SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Stent, SFA

Device Trade Name: Misago® RX Self-expanding Peripheral Stent

Device Procode: NIP

Applicant's Name and Address: Terumo Corporation, Tokyo, Japan
44-1, 2-chome Hatagaya
Shibuya-ku Tokyo

151-0072 Japan

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P140002

Date of FDA Notice of Approval: May 22, 2015

Priority Review: No

II. INDICATIONS FOR USE

The Misago® RX Self-expanding Peripheral Stent is indicated to improve luminal diameter in symptomatic patients with de novo or restenotic native lesions or occlusions of the superficial femoral artery (SFA) and/or proximal popliteal artery with reference vessel diameters ranging from 4mm to 7mm and lesion length up to 150mm.

III. CONTRAINDICATIONS

The Misago® RX Self-expanding Peripheral Stent is contraindicated in:

- Patients who exhibit angiographic evidence of severe thrombus in the target vessel or lesion site before/after undergoing Percutaneous Transluminal Angioplaty PTA procedure.
- Patients with contraindication to antiplatelet and/or anticoagulation therapy.
- Patients who are judged to have a lesion that prevents proper placement or deployment of the stent
- A lesion that is within an aneurysm or an aneurysm with a proximal or distal segment to the lesion.
- A lesion through which a guide wire cannot pass.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Misago® RX Self-expanding Peripheral Stent labeling.

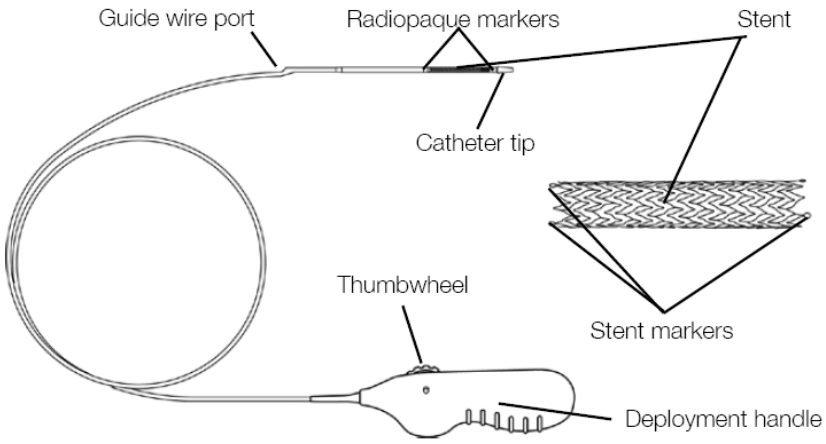
V. DEVICE DESCRIPTION

The Misago® RX Self-Expanding Peripheral Stent consists of a Nitinol stent ("stent") pre-mounted on the distal portion of a rapid exchange delivery catheter system ("delivery catheter"). The stent is made of a nickel-titanium alloy with three (3) radiopaque markers located at each end for a total of six (6) markers. The stent comes in different configurations of lengths and diameters (see Table 1). The distal part of the delivery catheter has a coaxial construction. The distal portion of the delivery catheter is constructed to allow coaxial passage of a guide wire that doesn't exceed 0.89mm (0.035") in diameter. Two inner shaft markers (radiopaque markers) are attached next to each end of the stent and allow confirmation under high-resolution fluoroscopy of the stent's position while in the patient's vessel before expansion. The stent deploys and self-expands by pushing down and rolling back a thumbwheel in the deployment handle while holding the handle in place (see Fig 1).

Table 1: Stent Configurations

Length / Diameter	40 mm	60 mm	80 mm	100 mm	120 mm	150 mm
6 mm	X	X	X	X	X	X
7 mm	X	X	X	X	X	X
8 mm	X	X	X	X		

Fig. 1 Diagram of Stent System



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of superficial femoral artery atherosclerotic disease:

- Non-invasive treatment (e.g., exercise, smoking cessation and/or drug therapy)
- Minimally invasive treatment (e.g., balloon angioplasty, endovascular stent or stent-graft placement, directional atherectomy)
- Surgical treatment (e.g., surgical bypass)

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Currently, the Misago® Peripheral Self-Expanding Stent System is available outside the US (OUS), including Japan and Europe. The Misago® Peripheral Self-Expanding Stent System for the treatment of lesions in the superficial femoral artery (SFA) has been available in Europe since 2008. No products have been withdrawn from the market in any country 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:

Table 2: Potential Adverse Effects

- Allergic reaction (contrast media, stent materials)
- Amputation of treated limb
- Arrhythmia
- Arterial dissection/perforation/rupture/injury
- Arterial embolism/thrombosis/occlusion
- Arterial spasm
- Fever
- Hemorrhage
- Hypotension/Hypertension
- Infection and pain at puncture site
- Leg Pain/Claudication
- Myocardial Infarction

- Arteriovenous fistula
- Bleeding/Hematoma
- Bradycardia/Palpitation
- Cerebral vascular accident
- Death
- Distal embolization
- Femoral pseudoaneurysm/Pseudoaneurysm formation
- Renal failure
- Restenosis
- Sepsis
- Stent fracture
- Stroke
- Thrombosis of target vessel
- Target lesion revascularization

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Biocompatibility

The biocompatibility of the Misago® RX Self-expanding Stent System was evaluated per the requirements of ISO 10993-1. Tests were conducted separately on sterilized product for: (1) the Misago® RX Delivery System and (2) the Misago® Stent.

For biocompatibility testing, the Misago® RX Delivery System was categorized as an externally communicating device having contact with circulating blood and cardiovascular tissue for a limited (<24 hours) duration. The Misago® Stent was categorized as an implant device with permanent (>30 days) blood contact.

All biocompatibility testing was conducted in accordance with:

- Guidance for Industry and FDA Staff: Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems (April 18, 2010)
- Good Laboratory Practice (GLP) Regulations per 21 CFR 58

Table 3 summarizes the biocompatibility testing conducted on devices representative of the final design.

