pharmacotherapy. Atherosclerotic risk factors may be reduced through lifestyle modifications such as cessation of smoking, weight reduction, lipid control, blood pressure control, and diabetes management.

VII. MARKETING HISTORY

The Assurant Cobalt device is CE Marked and has been commercially available in Europe since March 2008. Additionally, the Assurant Cobalt device is currently approved for commercial distribution in the following regulated countries: Australia, Belarus, Bosnia & Herzegovina, Brazil, China, Colombia, Croatia, Egypt, Guatemala, India, Israel, Macedonia, Mexico, New Zealand, Peru, Russia, Serbia, Taiwan, Thailand, Turkey, Uruguay, and Venezuela. Since commercialization, the Assurant Cobalt device has not been withdrawn from the market for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- acute myocardial infarction
- allergic reaction (contrast medium, drug, or stent material)
- aneurysm, pseudoaneurysm, or arteriovenous fistula
- angina or coronary ischemia
- arrhythmias
- bleeding complications from anticoagulant or antiplatelet medication requiring transfusion or surgical intervention
- death
- detachment and/or implantation of a component of the system
- embolization, arterial or other
- emergent or urgent surgery to perfuse limb or remove stent
- fever
- hematoma or hemorrhagic event
- hypotension or hypertension
- infection, local or systemic, including bacteremia or septicemia
- ischemia or infarction of tissue or organ
- pain at catheter insertion site
- pulmonary embolism
- renal failure or insufficiency secondary to contrast medium
- restenosis of vessel in stented segment
- stent malapposition or migration
- stent strut fracture
- stent thrombosis or occlusion
- stroke, cerebrovascular accident (CVA), or transient ischemic attack (TIA)
- target limb loss (amputation of toe, foot, and/or leg)
- vascular thrombosis or occlusion at puncture site, treatment site, or remote site
- vessel dissection, perforation, or rupture
- vessel spasm or recoil
- worsening claudication or rest pain

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. *In Vitro* Bench Testing

In vitro bench testing to support the safety and effectiveness of the Assurant Cobalt device was developed based on Medtronic's Product Development Process and is consistent with the FDA Guidance, *Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, January 13, 2005*. The relevant *in vitro* tests, outlined in the guidance document, and conducted to support the Assurant Cobalt device are summarized in Table 2. All test units were irradiated by E-Beam radiation at the maximum dose (55 kGy ± 8%) prior to testing, unless otherwise noted in the test report.

Table 2: Summary of *In Vitro* Testing

In Vitro Test	Test Purpose	Acceptance Criteria	Pass/Fail
Material Characterization			
Material Composition (Stent)	Chemical analysis conducted on the cobalt-chromium alloy (MP35N) verifies the stents are produced from material that conforms to the chemical composition requirements of ASTM F562 *Standard Specification for Wrought Cobalt-35 Nickel-20 Chromium-10 Molybdenum Alloy for Surgical Implant Applications*.	The stent components must meet ASTM F562 specifications.	Pass
Material Composition (Delivery System)	The compositions of the materials used to manufacture the Assurant Cobalt delivery system meet required material specifications.	The individual delivery system components must meet component specifications.	Pass

In Vitro Test	Test Purpose	Acceptance Criteria	Pass/Fail
Corrosion Resistance	The Assurant Cobalt stent was evaluated to assess the potentially corrosive effects of the *in vivo* environment on the stent, including pitting, fretting in the case of overlapped stents, and galvanic corrosion in the case of overlapped stents consisting of dissimilar materials.	The stent must exhibit localized fretting and pitting corrosion that is not worse than those of the Medtronic Bridge stent when tested in simulated blood. For characterization purposes only, galvanic corrosion was assessed by coupling the stent material to nitinol or 316L stainless steel.	Pass
Stent Dimensional and Functional Attributes			
Dimensional Verification	Stent diameters were measured pre- and post-balloon expansion.	All samples must meet product design specifications.	Pass
Percent Surface Area	This is a theoretical calculation performed to determine the amount of metal coming into contact with the vessel wall. The percent metal coverage predicts that the stent will support the vessel.	The percent surface areas for the 6 mm and 10 mm stents must be 7% - 20%.	Pass
Foreshortening	The length of the Assurant Cobalt stent was measured in the crimped condition and the expanded condition. These values are used to calculate the foreshortening of the stent.	Foreshortening must be $\leq$ 20%.	Pass
Stent Recoil	The difference in stent diameter at balloon inflation and after balloon deflation was calculated for each labeled stent diameter.	The measured recoil values must meet the following specifications: - 12.7% (6 mm) - 10.9% (7 mm) - 9.5% (8 mm) - 8.5% (9 mm) - 7.6% (10 mm)	Pass

In Vitro Test	Test Purpose	Acceptance Criteria	Pass/Fail
Stent Integrity	The Assurant Cobalt stent was inspected for defects following stent deployment.	No visible cracks or notches on any crown or weld can be observed at 45X mag at maximum expansion.	Pass
Radial Stiffness and Radial Strength	The reduction in diameter of the Assurant Cobalt stent due to external radial pressure was measured and compared to specifications.	Diametrical reduction must not be greater than 25% following exposure to 225 mmHg radial pressure load.	Pass
Mechanical Properties	The properties of the cobalt-chromium alloy (MP35N) used to manufacture the Assurant Cobalt stent were evaluated.	Raw materials used in stent manufacturing must meet specifications for yield strength, tensile strength and percent elongation, as documented in the Certificate of Conformance that accompanies each material lot from the vendor. The post-processing mechanical properties (ultimate tensile strength, yield strength, Poisson's ratio, elongation, elastic modulus, and endurance limit) were also characterized.	Pass