Table 3: Summary of Misago® RX Self-expanding Stent System Biocompatibility Testing

Test Name	Test Description	Delivery System	Stent
Cytotoxicity	ISO Colony Formation Assay with V79 Chinese Hamster Ovary Cells	Pass; Non-toxic	Pass; Non-toxic
Sensitization	ISO Guinea Pig Maximization	Pass; Non-sensitizing	Pass; Non-sensitizing
Irritation	ISO Intracutaneous Reactivity	Pass; Non-irritating	Pass; Non-irritating
Acute Systemic toxicity	ISO Systemic Toxicity	Pass; No evidence of systemic Toxicity	Pass; No evidence of systemic Toxicity
Pyrogenicity	USP Material Mediated Pyrogenicity	Pass; Non-pyrogenic	Pass; Non-pyrogenic
Hemocompatibility	MHLW Hemolysis (Direct and Indirect Contact)	Pass; Non-hemolytic	Pass; Non-hemolytic
	In Vivo Thrombogenicity	Pass; Non-thrombogenic	n/a[1]
	Complement Activation Assay	Pass; Non-activating	Pass; Non-activating

Test Name	Test Description	Delivery System	Stent
	(C3a and SC5b-9)		
Genotoxicity	ISO Bacterial Reverse Mutation Assay	n/a	Pass; Non-mutagenic
	ISO In vitro Mouse Lymphoma Assay	n/a	Pass; Non-mutagenic
	ISO Mouse Micronucleus Assay	n/a	Pass; Non-genotoxic

[1] Evaluated, instead, as a part of the animal studies outlined in Section C, below

Traditional biocompatibility studies were not conducted on the Misago® Stent for the following endpoints: *in vivo* thrombogenicity, subchronic toxicity, chronic toxicity and implantation. Instead, the potential for stent thrombogenicity, subchronic toxicity, chronic toxicity, and implantation issues were evaluated as part of other *in vivo* studies conducted to evaluate the safety and effectiveness of the stent in a vascular location, as described in Section C, below. These additional animal studies demonstrated a lack of thrombogenicity, inflammation and toxicity when stents were implanted in a clinically-relevant vascular implant location.

The omission of carcinogenicity testing for the Misago® stent was supported by information regarding the starting materials and processing of the finished device in conjunction with toxicity data from the literature

The information provided demonstrates that the Misago® RX Self-expanding Stent and Delivery System are biocompatible.

B. *In vitro* Bench Testing

The safety and effectiveness of the Misago® RX Self-expanding Peripheral Stent was supported by *in vitro* bench testing. This testing was consistent with the FDA Guidance, Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, April 18, 2010. The relevant *in vitro* tests outlined in the guidance document are summarized in Table 4 below. All testing was performed on finished, sterile devices unless otherwise specified.

Table 4: Summary of *in vitro* Test Results

Test	Purpose	Acceptance Criteria	Results
Stent Materials Composition	To verify that the stent materials conform to the chemical composition requirements of ASTM F2063 and ASTM F560.	The stent materials must meet ASTM F2063 and ASTM F560 specifications	The stent materials met the acceptance criteria specified in ASTM F2063 and ASTM F560
Delivery system Material Composition	The composition of the materials used in the delivery system meet required material specifications	All materials must meet material specifications	The delivery system materials met the predetermined acceptance criteria
Austenite Finish Transition Temperature (AF)	To assure that the stent fully deploys under normal body temperature.	Stent fully deploys at 18-28^{o}C	The results met the Austenite Finish Transition Temperature (AF) acceptance criteria
Pitting and Crevice Corrosion Potential	This test determines if the stent is corrosion resistant.	This test measured the rest potential of the stent for an hour in the simulated physiological fluid and then conducted the anode polarizing test from Rest potential state. Breakdown potential should not be less than 300mV	The stent materials met the acceptance criteria specified. The breakdown potential was greater than 300 mV. The stent was determined to be corrosion resistant
Fretting Corrosion	This test determines if the stent is corrosion resistant caused by fretting motions	This test measured the rest potential of the stent for an hour in the simulated physiological fluid and then conducted the anode polarizing test from Rest potential state. Breakdown potential should not be less than 300mV	The stent materials met the acceptance criteria specified. The stent was determined to be resistant to fretting corrosion following 10M cycles of accelerated durability testing in an overlapping configuration
Galvanic Corrosion	This test determines if the stent is corrosion resistant.	The corrosion rate was calculated from the obtained value of Galvanic current. Corrosion rate should be 2μm/year or less.	The stent materials met the acceptance criteria specified. The stent was determined to be corrosion resistant
Dimensional Verification	To confirm the stent will be within dimensional specification when implanted in the patient.	Stent diameter ($\pm$ 0.5 mm) and stent length ($\pm$ 10%) was confirmed to be within specification when it is in an unconstrained condition heated at 37±2^{o}C	The stent dimensions were verified to meet the post deployment acceptance criteria

Test	Purpose	Acceptance Criteria	Results
Percent Surface Area	To determine the surface area of the stent	The percent surface area was confirmed to be within specification (within 10 to 20%) through theoretical calculations	The stent percent surface area was verified to meet the acceptance criteria
Foreshortening	To determine if the stent length shortens once deployed	The change in stent length post deployment should be within 10% of the original length	The stent length post deployment was verified to be within 10% of the original length
Stent Integrity	Determine if there are any abnormalities on the stent	No scratches, bends, collapsed areas or adhered foreign materials	The stents were verified to meet the acceptance criteria
Radial Stiffness and Radial Strength	Determine the radial force that the stent applies at different diameters	The stent must meet the predetermined radial force (>2.5N/cm,<12.5N/cm) at different diameters	The stents were verified to meet the radial stiffness and strength acceptance criteria
Mechanical Properties of Stent Material	To specify the mechanical properties of incoming and post processing stent material	Incoming material must meet the predetermined specifications (ASTM F2063 and ASTM F560). Post processing material was studied for characterization purpose	The stents were verified to meet the acceptance criteria
Endurance Limit	Determine the endurance limit of post processing stent material	Endurance limit study was for Fatigue analysis	It was determined that the endurance limit is 0.66%.
Strain Fatigue Analysis	To confirm the long term endurance of the stent under clinically relevant condition	The fatigue safety factor has to be greater than 1 over 10 years simulated implant life for the following conditions: – Pulsatile – Bending – Axial compression – Torsion – Focal radial compression – Uniform radial compression – Pulsatile with Bending – Pulsatile with Axial compression – Pulsatile with Torsion	The stents were verified to meet the acceptance criteria