In Vitro Test	Test Purpose	Acceptance Criteria	Pass/Fail
Stress Analysis	The durability and integrity of the Assurant Cobalt stent was evaluated using Finite Element Analysis (FEA). The FEA evaluated the ability of the stent to withstand crimping onto the catheter, deployment, and the loading that it may experience *in vivo*.	For the 8 mm and 10 mm diameter stents, the mean and alternating must lie to the left of the Gerber parabola of the fatigue life diagram when simulated in vivo load conditions were applied.	Pass
Fatigue Analysis	The durability and integrity of the Assurant Cobalt stent was evaluated using accelerated cycle-to-life endurance testing (S/N) and analysis. The S/N testing evaluated the highest strain location of the stent.	Models of stents deployed in both single and overlapped configurations must not experience a loss of radial integrity after application of 420 million cycles (to simulate 10 years of pulsatile cycles).	Pass
Accelerated Durability Testing	The Assurant Cobalt stents were overlapped in a simulated artery and then placed in an accelerated radial fatigue durability test for 420 million cycles (to simulate 10 years of pulsatile cycles).	Stents deployed in both single and overlapped configurations must not experience a loss of radial integrity after application of 420 million cycles (to simulate 10 years of pulsatile cycles).	Pass
MRI Safety and Compatibility	The heating, translation, torque, and artifact generation of the Assurant Cobalt stent was evaluated using MR field strengths of 1.5 and 3 Tesla, per ASTM F2052, ASTM F2213, ASTM F2182, and ASTM F2119 standards,	The stent must demonstrate acceptable MR compatibility. The results are reflected in the Instructions For Use (IFU) as "MR Conditional" according to ASTM F2503.	Pass

In Vitro Test	Test Purpose	Acceptance Criteria	Pass/Fail
Radiopacity	The radiopacity of the Assurant Cobalt stent was evaluated during *in vitro* testing.	The visibility of the stent under fluoroscopic imaging must be the same as or greater than that of the Bridge stent.	Pass
Delivery System Dimensional and Functional Attributes			
Delivery, Deployment and Retraction	The ability of the Assurant Cobalt Stent System to deliver the stent to the intended location according to the instructions for use without damage to the stent was evaluated qualitatively.	The delivery catheter must reliably deliver the stent to the intended location. The stent must deploy easily and accurately, and there must be no damage to the stent or balloon during deployment and retraction.	Pass
Balloon-Rated Burst Pressure (RBP)	System pressure capability testing was carried out to demonstrate that the Assurant Cobalt stent delivery system will not experience loss of integrity at or below rated burst pressure.	The test data must indicate with 95% confidence that 99.9% of all devices will not fail at or below the RBP of 12.0 atm for the 6 – 8 mm diameter stents, and the RBP of 10.0 atm for the 9 – 10 mm diameter stents.	Pass
Balloon Fatigue	The Assurant Cobalt delivery system was tested to measure its ability to withstand 10 fatigue cycles at rated burst pressure.	The test data must indicate with 95% confidence that 90% of samples will withstand 10 fatigue cycles at the RBP values stated above.	Pass

In Vitro Test	Test Purpose	Acceptance Criteria	Pass/Fail
Stent Diameter vs. Balloon Pressure	Stent IDs were measured at nominal and rated burst pressures.	No specifications were set. The test data were used to construct the balloon compliance chart provided in the device labeling.	Pass
Catheter Bond Strength	The tensile strengths of the Assurant Cobalt delivery system bonds (balloon-bilumen, inner shaft-bilumen, and bifurcate-shaft) were measured and evaluated against specifications.	Balloon-bilumen: - Break > 20.0 N - Yield > 17.8 N Inner shaft-bilumen: - Break > 5.0 N Bifurcate-shaft: - Break > 17.8 N	Pass
Crossing Profile	The maximum crossing profile of the Assurant Cobalt delivery system was measured and evaluated against specifications.	The crossing profile must be less than 0.083" (2.11mm).	Pass
Balloon Inflation and Deflation Time	Inflation and deflation times to and from the rated burst pressure for the Assurant Cobalt device were measured and evaluated.	Balloon inflation and deflation times must be less than 25 and 30 seconds, respectively.	Pass
Stent Securement for Unsheathed Stents	Stent securement of the Assurant Cobalt device was measured and evaluated.	The tests data must indicate with 95% confidence that 95% of all devices will retain the stent under a minimum applied load of 170 g_f (1.67N).	Pass

B. Sterilization

The Assurant Cobalt device is E-Beam sterilized in compliance with ISO 11137:2006 and EN 556-1. Routine sterilization dose audits and continuous monitoring of bioburden levels are performed to confirm that the sterilization process is effective in eradicating viable microorganisms. Results obtained from sterilization studies demonstrate that the Assurant Cobalt device will maintain a Sterility Assurance Level (SAL) of 10^{-6} when sterilized at a minimum dose of 25 kGy.

C. Packaging and Device Shelf Life

Packaging qualification testing was performed for the Assurant Cobalt device which is packaged in a preformed tray, sealed in a packaging pouch and placed in a folding carton. A 2-year shelf-life has been established for the product.