Test	Purpose	Acceptance Criteria	Results
Pulsatile Durability	Determine if the stent will fracture due to the movement of the vessel caused by the blood pressure	The fracture rate of the stent after 400 million cycles (simulate 10 years) needs to meet the predetermined criteria (less than 3 fractures in each stent)	The stents were verified to meet the acceptance criteria
Multi-Axis Durability	Determine if the stent will fracture due to the movement of the leg	After 10 million cycles (simulate 10 years) under the following conditions: – Pulsatile – Bending – Axial compression – Torsion – Focal radial compression – Uniform radial compression – Pulsatile with Bending – Pulsatile with Axial compression – Pulsatile with Torsion The fracture rate of the stent needs to meet the predetermined criteria (no Type 3, 4 and 5 fractures each stent)	The stents were verified to meet the acceptance criteria
MRI Safety (Image Artifacts, Magnetically Induced Forces, Torque, and Heating)	To assess the MRI safety and compatibility of the implantable stent	The presence of the stent must not pose an additional unacceptable risk to patient when subjected to 1.5 T and 3.0 T magnetic fields (per requirements of ASTM F2052-60e1, ASTM F2213-06,)	The test results demonstrated the stent does not pose additional unacceptable risk to the patient. The stent was determined to be MR Conditional according to ASTM2503-05
Radiopacity	Determine if the stent and delivery system are visible under radioscopy (imaging used during implantation)	Stent system needs to be equivalent to comparable devices.	The stents were verified to meet the acceptance criteria
Crush Resistance	The stent must resist collapsing under compression forces and then it must returns to its original diameter when the force is removed	The force required to crush the stent ½ of the diameter was within specification (greater than 0.29N/cm but less than 1.27N/cm) and then returns to its original diameter	The stents were verified to meet the acceptance criteria

Test	Purpose	Acceptance Criteria	Results
Kink Resistance	Determine if the stent will kink in the vessel	Stent should not kink (reduced by ½ its diameter) when the curvature of the vessel has a radius of 12.5mm	The stents were verified to meet the acceptance criteria
Bond Strength of catheter	Confirm the strength of the catheter	Tensile strength of catheter must meet the predetermined specifications: Distal tip; $\geq$14.7N Proximal shaft / Opening; $\geq$14.7N Proximal shaft / Hemostatic body; $\geq$14.7N Proximal marker; $\geq$19.6N Sheath / Release wire; $\geq$19.6N	The delivery catheters were verified to meet the acceptance criteria
Crossing Profile of catheter	Determine the outer diameter of the catheter and compatibility with the delivery catheter	Outer diameter of the catheter must meet the predetermined specification in order to be compatible with a 6Fr catheter (crossing profile of 2.12mm or less)	The delivery catheters were verified to meet the acceptance criteria
Corrosion Resistance of Catheter	Assure that the catheter is corrosion resistant	No corrosion on the metallic part of the catheter when subjected to a predetermined corrosive environment	The delivery catheters were verified to meet the acceptance criteria
Surface of catheter	Assure there are no surface defects on the delivery system	Catheter must meet the predetermined specification for surface defects (Presence of flaw, bent, collapse or adhesion of foreign particles) through visual inspection and tactile feel	The delivery catheters were verified to meet the acceptance criteria
Designation of Nominal Size of catheter	Determine if the catheter is the proper size	Catheter must meet the predetermined specification for length ($\pm$50mm) and diameter (Proximal shaft outer diameter 1.02-1.06mm, Stent mounted part outer diameter 2.03-2.08mm)	The delivery catheters were verified to meet the acceptance criteria
Guiding Sheath/Guidewire Compatibility of catheter	Determine if the delivery system will be compatible with the guiding sheath and guidewire	Delivery system must be compatible with the guiding sheath and guidewire during simulated use.	The delivery catheters were verified to meet the acceptance criteria

Test	Purpose	Acceptance Criteria	Results
Trackability of catheter	Determine the trackability of the catheter through a guiding sheath	Under simulated use conditions the delivery system must be comparable to currently approved devices	The delivery catheters were verified to meet the acceptance criteria
Pushability of catheter	Determine the pushability of the catheter	Under simulated use conditions the delivery system must be comparable to currently approved devices	The delivery catheters were verified to meet the acceptance criteria
Flexibility of catheter	Determine the flexibility of the catheter	Under simulated use conditions the delivery system must be comparable to currently approved devices	The delivery catheters were verified to meet the acceptance criteria
Deployment Accuracy of catheter	Determine the deployment accuracy of the catheter	Under simulated use conditions the delivery system must be comparable to currently approved devices	The delivery catheters were verified to meet the acceptance criteria
Ease of withdrawal of catheter	Determine the ease of withdrawal of the catheter	Under simulated use conditions the delivery system must be comparable to currently approved devices	The delivery catheters were verified to meet the acceptance criteria
Force to Deploy of catheter	Determine the force to deploy the catheter	The force to deploy should be within predetermined specification (less than 14.7N for 40mm, 60mm, 80mm, and 100mm length stent products; less than 19.6N for 120mm and 150mm length stent products)	The delivery catheters were verified to meet the acceptance criteria
Torque Strength of catheter	Determine torque strength of catheter	Torque strength of catheter must remain functional after rotating the delivery system 720^{o}	The delivery catheters were verified to meet the acceptance criteria

C. Animal Studies

The Misago® RX Self-expanding Peripheral Stent was subjected to a series of three (acute, subacute and chronic GLP animal studies. The *in vivo* animal studies demonstrated the safety and overall product performance of the Misago® RX Self-expanding Peripheral Stent *in vivo* in a total of 78 porcine models. Table 5 summarizes the results of the GLP studies conducted on finished, sterile devices.

Table 5. Summary Results of the GLP Animal Studies

Study Type	Study Numbers Test or Control	Endpoints	Outcome
Subacute and Chronic Systemic ToxicityTesting in Porcine Ilio-femoral Artery (30 and 180 days implantation)	48 swine implanted with either S.M.A.R.T (Cordis Corp) control (P120002) or TRE-1181 Terumu stents in 24 overlapping pairs.	Acceptable Performance and Handling, No unexplained in-life morbidity or mortality, acceptable healing and low to no injury as assessed angiographically, grossly, and histologically. In life clinical chemistry and hemograms also within normal limits	The Misago Stent was deployed without complications in the swine ilio-femoral arterial circulation. There was no indication of systemic toxicity at 30 and 180 days after the stent implantation. The stent proved to have good hemocompatibility and displayed a positive healing response with a thin layer of neointima, reendotheliazation and a minimal level of inflammatory cell infiltration at 30 and 180 days follow-up time points.
Performance Study in Porcine External Iliac Artery (acute, 30 and 90 days implantation)	24 swine implanted with either single or overlapping TRE1181 Terumu or S.M.A.R.T (Cordis Corp) control stents.	Acute Performance and Handling, 30 and 90-day in-life, angiographic, gross, and histologic outcomes	This *in vivo* study was conducted to evaluate the fatigue, integrity and performance of the Misago stent and delivery system at Day 30 and Day 90. The stents were deployed with no issues in the porcine external iliac arteries. Follow-up angiograms of the stents demonstrated good stent apposition with brisk antegrade flow and no evidence of stent fracture.

Acute Performance Study of Longest Stent System in Porcine Iliac/Femoral Artery	Six swine implanted with 150mm length Misago final stent design and delivery system using a trans-femoral approach. Performance attributes were compared to the 150mm S.M.A.R.T (Cordis Corp) attributes	Acute performance and handling, including radiographic evaluation in terminal study design.	To verify clinical risks of the Misago peripheral self-expanding stent system of 150 mm stent, the Misago stent was deployed in porcine iliac/femoral artery to determine the acute results. The results of acute handling and procedural outcomes with the Misago peripheral self-expanding stent system were good to excellent. This study did not demonstrate any new safety issues.

D. Additional Studies

The Misago® RX Self-expanding Peripheral Stent is sterilized by ethylene oxide. Validation of the sterilization method to ensure a Sterility Assurance Level (SAL) of 10^{-6} has been conducted in accordance with *EN ISO 11135-1:2007 Sterilization of health care products-Ethylene oxide-Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices.*

Packaging qualification and device verification testing was performed on the Misago® RX Self-expanding Peripheral Stent which are packaged in a tube attached to a card, sealed in a tyvek pouch. The pouch is placed in a shelfpack. A shelf life of 3 years has been established for the Misago® RX Self-expanding Peripheral Stent based on product and package shelf life testing.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed two clinical studies in the US and out of the US (OUS) to establish a reasonable assurance of safety and effectiveness of stenting the superficial femoral artery (SFA) and/or proximal popliteal artery with the Misago® RX Self-expanding Peripheral Stent in symptomatic patients with *de novo* or restenotic native lesions or occlusions with reference vessel diameters ranging from 4mm to 7mm and lesion length up to 150mm. Because the US and OUS studies were performed under similar protocols at approximately the same time, the clinical data from the two studies can be viewed as two cohorts in one combined study. The combined study was performed in the United States (US), Japan (JP), Taiwan (TW) and South Korea (KR) under IDE # G100010. This study is called the OSPREY – **O**cclusive/**S**tenotic **P**eripheral artery **RE**vascularization Stud**Y**. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between April 2010 and July 2012. The database for this PMA reflected data collected through July 2013 and included 261 patients. There were 31 sites within the United States, 7 sites in Japan, 3 sites in Taiwan and 1 site in South Korea.

The study was a prospective, multi-center, one arm clinical study. In the US, this was a multi-center, single-arm, non-randomized, prospective clinical trial to investigate the safety and effectiveness of the flexible Misago® RX Self-expanding Peripheral Stent delivered via a rapid-exchange (RX) unit for the treatment of focal atherosclerotic disease in the superficial femoral artery (SFA). In Japan, there are two arms of the study: 50 subjects received the Misago® stent (stent arm) and 51 subjects received percutaneous transluminal angioplasty (PTA) with potential bailout stent implantation. This US/Japan pivotal study enrolled a total of 261 subjects who were implanted with the Misago® stent: 201 in the U.S., 50 in Japan (stent arm), as well as 10 additional subjects in Taiwan and South Korea.

All angiographic, X-ray and Duplex Ultrasound images obtained during the study were anonymized and sent to a core laboratory for independent analysis.

The CEC was composed of physicians who are interventional and/or non-interventional cardiologists, who were not participating in this study, and who are not affiliated with Terumo. The CEC was charged with the development of specific criteria used for the review and categorization of serious adverse events (SAE) and suspected Unanticipated Adverse Device Effects (UADEs). The CEC established rules outlining the minimum amount of data required and the algorithm followed in order to classify SAEs and UADEs. All members of the CEC meet regularly to review and adjudicate all SAEs and UADEs from enrollment through 12 month follow-up visit. All appropriate data was adjudicated by the CEC. The CEC also

review and classify all deaths that occur throughout the trial. The CEC forwarded an adjudication report of events as outlined in the CEC charter.

The DSMB was appointed to monitor subject safety by periodically reviewing safety data from the study. The DSMB established guideline criteria for considering a recommendation to stop the study for safety reasons. The DSMB reviewed adverse events and other relevant study data and made recommendations regarding continuation of the study to the Sponsor.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the OSPREY study was limited to patients who met the following inclusion criteria:

Inclusion Criteria Pre-procedure:

- Female or male age ≥ 18 years and of legal consent
- Subjects must be willing to comply with the specified follow-up evaluation schedule.
- Informed consent (signed and dated) prior to any study-related evaluation or procedures
- Symptomatic leg ischemia without tissue loss by Rutherford classification (category 2, 3 or 4). (Index Limb only)
- Resting ABI of < 0.9, or abnormal exercise ABI

Inclusion Intra-procedure:

- *De novo* lesion(s) (one or multiple) with > 50% stenosis, or occlusion which required treatment, and a total lesion length of ≥ 40mm and ≤ 150mm of the above-the-knee SFA in one limb. The target lesion(s) should have been treatable with no more than two overlapping stents, minimizing the stent overlap up to 10mm (by visual estimate). (Recommended overlap of ≥ 5 and ≤ 10mm by visual estimate)
- All lesions were at least 3 cm above the knee joint, defined as the distal end of the femur at the knee joint, and at least 2 cm distal to the origin of the profunda artery.
- Reference vessel diameter of ≥ 4.0mm and ≤ 7.0mm
- Target lesion length of ≥ 40mm and ≤ 150mm
- Patent popliteal artery (no stenosis > 50%) and at least one patent tibioperoneal run-off vessel with < 50% stenosis confirmed by angiography within 30 days of enrollment.

Patients were not permitted to enroll in the OSPREY study if they met any of the following exclusion criteria:

*(Those criteria marked with an asterisk were reviewed intra-procedurally.)