D. *In Vivo* Animal Studies

The Assurant Cobalt device has been evaluated in a series of acute and chronic animal studies. The aim of the studies was to demonstrate acceptable functional performance of the subject devices in an *in vivo* environment and to ensure that the devices do not cause untoward hemodynamic, vascular or other biological (e.g. thrombotic events, etc.) responses. Acute performance characteristics of the stent system were also evaluated in each study. These studies were conducted in a heparinized animal model.

Table 3 summarizes the animal studies conducted using the Assurant Cobalt device. The chronic 180-day and 90-day studies were conducted in accordance with Good Laboratory Practices (GLP) per 21 CFR 58. The remaining studies were non-GLP studies, conducted in accordance with the study protocol and applicable testing facility and test site procedures.

All stents were successfully deployed, and all animals survived to the scheduled pre-determined study endpoints. The devices did not elicit any untoward hemodynamic, vascular or other biological (e.g., thrombotic events) responses. Proximal migration of stents occurred post-implant in some cases of the GLP study but was determined to be animal model-specific, most likely from vascular spasm and the naturally more compliant nature of arteries in young experimental research swine.

Table 3: Summary of Animal Studies Performed on the Assurant Cobalt Device

Study Type	# of Animals and # of Stents	Follow-up Duration	Relevant Findings
Chronic Safety (180 day)	22 Porcine 22 Stents (9 stents implanted and 2 sham procedures at each time-point)	30 days & 180 days	At both 30 and 180 days, the Assurant Cobalt stents were well tolerated. Acute performance of the Assurant Cobalt stent equals or exceeds currently available competitive peripheral devices.

Study Type	# of Animals and # of Stents	Follow-up Duration	Relevant Findings
A 60-day Evaluation of Overlapped Assurant Cobalt Stents	8 Porcine 16 stents (8 overlapped stent pairs)	60 days	At 60-days, the Assurant Cobalt stents performed comparably in single stented and overlapped configurations in safety-related parameters. The stents delivered well into the contralateral iliac arteries, as demonstrated by consistently high acute performance characteristic ratings.
A 28-day Evaluation of Overlapped Assurant Cobalt Stents	8 Porcine 16 Stents (8 overlapped stent pairs)	28 days	At 28-days, the Assurant Cobalt stents performed comparably in single stented and overlapped configurations in safety-related parameters. The stents delivered well into the contralateral iliac arteries, as demonstrated by consistently high acute performance characteristic ratings.
Acute Performance	2 Porcine 4 Stents	Acute study	This study demonstrated that the longest length Assurant Cobalt Iliac Balloon-Expandable Stent (60 mm), delivered contralaterally, showed comparable or greater performance when compared to physician's prior experience with competitive peripheral balloon expandable stents.
A 90-day Evaluation of Overlapped Assurant Cobalt Stents	7 Porcine 14 Stents (7 overlapped stent pairs)	90 days	At 90-days, the Assurant Cobalt stents performed comparably in single stented and overlapped configurations in safety-related parameters. The stents delivered well into the iliac arteries, as demonstrated by consistently high acute performance characteristic ratings.

E. Biocompatibility

The biocompatibility of the Assurant Cobalt device was evaluated per the requirements of ISO 10993. Tests were conducted on E-beam irradiated stents and stent delivery systems. All testing was performed in accordance with FDA Good Laboratory Practice (GLP) regulations (21 CFR, Part 58).

Tests conducted on the Assurant Cobalt device are appropriate for an implant device that is in permanent contact with circulating blood (>30 days) and an externally communicating device that is in limited contact with circulating blood (<24 hours). Table 4 and Table 5 summarize the biocompatibility testing performed. All test results indicate that the materials and process used to manufacture the Assurant Cobalt device are biocompatible and suitable for their intended use.

Table 4: Summary of Biocompatibility Test Results for the Assurant Cobalt Stent (a permanent implant in contact with circulating blood for >30 days)

Test	Test Description	Result
Cytotoxicity	MEM Elution (ISO 10993-5)	Pass (Non-toxic)
Sensitization	Maximization Sensitization Study (ISO10993-10)	Pass (Non-sensitizing)
Irritation or Intracutaneous Reactivity	Acute Intracutaneous Reactivity (ISO10993-10)	Pass (Non-irritant)
Systemic Toxicity	Material Mediated Pyrogen (ISO10993-11)	Pass (Non-toxic)
	Acute Systemic Toxicity (ISO10993-11)	Pass (Non-toxic)
Genotoxicity	Bacterial Reverse Mutation (ISO10993-3)	Pass (Non-mutagenic)
	Chromosomal Aberration (ISO10993-3)	Pass (Non-mutagenic)
	Mouse Peripheral Blood Micronucleus (ISO10993-3)	Pass (Non-mutagenic)
Implantation	Muscle Implantation 12 week (ISO10993-6)	Pass (Non-irritant)
Interactions with Blood	Complement Activation - SC5b-9 (ISO10993-4)	Pass (Non-activator)
	Complement Activation - C3a (ISO10993-4)	Pass (Non-activator)
	Hemolysis (ISO10993-4)	Pass (Non-hemolytic)

Table 5: Summary of Biocompatibility Test Results for the Assurant Cobalt Stent Delivery System (an externally communicating device in limited contact with circulating blood (<24 hours)