- Pre-existing autoimmune disease
- Pre-existing terminal illness with life expectancy < 3 years

- Participation in another investigational device or therapeutic intervention trial within the past three (3) months
- Previous enrollment in this study
- Previous bypass surgery or stenting in the SFA or distally (No treatment of any kind adjacent to the target lesion or distally was permitted.)
- Scheduled for a staged procedure to treat lesions within the aorta or run-off after enrollment
- Co-existing aneurysmal disease of the aorta, iliac artery, SFA, or popliteal arteries requiring treatment
- Any inflow disease of the ipsilateral pelvic arteries (> 50 percent stenosis or occlusion) that had not been treated prior to enrollment (treatment of iliac arteries before SFA intervention was permitted, except for common femoral stenosis)*
- A recent (< 6 week) history of clinically significant gastrointestinal bleeding, major surgery, myocardial infarction or untreated coagulopathy
- Known sensitivity or allergy to aspirin, radiographic contrast agents (that cannot be pre-treated adequately), Nitinol, gold, or both heparin and bivalirudin
- Angiographic evidence of acute thrombus*
- Sudden worsening of symptoms in the last 30 days
- Subjects with acute/chronic renal dysfunction or estimated glomerular filtration rate (eGFR) < 30 ml/min. Chronic hemodialysis subjects were not eligible for this protocol. (Terumo defines dysfunction as eGFR < 30 for this protocol)
- Severe calcification or excessive tortuosity at target lesion*
- Subjects unable to tolerate anticoagulant therapy or antiplatelet therapy
- Women who were currently pregnant. (A negative pregnancy test for female subjects of child bearing potential was required.)
- The target lesion(s) could not be successfully crossed with a guide wire.*
- Lower extremity deep venous thrombosis in the study limb within the prior 30 days
- Chronic venous disease with active or recent (< 30 day) skin ulceration.
- Known or suspected active systemic infection
- Two (2) months previous history of non-hemorrhagic stroke and/or history of hemorrhagic stroke
- Treatment that required access via upper extremity, popliteal artery, or pedal artery
- Evidence of severe or uncontrolled systemic disease of any condition which in the investigator's opinion made it undesirable for the subject to participate in the trial or which would jeopardize compliance with the protocol.
- Use of re-entry, ablative or atherectomy devices to cross the lesion*

2. Follow-up Schedule

All subjects were scheduled to return for follow-up evaluations at 30 days, 6 months, 12 months, 24 months, and 36 months post-procedure. All follow-up dates were calculated based on a 30 day calendar month. Table 6 provides a summary of study requirements throughout the study.

Table 6: Study Follow-up Plan

Assessment	Pre-Procedure*	Intra-Procedure	Post-Procedure	30 Day	6 Month	12 Month	24 Month	36 Month	Discontinued
Informed Consent	X								
Inc/Exc Criteria	X	X							
Medical and PVD History	X								
Physical Exam	X								
Concomitant Medications[1]	X	X	X	X	X	X	X	X	X
Vital signs[2]	X[2a]		X	X	X	X	X	X	X
Angiography		X	X						
Hematology / Chemistry[3]	X		X**						
ECG	X		X	X					X
Rutherford Classification	X			X	X	X	X	X	X
Ankle Brachial Index[4]	X			X	X	X	X	X	X
QOL Questionnaire: SF36[5]	X			X	X	X	X		X
QOL Questionnaire: Walking Impairment[6]	X			X	X	X	X		X
Duplex Ultrasound				X		X			X
X-ray			X		X	x	X	X	X
Adverse Event* Monitoring**			X	X	X	X	X	X	X

[1] All concomitant medications reviewed
[2] Vital signs included blood pressure, heart rate and respiration rate
[2a] Vital signs at pre-procedure included blood pressure, heart rate, respiration rate, and temperature.
[3] CBC, Electrolytes, BUN, Creatinine, Glucose, Pregnancy Test (pre-procedure only; Female subjects of childbearing potential), INR, PTT, eGFR
[4] ABI measured consistently in affected limb at all visits unless not clinically possible.
[5] SF-36 self-administered by the subject
[6] Walking Impairment Questionnaire administered by the Study Coordinator

If a subject returned for the treatment of restenosis and/or clinical ischemia related to the treated lesion ABI, DUS, and X-ray to be performed. If a subject required a revascularization procedure of the target lesion (TLR) the ABI, Rutherford, DUS, and QOL questionnaires are not required during subsequent follow-up visits.