Test	Test Method	Result
Cytotoxicity	MEM Elution (ISO 10993-5)	Pass (Non-toxic)
Sensitization	Maximization Sensitization study (ISO10993-10)	Pass (Non-sensitizing)
Irritation or Intracutaneous Reactivity	Acute Intracutaneous Reactivity (ISO10993-10)	Pass (Non-irritant)
Systemic Toxicity	Material Mediated Pyrogen (ISO10993-11)	Pass (Non-toxic)
	Acute Systemic Toxicity (ISO10993-11)	Pass (Non-toxic)
Interactions with Blood	Complement Activation - SC5b-9 (ISO10993-4)	Pass (Non-activator)
	Complement Activation - C3a (ISO10993-4)	Pass (Non-activator)
	Hemolysis (ISO10993-4)	Pass (Non-hemolytic)
	Thrombosis (ISO10993-4)	Pass
Physicochemical Testing	USP Purified Water extract (ISO10993-18)	Pass
Physicochemical Testing	Alternative extract – Isopropyl Alcohol (ISO10993-18)	Pass

X. SUMMARY OF PRIMARY CLINICAL STUDY

The ACTIVE (Use of the Assurant Cobalt Stent System in the Treatment of Iliac Vessel Disease) Study was a non-randomized prospective, multicenter, single-arm study performed to support the safety and effectiveness of the Assurant Cobalt Iliac Balloon-Expandable Stent System in the treatment of de novo and restenotic lesions in iliac arteries of subjects with Peripheral Artery Disease (PAD). A summary of the clinical study is presented below. The ACTIVE Clinical Study Report described the 9-Month data for 123 subjects enrolled in the trial from October 20, 2008 to February 25, 2010. Data presented to FDA were collected through the 9-Month Follow-Up Visit for all enrolled and eligible subjects through the database snapshot date of February 11, 2011. Data from this clinical study were the basis for the PMA approval decision.

A. Study Design

A summary of the clinical study is presented below.

1. Clinical Inclusion and Exclusion Criteria

   Subjects were allowed to have multiple vessel disease and treatment in up to two target lesions (one per limb). In addition, treatment of up to two non-target lesions was permitted during the Index procedure but prior to enrollment.

   Target lesion(s)

   - Only one target lesion was allowed per limb
   - If bi-lateral treatment was planned with the investigational device NO non-target lesions were allowed.
   - Up to two stents may have been used per target lesion.
   - Non-target lesion(s)
   - Up to two non-target lesions may have been treated in the contralateral limb.
   - Treatment of the non-target lesions could not involve the investigational device.
   - Treatment of the non-target lesions must have been performed during the same setting but prior to treating the target lesion.

   Optimal results must have been obtained for the non-target lesions prior to enrolling the subject into the ACTIVE study. Results were deemed optimal when all of the following criteria were met:

   - Residual stenosis no greater than 30%
   - Free of filling defects or edge dissections worse than Grade A per NHLBI
   - No serious adverse event

   Non-target lesions were not included in the primary or secondary analyses.

   Inclusion Criteria

   1. The subject is ≥ 18 years old;
   2. Female subjects of childbearing potential with a negative pregnancy test within 7 days before treatment;
   3. The subject or subject's legal representative has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board of the respective investigational site;

4. The lesion(s) is either *de novo* or restenotic in nature, located in the common iliac artery and/or the external iliac artery;
5. The subject is symptomatic (Fontaine stage II or III) with a target lesion stenosis ≥ 50% and ≤ 100%
6. The target vessel(s) reference diameter is ≥ 6 mm and ≤ 10 mm by visual estimate;
7. The lesion length is ≤ 100 mm (10 cm);
8. Subject agrees to comply with specified follow-up evaluations and visits.

Exclusion Criteria

1. The subject has either excessive peripheral artery disease, unresolved fresh thrombus in the target lesion/vessel or if the target lesion/vessel is excessively tortuous, occluded, or heavily calcified precluding safe insertion of PTA devices;
2. The subject has any tissue loss in the target extremities defined by the Fontaine scale as stage IV;
3. The target lesion has a previous stent, or is located within a prosthetic vascular bypass graft or within 1 cm of a graft anastomosis;
4. The target lesion is located within an aneurysm or associated with an aneurysm in the vessel segment either proximal or distal to the target lesion;
5. The subject had a previous iliac artery bypass surgery which involves the target lesion or target vessel;
6. The lesion requires treatment other than PTA prior to stent placement;
7. The subject has other lesions requiring treatment or requires surgery within 30 days of the procedure (pre or post) with the exception of the non-target lesion(s).
8. The subject has inadequate distal run-off as angiographically evidenced by occlusion of either the common femoral artery or of both the superficial femoral artery AND the deep femoral artery (profunda femoris);
9. The subject has a known allergy or contraindication to aspirin, heparin, ticlopidine **or** clopidogrel, cobalt chromium, or a sensitivity to contrast media which cannot be adequately pre-medicated;
10. The subject has a history of bleeding diatheses or coagulopathy or will refuse blood transfusions;
11. The subject has impaired renal function (creatinine > 2.5 mg/dl);

12. The subject has a known platelet count <80,000 cells/mm^3 or >700,000 cells/mm^3, or a WBC of <3,000 cells/mm^3 within 7 days prior to the index procedure;

13. The subject is participating in another investigational device or drug study and has not completed the primary endpoint(s) or that clinically interferes with the ACTIVE Study endpoints;

14. The subject has previously been enrolled in the ACTIVE Study;

15. The subject has a known medical condition that will cause them to be non-compliant with the study protocol or is associated with a life expectancy of less than 12 months.

1. Follow-up Schedule

   After hospital discharge, patients were required to return to the study center for clinical assessments on Day 30 ± 5 days and 9 months ± 30 days. Ischemic testing, Duplex scans, ABI, toe brachial index (TBI), Fontaine Scale Classification, and walking assessment were performed at the Day 30 and 9 month visits. Additionally, an angiogram was performed as needed to assess the safety and effectiveness of the Assurant Cobalt Stent.