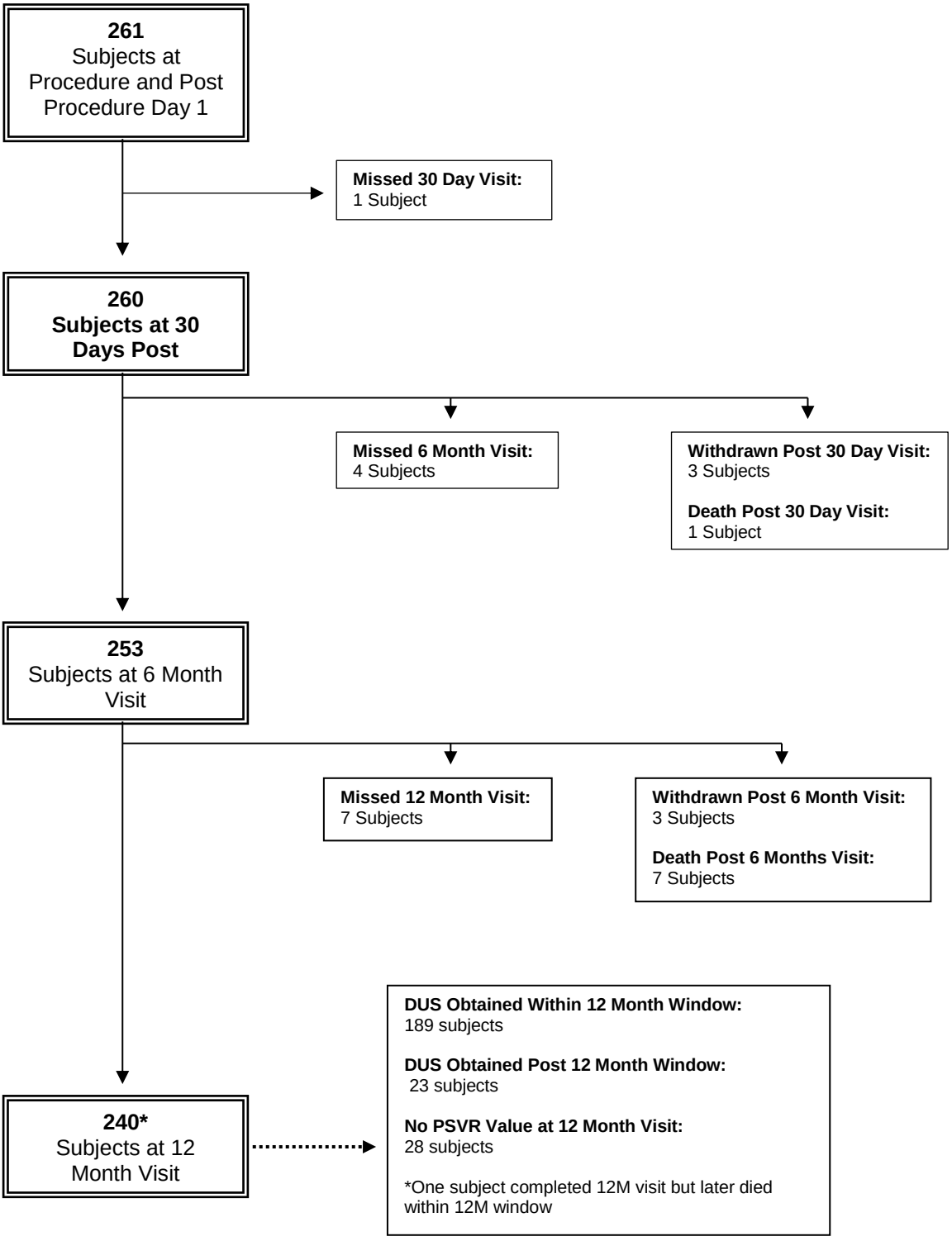
3. Clinical Endpoints

With regards to safety, the primary safety endpoint for this study was freedom from a major adverse event (MAE) at 30 days post-procedure. A MAE was defined as TLR, amputation of the treated limb, or death. Study success was based on the proportion of patients with freedom from MAE at 30 days post-procedure when tested against a performance goal of 88% using the lower bound of the 95% confidence interval.

With regards to effectiveness, the primary effectiveness endpoint was defined as stent patency at 12 months as evidenced by a peak systolic velocity ratio (PSVR) < 2.0 from DUS obtained within the 12 month visit window. Because patency beyond the 12 month visit window may be considered as patency at 12 months, the out-of-window patency is imputed as treatment success. It also regarded missing data as loss of patency under the intention to treat (ITT) analysis.

B. Accountability of PMA Cohort

At the time of database lock, of 261 patients enrolled in the PMA study, 92% (240) patients are available for analysis at the completion of the study, the 12 month post-procedure visit.



C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a peripheral stent study performed in the US.

The target population included men and women, ≥ 18 years of age, having symptomatic leg ischemia without tissue loss (Rutherford category 2, 3 or 4) and a resting ABI of < 0.9 arising from one or multiple *de novo* SFA lesion(s) with > 50% stenosis or occlusion with a total lesion length of ≥ 40mm and ≤ 150mm at least 3cm above-the-knee. Baseline demographics and clinical characteristics are summarized in Table 7 and 8. It was determined that the data was poolable between sites in the US, Japan, Taiwan and Korea.

Table 7: Baseline Demographics and Clinical Characteristics

Characteristic	Mean ± SD
Age at implant (years)	69.3 ± 10.0
Gender (% Male)	64.8% (169/261)
Race/Ethnicity	
Caucasian	69.0% (180/261)
Asian	23.0% (60/261)
Black	6.9% (18/261)
Hispanic	1.1% (3/261)
Diabetes Mellitus	47.9% (125/261)
Smoking history	
Yes, Current	42.1% (110/261)
Yes, Previous	40.6% (106/261)
BMI (kg/m2)	28.2 ± 5.8
Rutherford score	
Rutherford – 2	48.3%(126/261)
Rutherford – 3	47.1%(123/261)
Rutherford – 4	4.6% (12/261)
ABI	0.7 ± 0.1
Percent of diameter stenosis (angiography)	86.5 ± 12.1
Lesion length (mm)	83.8 ± 41.3

Table 8: Baseline Lesion Characteristics (Core Lab Reported)

Parameter	N Mean ± SD or % (n/N)
Location	
Left	49.0% (128/261)
Right	51.0% (133/261)
Arterial segment	
Proximal SFA	12.3% (32/261)
Middle SFA	53.6% (140/261)
Distal SFA	33.3% (87/261)
Other	0.8% (2/261)
Lesion length (mm)	261 83.8 ± 41.3
Proximal Reference Vessel Diameter (mm)	261 5.1 ± 1.0
Distal Reference Vessel Diameter (mm)	261 5.1 ± 1.0
Segment Minimum Lumen Diameter (mm)	261 1.1 ± 0.9
Bend	80.1% (209/261)
Eccentricity	
Concentric	59.8% (156/261)
Eccentric	40.2% (105/261)
Thrombus	
None	98.5% (257/261)
Possible	0.4% (1/261)
Small	0.0% (0/261)
Moderate	0.8% (2/261)
Large	0.4% (1/261)
Total occlusion	0.0% (0/261)
Calcification	
None	33.3% (87/261)
Moderate	35.2% (92/261)
Severe	31.4% (82/261)
Tortuosity	
None	100.0% (261/261)
Moderate	0.0% (0/261)
Severe	0.0% (0/261)
Ulceration	20.7% (54/261)
Aneurysm	1.1% (3/261)
Pre-TIMI flow	
0	24.1% (63/261)
1	1.9% (5/261)
2	0.8% (2/261)
3	67.8% (177/261)
NA	5.4% (14/261)
TASC II Classification	
TASC II type A lesions	55.6% (145/261)
TASC II type B lesions	37.5% (98/261)
TASC II type C lesions	6.9% (18/261)
TASC II type D lesions	0.0% (0/261)

Parameter	N Mean ± SD or % (n/N)
Inflow tract stenosis	
< 50%	60.9% (159/261)
> 50%	8.8% (23/261)
NA	30.3% (79/261)
Distal runoff vessels	
1	27.2% (71/261)
2	32.2% (84/261)
3	20.3% (53/261)
NA	13.4% (35/261)
Patency of anterior tibial artery	46.5% (105/226)
Patency of posterior tibial artery	61.1% (140/229)
Patency of peroneal artery	69.0% (156/226)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the US/Japan/Taiwan and Korea cohort of 261 patients available for the 12 month evaluation.

Overall, the OSPREY data provided reasonable assurance of safety and effectiveness of the Misago® RX Self-expanding Peripheral Stent for use in the intended population.

The primary safety endpoint for this study was freedom from Major Adverse Events (MAE) at 30 days post-procedure. MAE was defined as a target lesion revascularization (TLR), amputation of the treated limb, or death (all-cause). Study success was based on the proportion of patients with freedom from MAE at 30 days post-procedure when tested against a performance goal of 88%, using the lower bound of the 95% confidence interval. The lower confidence interval exceeded the pre-specified performance goal indicating the study met its primary safety endpoint and is summarized in Table 9.

Table 9: Primary Safety Endpoint

Primary Safety Endpoint	% (n/N)	95% CL	Inference
Freedom from MAE at 30 Days post-enrollment (ITT)	99.2% (259/261)	97.1%, 100.0%	H_0 rejected
Sub-Analysis by Set:			
Freedom from MAE at 30 Days post-enrollment (mITT)	99.2% (259/261)	97.1%, 100.0%	H_0 rejected
Freedom from MAE at 30 Days post-enrollment (PP)	99.2% (255/257)	97.0%, 100.0%	H_0 rejected

Adverse effects that occurred in the PMA clinical study:

Adverse Events (AEs) occurring within 12 months (390 days) of the procedure are summarized in Table 10 below. AEs were coded according to MedDRA (Medical Dictionary for Regulatory Activities), system organ class (SOC) and Preferred Term (PT). Overall, 85.1% (222/261) subjects experienced an AE during the study; 45.2% (118/261) experienced an AE within 30 days, 53.3% (139/261) experienced an AE between 30 days and 6 months, and 55.9% (146/261) experienced an AE between 6 and 12 months.

Table 10: Summary of Adverse Events

Adverse Event by SOC and PT	Overall % (n)	Within 30 Days % (n)	30 Days-6 Months % (n)	6 Months-12 Months % (n)
Any adverse event	85.1% (222)	45.2% (118)	53.3% (139)	55.9% (146)
SOC: Blood And Lymphatic System Disorders	6.1% (16)	0.8% (2)	3.1% (8)	3.1% (8)
PT: Anaemia	5.0% (13)	0.8% (2)	1.9% (5)	2.7% (7)
SOC: Cardiac Disorders	16.1% (42)	3.8% (10)	6.5% (17)	9.6% (25)
PT: Acute Myocardial Infarction	2.3% (6)	0.8% (2)	0.8% (2)	1.5% (4)
PT: Angina Pectoris	3.4% (9)	0.4% (1)	1.1% (3)	1.9% (5)
PT: Atrial Fibrillation	2.3% (6)	0% (0)	0.8% (2)	1.9% (5)
PT: Cardiac Failure Congestive	2.7% (7)	0% (0)	1.1% (3)	1.9% (5)
PT: Coronary Artery Disease	3.1% (8)	0.4% (1)	0.4% (1)	2.3% (6)
SOC: Congenital, Familial And Genetic Disorders	0.4% (1)	0% (0)	0.4% (1)	0% (0)
SOC: Ear And Labyrinth Disorders	0.4% (1)	0.4% (1)	0% (0)	0% (0)
SOC: Endocrine Disorders	1.1% (3)	0% (0)	0.4% (1)	0.8% (2)
SOC: Eye Disorders	4.2% (11)	0.4% (1)	3.1% (8)	0.8% (2)
PT: Cataract	2.3% (6)	0.4% (1)	1.9% (5)	0% (0)
SOC: Gastrointestinal Disorders	17.2% (45)	4.6% (12)	8.4% (22)	8.0% (21)
PT: Constipation	3.4% (9)	1.1% (3)	1.9% (5)	0.8% (2)
PT: Diarrhoea	3.4% (9)	0.4% (1)	1.9% (5)	1.1% (3)
PT: Nausea	3.1% (8)	1.1% (3)	0.4% (1)	1.5% (4)
SOC: General Disorders And Administration Site Conditions	18.4% (48)	8.4% (22)	6.1% (16)	6.9% (18)
PT: Chest Discomfort	2.3% (6)	1.1% (3)	0.8% (2)	0.4% (1)
PT: Non-Cardiac Chest Pain	2.3% (6)	0.4% (1)	0.4% (1)	1.5% (4)
PT: Oedema Peripheral	4.2% (11)	2.3% (6)	1.9% (5)	0.4% (1)
SOC: Hepatobiliary Disorders	2.7% (7)	0.4% (1)	0.4% (1)	1.9% (5)
SOC: Immune System Disorders	2.3% (6)	1.1% (3)	0.4% (1)	0.8% (2)
PT: Drug Hypersensitivity	1.9% (5)	0.8% (2)	0.4% (1)	0.8% (2)
SOC: Infections And Infestations	18.8% (49)	3.8% (10)	10.0% (26)	9.6% (25)
PT: Bronchitis	2.7% (7)	0.4% (1)	1.5% (4)	0.8% (2)
PT: Cellulitis	3.8% (10)	1.1% (3)	1.9% (5)	0.8% (2)
PT: Pneumonia	3.4% (9)	0.4% (1)	1.5% (4)	1.5% (4)
PT: Urinary Tract Infection	3.1% (8)	0.4% (1)	1.5% (4)	1.1% (3)
SOC: Injury, Poisoning And Procedural Complications	27.2% (71)	6.5% (17)	10.0% (26)	15.3% (40)
PT: Arterial Restenosis	1.9% (5)	0% (0)	0.8% (2)	1.1% (3)
PT: Peripheral Artery Restenosis	15.7% (41)	0.8% (2)	5.0% (13)	10.7% (28)
PT: Procedural Hypertension	2.7% (7)	2.7% (7)	0% (0)	0% (0)