2. Clinical Endpoints

   The primary endpoint of the ACTIVE study was major adverse events (MAE) at 9 months, defined as device and/or procedure related death, target limb loss and/or clinically-driven target lesion or target vessel revascularization (TLR/TVR). The secondary endpoints were primary patency rate of the target vessel(s) at 9 months as determined by Duplex ultrasound scan, acute success, clinical success, hemodynamic success at 30 days and 9 months, and all cause mortality at 30 days, 9 months and 3 years. All secondary endpoints were presented descriptively by reporting the number and percentage of subjects who met the endpoint definition.

B. Accountability of PMA Cohort

Of the 123 subjects enrolled, 122 subjects were eligible for the 30-Day Follow-up Clinical Visit. One (1) subject withdrew consent from the study at 29 days post-procedure. Table 6 shows detailed subject accountability through the 9-Month Follow-up Visit.

Table 6: Subject Follow-up Compliance

Subject Compliance	N=123
30-Day Follow-up	
Eligible Subjects[a]	122
Follow-up Compliance within Window[b] (%)[c]	80.3 (98/122)
Follow-up outside of Window[b] (%)[c]	18.0 (22/122)
No Follow-up (%)[c]	1.6 (2/122)
Follow-up within or outside of Window[b] (%)[c]	98.4 (120/122)
9-Month Follow-up	
Eligible Subjects[a]	120
Follow-up Compliance(%)[c]	72.5 (87/120)
Follow-up outside of Window[b] (%)[c]	21.7 (26/120)
No Follow-up (%)[c]	5.8 (7/120)
Follow-up within or outside of Window[b] (%)[c]	94.2 (113/120)

[a] Eligible subjects are all subjects who are enrolled by snapshot date and 1) had a follow-up at or after the lower limit of the window, or 2) were enrolled and have reached the upper limit of th e
window, or 3) were lost to follow-up before the upper limit of the window
[b] Within window visits are defined as: 30 days ± 5 days, 9 months ± 30 days
[c] Percentage based on number of subjects who had follow-
up divided by number of eligible subjects
N = Intent-to-treat Population
Note: Site Reported Table

C. Study Population Demographics and Baseline Parameters

Patients 18 years of age and older with symptomatic ischemic Peripheral Artery Disease (PAD) (Fontaine stage II or III), with stenotic lesions ≥50% and ≤100% in the common or external iliac arteries, with target vessel reference diameters ≥6.0 mm and ≤10.0 mm by visual estimate, and lesion lengths ≤100 mm which were amenable to percutaneous treatment by placement of a vascular stent, were eligible for this study. Multiple vessel disease, de novo target lesions, and restenotic lesions that had not undergone percutaneous interventional treatment using the same access site to any vessel within a minimum of 30 days prior to enrollment into the study, were included. Tables 7–9 present the subject demographics, angiographic morphology data, and angiographic quantitative analysis.

Table 7: Subject Demographic, Medical History, and Risk Factors[a]

	N=123
Age (n = 123)	**Years**
Mean ± SD	65.5 ± 10.6
Median	66.4
Min, Max	41, 86
Sex	**% (m/n)**
Male	56.1(69/123)
Female	43.9(54/123)
Medical History and Risk Factors	**% (m/n)**
Diabetes Mellitus	38.2 (47/123)
Type I	2.4 (3/123)
Type II	35.8 (44/123)
Dyslipidemia	74.8 (92/123)
Hypertension	82.9 (102/123)
Cigarette Smoking During the Past Year	50.4 (62/123)
Currently Smoking Cigarettes	42.3 (52/123)
History of Coronary Artery Disease	66.7 (82/123)
History of COPD	28.0 (33/118)
Previous MI	26.5 (31/117)
Previous Peripheral Vascular Disease (other than iliac)	63.4 (78/123)
Previous PTA/Stenting to Target Limb	8.1 (10/123)
Previous Aorta/Peripheral Bypass to Target Limb	2.4 (3/123)

[a] Based on number of subjects with available data
N = Intent-to-treat population
m = number of subjects in the category
n = number of subjects in the study group with sufficient data for analysis
Note: All subjects had known values for the tabulated variables, with the exception of history of COPD and Previous MI for which a value of unknown was entered by the Investigational Site.
Note: Site Reported Table

Table 8: Angiographic Morphology Data

Lesion Characteristic	Lesions[a] = 159 % (m/n)
Pre-procedure Assessment	
Eccentric	24.5 (39/159)
Ulceration	5.7 (9/159)
Calcification	
None/mild	42.6 (66/155)
Moderate	36.1 (56/155)
Severe	21.3 (33/155)
Thrombus	0.0 (0/159)
Postprocedure Assessment	
Dissection Grade	
0 (no dissection)	100.0(159/159)
A	0.0(0/159)
B	0.0(0/159)
C	0.0(0/159)
D	0.0(0/159)
E	0.0(0/159)
F	0.0(0/159)

[a] Lesions as reported by the Angiographic Core Laboratory
m = number of lesions in the category
n = number of lesions in the study group with sufficient data for analysis

Table 9: Angiographic Quantitative Analysis

	Lesions[a] =159			
	n	Mean ± SD	Median	Min, Max
Reference Vessel Diameter (mm)	159	7.619 ± 1.183	7.645	4.74, 10.80
Lesion Length (total) (mm)	154	29.430 ± 14.659	26.400	1.00, 88.46
Lesion Preprocedure Percent Stenosis (most severe)	159	68.735 ± 14.221	67.001	45.49, 100.00
Lesion Preprocedure Minimum Lumen Diameter (mm)	159	2.387 ± 1.171	2.470	0.00, 5.70
Lesion Postprocedure Percent Stenosis (most severe)	159	14.615 ± 6.989	13.944	1.30, 33.63
Lesion Postprocedure Minimum Lumen Diameter (mm)	159	6.584 ± 1.157	6.560	3.81, 9.52
Acute gain (mm)	159	4.197 ± 1.238	4.130	1.30, 8.82

[a] Lesions as Angiographic Core Laboratory Reported
n = number of lesions in the study group with sufficient data for analysis

D. Safety and Effectiveness Results

1. Primary Safety and Effectiveness Endpoint

The primary analysis of safety and effectiveness was based on the 9-Month patient group of 123 patients. The primary endpoint of major adverse events (MAE) is a composite of procedure related mortality, target limb loss, and clinically driven target lesion or target vessel revascularization (TLR/TVR). Mathematical representations of the primary endpoint hypotheses are provided below:

H_0: $P_{ASSURANTCOBALT} \geq P_{PG}$
H_A: $P_{ASSURANTCOBALT} < P_{PG}$

where:

$P_{ASSURANTCOBALT}$ = Observed 9 months MAE rate in the ACTIVE study; and

P_{PG} = Performance Goal (PG) of 17% for the 9-month MAE rate, as derived from literature reports of iliac artery interventions.

Using these hypotheses and assuming a subject drop-out rate of 15% and an anticipated MAE rate at 9 months of 8.5%, and with a 1-sided alpha error (α) of 0.05 and beta (β) error of 20% (resulting in 80% power), the required sample size for the study was 123 subjects.

The analysis of overall MAE rate at 9 months was 0.8% (1/121) (95% CI, 0.0%, 3.9%). The clinically driven TLR and TVR rates at 9 months were both 0.8% (1/121) (95% CI, 0.0%, 3.9%). The MAE results were substantially lower than the performance goal of 17% specified in the study hypothesis; therefore the primary hypothesis was demonstrated. These results are presented in Table 10.

Table 10: Primary Endpoint and Details of Major Adverse Events through 9 Months

	N = 123	
Primary Endpoint	**% (m/n)[a]**	**% Exact One-side Upper 95% CI**
MAE to 9 Months	0.8% (1/121)	(0.0%, 3.9%)
Death (Device and/or Procedure Related)	0.0% (0/121)	(0.0%, 2.4%)
Device Related	0.0% (0/121)	(0.0%, 2.4%)
Procedure Related	0.0% (0/121)	(0.0%, 2.4%)
Target Limb Loss	0.0% (0/121)	(0.0%, 2.4%)
TLR	0.8% (1/121)	(0.0%, 3.9%)
TL-PTA[b]	0.8% (1/121)	(0.0%, 3.9%)
TL-Iliac Bypass Graft	0.0% (0/121)	(0.0%, 2.4%)
TVR	0.8% (1/121)	(0.0%, 3.9%)
TV-PTA[c]	0.8% (1/121)	(0.0%, 3.9%)
TV-Iliac Bypass Graft	0.0% (0/121)	(0.0%, 2.4%)

[a] Percentage based on the number of subjects with sufficient follow-up for 9-month MAE assessment. Insufficient follow-up for 9-month MAE assessment is defined by a) withdrawn before 240 days without having MAE events, b) lost to follow-up before 240 days without having MAE events and had no contact thereafter, or c) any death unrelated to the device and/or procedure before 240 days without having MAE events.
[b] Target Lesion Percutaneous Transluminal Angioplasty
[c] Target Vessel Percutaneous Transluminal Angioplasty

Only one subject was deemed to have met the criteria defined in the protocol for a major adverse event. This subject had a target lesion/vessel revascularization 10 days postprocedure. This subject was reported as not taking aspirin or clopidogrel after being discharged from the hospital.

During review of the PMA, FDA also requested independent Angiographic Core Laboratory visual assessment from all patients who had follow up angiograms for any reason, in order to ascertain if the stent migration that was seen in the preclinical swine studies was manifested clinically. The sponsor provided Angiographic Core Laboratory visual assessment of 9 (nine) patients for which there were angiograms performed at points ranging from one day to 13 months following stent implant. No migrations were reported. Based on this information, the Agency believes that the findings in the animal study were related to the differences in compliance between native swine lower limb vessels, the particular method of radiographic evaluation and/or its associated error.

FDA's review of the clinical information determined that the study outcomes provide a reasonable assurance that the device, when used as directed, is safe and effective for its intended use. There were no unanticipated adverse device effects reported in the ACTIVE study and the rates of adverse events are acceptably low, considering the comorbid conditions of the patients in the study population.

Summary of Adverse Events that occurred in the ACTIVE Study

An independent Clinical Events Committee (CEC) developed specific criteria for the categorization of clinical events and clinical endpoints in this study. The specific criteria related to device and/or procedure related death, target limb loss, and clinically driven target lesion/vessel revascularization. Sites also reported adverse events and serious adverse events. System organ class was assigned via MedDRA coding by the Medtronic Clinical Trial Safety Department (Table 11).

Table 11: Adverse Events through 9 Months

System Organ Class	N = 123 % (m/n)
Blood and Lymphatic System Disorders	6.5 (8/123)
Cardiac Disorders	16.3 (20/123)
Ear and Labyrinth Disorders	0.8 (1/123)
Endocrine Disorders	0.8 (1/123)
Eye Disorders	0.8 (1/123)
Gastrointestinal Disorders	11.4 (14/123)
General Disorders and Administration Site Conditions	13.8 (17/123)
Hepatobiliary Disorders	1.6 (2/123)
Infections and Infestations	13.8 (17/123)
Injury, Poisoning and Procedural Complications	11.4 (14/123)
Investigations	1.6 (2/123)
Metabolism and Nutrition Disorders	6.5 (8/123)
Musculoskeletal and Connective Tissue Disorders	17.9 (22/123)
Neoplasms; Benign, Malignant and Unspecified (Including Cysts and Polyps)	0.8 (1/123)
Nervous System Disorders	6.5 (8/123)
Psychiatric Disorders	0.8 (1/123)
Renal and Urinary Disorders	7.3 (9/123)
Reproductive System and Breast Disorders	0.8 (1/123)
Respiratory, Thoracic, and Mediastinal Disorders	8.9 (11/123)
Skin and Subcutaneous Tissue Disorders	7.3 (9/123)
Surgical and Medical Procedures	0.8 (1/123)
Vascular Disorders	26.0 (32/123)

N = Intent-to-treat population
m = number of subjects in the category
n = number of subjects in the study group with sufficient data for analysis
Note: Site Reported Table

2. Secondary Endpoints

The results for secondary endpoints of primary patency rate of the target vessel at 9 months as determined by the Duplex Ultrasound Core Lab, acute success (device, lesion, and procedure), clinical success, hemodynamic success at 30 days and 9 months, and all-cause mortality at 30 days and 9 months, are shown in Table 12.

Table 12: Secondary Endpoints

Subjects [a] = 123 Lesions[b] = 141 Lesions[c] = 159 Limbs[d] = 159		
Secondary Endpoints	**% (m/n)[e]**	**% Exact Two-sided Upper 95% CI**
Primary Patency Rate at 9 Months	100.0% (141/141)	(97.4%, 100.0%)
Device Success[f]	97.5% (155/159)	(93.7%, 99.3%)
Lesion Success[g]	97.5% (155/159)	(93.7%, 99.3%)
Procedure Success[h]	96.7% (119/123)	(91.9%, 99.1%)
Clinical Success at 30 Days[i]	88.2% (134/152)	(81.9%, 92.8%)
Clinical Success at 9 Months[i]	90.4% (132/146)	(84.4%, 94.7%)
Hemodynamic Success at 30 Days[j]	64.1% (98/153)	(55.9%, 71.6%)
Hemodynamic Success at 9 Months[j]	55.2% (79/143)	(46.7%, 63.6%)
Hemodynamic Success at 30 Days[k]	75.8% (116/153)	(68.2%, 82.4%)
Hemodynamic Success at 9 Months[k]	80.1% (117/146)	(72.7%, 86.3%)
All-Cause Mortality to 30 Days[l]	0.0% (0/123)	(0.0%, 3.0%)
All-Cause Mortality to 9 Months[o]	0.0% (0/121)	(0.0%, 3.0%)

[a] Intent-to-treat population
[b] Lesions as reported by Duplex Core Laboratory
[c] Lesions as reported by Angiographic Core Laboratory
[d] Limbs as reported by site
[e] Percentage based on number of lesions with available data (clinical and hemodynamic success based on number of targeted limbs at related time point; procedure success and all-cause mortality on subject level)
[f] Device Success defined as angiographic evidence of <30% final residual stenosis of the target lesion using only the assigned device
[g] Lesion Success defined as angiographic evidence of <30% final residual stenosis of the target lesion using any percutaneous method
[h] Procedure Success defined as angiographic evidence of <30% final residual stenosis of the target lesion after stent placement and no occurrence of a procedure related MAE prior to hospital discharge (for subjects with more than one lesion stented the worse case is counted)
[i] Clinical success defined as the improvement of Fontaine classification by at least one stage above the pretreated (preprocedure) clinical value
[j] Hemodynamic success (protocol defined): an improvement in ankle-brachial index (ABI) or toe brachial index (TBI) >0.10 over preprocedure level and not deteriorated by >0.15 from first postprocedure level
[k] Hemodynamic success (alternative definition)1: 'sustained hemodynamic improvement' consists of

1 Diehm N, Pattynama PM, Jaff MR, Cremonesi A, et al. Clinical endpoints in peripheral endovascular revascularization trials: a case for standardized definitions. *Eur J Vasc Endovasc Surg.* 2008;36:409-419.

persistent improvement of ABI/TBI values with ≥ 0.10 as compared to baseline values or to ABI/TBI ≥ 0.9 throughout follow-up without need for repeated TLR in surviving subjects
[l] Subjects are considered unevaluable for all-cause mortality at 30 days if a) withdrawn before 25 days or b) lost to follow-up before 25 days and had no contact thereafter
[o] Subjects are considered unevaluable for all-cause mortality at 9 months if a) withdrawn before 240 days or b) lost to follow-up before 240 days and had no contact thereafter
m = number of subjects in the category
n = number of subjects in the study group with sufficient data for analysis
Note: Site, CEC, Duplex and Angiographic Core Laboratory Reported Table

The data from the secondary analyses were determined by FDA to provide a reasonable assurance of maintained patency of the iliac lesion and relieved symptoms of claudication in a substantial proportion of the study population.

3. Subgroup Analyses

Applicability to Pediatric Populations

Peripheral artery disease is not typically found in pediatric populations excepting rare homozygous lipid disorders. Accordingly, the safety and effectiveness of the Assurant Medtronic in pediatric populations was not studied in the ACTIVE trial.

ACTIVE Study Results by Gender/Sex

The ACTIVE trial accrued a total of 54 (43.9%) female and 69 (56.1%) male subjects. A total of 52 (43.0%) female and 69 (57%) male subjects were evaluable for the primary safety endpoint of major adverse events (MAE) at 9 months. Female and male subjects had similar MAE rates (0.0% and 1.4%, respectively; $p > 0.99$ for difference in rates) with an overall MAE rate of 0.8%. In addition, lesions in 67 (47.5%) female and 74 (52.5%) male subjects were evaluable for the primary effectiveness endpoint of primary patency at 9 months. Primary patency rate was 100% in females and 100% in males for an overall rate of 100%. These findings indicate similar safety and effectiveness outcomes for males and females. Iliac stent specific outcomes are presented separately for male and female subjects as summarized in Tables 13 and 14.

Table 13: Primary Endpoints to 9 Months by Gender/Sex

		N=123
Primary Endpoint	Male%(m/n)[a]	Female% (m/n)
MAE to 9 Months	1.4% (1/69)	0.0%(0/52)
Death (Device and/or Procedure Related)	0.0% (0/69)	0.0%(0/52)
Device Related	0.0% (0/69)	0.0% (0/52)
Procedure Related	0.0% (0/69)	0.0% (0/52)
Target Limb Loss	0.0% (0/69)	0.0% (0/52)
TLR	1.4% (1/69)	0.0% (0/52)
TL-PTA	1.4% (1/69)	0.0% (0/52)
TL-Iliac Bypass Graft	0.0% (0/69)	0.0% (0/52)
TVR	1.4% (1/69)	0.0% (0/52)
TV-PTA	1.4% (1/69)	0.0% (0/52)
TL-Iliac Bypass Graft	0.0% (0/69)	0.0% (0/52)

[a]Percentage based on number of evaluable subjects for MAE. Subjects are considered unevaluable for MAE to 9 months if a) withdrawn before 240 days without having MAE events or b) lost to follow-up before 240-days without having MAE events and had no contact thereafter or c) any device and/or procedure-unrelated death before 240-days without having MAE events

N= Intent-To-Treat Population

M= number of subjects in the category

n= number of subjects in the study group with non-missing data

Table 14: Secondary Endpoints to 9 Months by Gender/Sex

Secondary Endpoint	Male%(m/n)[a]	Female% (m/n)[a]
Primary Patency Rate at 9 Months	100% (74/74)	100% (67/67)
Device Success[b]	98.8% (84/85)	95.9% (71/74)
Lesion Success[c]	98.8% (84/85)	95.9% (71.74)
Procedure Success[d]	98.6% (68/69)	94.4%(51/54)
Clinical Success at 30 Days[e]	89.2% (74/83)	87% (60/69)
Clinical Success at 9 Months[e]	88.3% (68/77)	92.8% (64/69)
Hemodynamic Success at 30 Daysf	63.5% (54/85)	64.7% (44/68)
Hemodynamic Success at 9	59.2% (45/76)	50.7%(34/67)

Months[f]		
All Cause Mortality to 30 Days[g]	0.0% (0/69)	0.0%(0/54)
All Cause Mortality to 9 Months[h]	0.0% (0/69)	0.0% (0/52)

[a] Percentage based on number of lesions with available data (clinical and hemodynamic success based on number of targeted limbs at related time point; procedure success and all cause mortality on subject level)
[b] Device Success defined as angiographic evidence of <30% final residual stenosis of the target lesion using only the assigned device
[c] Lesion Success defined as angiographic evidence of <30% final residual stenosis of the target lesion using any percutaneous method
[d] Procedure Success defined as angiographic evidence of <30% final residual stenosis of the target lesion after stent placement and no occurrence of a procedure related MAE prior to hospital discharge (for subjects with more than one lesion stented the worse case is counted)
[e] Clinical success defined as the improvement of Fontaine classification by at least one stage above the pretreated (pre-procedure) clinical value
[f] Hemodynamic success defined as an improvement in ankle-brachial Index (ABI) or toe brachial index (TBI) > 0.10 over pre-procedure level and not deteriorated by > 0.15 from first post-procedure level
[g] Subjects are considered unevaluable for all cause mortality at 30 days if a) withdrawn before 25 days or b) lost to follow-up before 25 days and had no contact thereafter
[h] Subjects are considered unevaluable for all cause mortality at 9 months if a) withdrawn before 240 days or b) lost to follow-up before 240 days and had no contact thereafter
N = Intent-To-Treat Population m = number of subjects in the category
n = number of subjects in the study group with non-missing data Note: Site, CEC, Duplex and Angiographic Core Laboratory Reported Table

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

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

XII. CONCLUSION.S DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety and Effectiveness Conclusions

The preclinical and clinical studies indicate that the Assurant Cobalt device meets or exceeds safety and performance specifications. A multi-center clinical trial has demonstrated that the Assurant Cobalt device is safe and effective for its intended use as a treatment for iliac artery disease in the indicated population. Results from preclinical and clinical evaluations provide valid scientific evidence and reasonable assurance that the device is safe and effective; therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the labeling and Instructions for Use (IFU).

XIII. CDRH DECISION

CDRH issued an approval order on October 26, 2011.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.