Adverse Event by SOC and PT	Overall % (n)	Within 30 Days % (n)	30 Days-6 Months % (n)	6 Months-12 Months % (n)
PT: Wound Complication	1.9% (5)	1.5% (4)	0.4% (1)	0% (0)
SOC: Investigations	3.1% (8)	1.9% (5)	0.4% (1)	1.1% (3)
SOC: Metabolism And Nutrition Disorders	6.5% (17)	0.8% (2)	2.7% (7)	3.1% (8)
SOC: Musculoskeletal And Connective Tissue Disorders	23.4% (61)	8.8% (23)	10.3% (27)	6.5% (17)
PT: Arthralgia	2.3% (6)	0.8% (2)	1.1% (3)	0.4% (1)
PT: Back Pain	8.0% (21)	4.2% (11)	2.3% (6)	1.5% (4)
PT: Muscle Spasms	1.9% (5)	1.1% (3)	0.8% (2)	0% (0)
PT: Pain In Extremity	5.4% (14)	1.5% (4)	1.9% (5)	2.3% (6)
SOC: Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	4.6% (12)	0% (0)	2.3% (6)	2.3% (6)
SOC: Nervous System Disorders	15.7% (41)	2.3% (6)	6.9% (18)	7.3% (19)
PT: Hypoaesthesia	2.3% (6)	0% (0)	1.9% (5)	0.4% (1)
SOC: Psychiatric Disorders	3.8% (10)	0.8% (2)	1.9% (5)	1.5% (4)
SOC: Renal And Urinary Disorders	4.6% (12)	0.4% (1)	2.3% (6)	2.3% (6)
PT: Renal Failure Acute	3.1% (8)	0% (0)	1.5% (4)	1.5% (4)
SOC: Reproductive System And Breast Disorders	1.1% (3)	0% (0)	0% (0)	1.1% (3)
SOC: Respiratory, Thoracic And Mediastinal Disorders	11.9% (31)	1.9% (5)	3.8% (10)	6.1% (16)
PT: Chronic Obstructive Pulmonary Disease	2.3% (6)	0% (0)	0.8% (2)	1.5% (4)
PT: Cough	3.1% (8)	0.8% (2)	1.5% (4)	0.8% (2)
SOC: Skin And Subcutaneous Tissue Disorders	10.0% (26)	3.4% (9)	3.8% (10)	3.8% (10)
PT: Pruritus	2.3% (6)	1.1% (3)	0.4% (1)	0.8% (2)
PT: Rash	1.9% (5)	0% (0)	1.5% (4)	0.4% (1)
SOC: Surgical And Medical Procedures	0.4% (1)	0% (0)	0.4% (1)	0% (0)
SOC: Vascular Disorders	38.3% (100)	18.4% (48)	14.6% (38)	16.9% (44)
PT: Femoral Artery Dissection	4.6% (12)	4.2% (11)	0% (0)	0.4% (1)
PT: Femoral Artery Occlusion	1.9% (5)	0% (0)	0% (0)	1.9% (5)
PT: Haematoma	5.0% (13)	4.2% (11)	0.4% (1)	0.4% (1)
PT: Hypertension	8.4% (22)	3.4% (9)	1.1% (3)	3.8% (10)
PT: Hypotension	2.3% (6)	0.8% (2)	0.8% (2)	0.8% (2)
PT: Intermittent Claudication	10.3% (27)	1.5% (4)	4.6% (12)	5.7% (15)
PT: Peripheral Artery Stenosis	6.1% (16)	0.4% (1)	4.6% (12)	2.3% (6)
PT: Peripheral Embolism	3.1% (8)	2.7% (7)	0% (0)	0.4% (1)
PT: Peripheral Vascular Disorder	2.3% (6)	0.4% (1)	1.1% (3)	1.1% (3)
MedDRA Perferred Terms shown where number of subjects with event is 5 or more				

Secondary Endpoint Safety Analysis:

The Major Adverse Event rate at 12 months post-procedure was 16.1% (42/261). MAE rates and additional safety endpoints are described in table 11 below. Freedom from TLR at 12 months was also evaluated (Figure 4).

Table 11: Secondary Safety Endpoints and Major Adverse Events

Secondary Safety Endpoint	% (n/N)
MAEs through 30 days	0.8% (2/261)
TLR	0.8% (2/261)
Amputation	0.0% (0/261)
Deaths through 30 days	0.0% (0/261)
MAEs through 12 months	16.1% (42/261)
TLR[1]	13.0% (34/261)
Amputation	0.0% (0/261)
Deaths through 12 months	3.4% (9/261)
Device failures through 12 months	1.3% (3/234)
Failure/Malfunctions	0.4% (1/261)
Stent fracture evidenced by plain film X-ray	1.3% (3/234)
Device related peri-procedural complications	2.3% (6/261)
Significant Distal Embolization in Target Limb	2.3% (6/261)
Thrombosis of Target Vessel	0.4% (1/261)
Any device related adverse event	19.5% (51/261)

[1]In the Combined Cohort, a total of 40 TLR events within 12 months of procedure occurred in 34 subjects. One subject with TLR also died within 12 months of procedure.

Stent Fracture Analysis:

X-rays for 324 stents (234 subjects) were available for analysis by the angiographic core laboratory to evaluate stent fractures at 12 months post-procedure. The stent fracture rate at 12 months was 0.9% (3/324 stents) and is summarized in Table 12 below. The per subject stent fracture rate was 1.3% (3/234).

Table 12: Summary of Stent Fractures by Stent

Parameter	At 12 Month % (n/N)
Stent fracture	0.9% (3/324)
Fracture type	
I – Single strut fracture only	0.3% (1/324)
II – Multiple single strut fractures that occur at different sites	0.0% (0/324)
III - Multiple strut fractures resulting in complete transection of the stent, without displacement of the stent segment	0.3% (1/324)
IV - Multiple strut fractures resulting in displacement of segments of the stent	0.3% (1/324)[1]
V - Spiral fractures that denotes a spiral dissection of a stent	0.0% (0/324)
Fracture location	
Proximal	0.3% (1/324)
Middle	0.3% (1/324)
Distal	0.3% (1/324)

[1]Caused by physician during non-study peripheral intervention

2. Effectiveness Results

The analysis of effectiveness was based on the 261 evaluable subjects at the 12-month time point. Key effectiveness outcomes are presented in Tables 13 and 14.

The primary effectiveness endpoint was defined as stent patency at 12 months as evidenced by a peak systolic velocity ratio (PSVR) < 2.0 from DUS obtained within the 12 month visit window, thereby excluding DUS data collected outside the visit window; it also regarded missing data as loss of patency under the ITT analysis. The ITT cohort included all 261 subjects, the mITT cohort had 226 subjects (excluded subjects with unknown primary effectiveness endpoint) and the PP cohort had 222 subjects (excluded subjects that failed to meet all eligibility criteria). In the ITT analysis 54.0% (141/261) of subjects met the primary effectiveness endpoint and were noted to have patent stents at 12 months as evidenced by PSVR < 2.0 and freedom from a TLR event. The primary effectiveness endpoint was met in 141/226 subjects (62.4%) in the mITT cohort and in 139/222 subjects (62.6%) in the PP cohort. The lower bound of the two-sided 95% confidence interval was 48.0% in the ITT cohort. The primary efficacy objective evaluating a 12 month patency rate of 66% or more was not met.

Table 13: Primary Effectiveness Endpoint (ITT including late DUS)

Primary Effectiveness Endpoint PSVR < 2.0	% (n/N)	Hypotheses	95% CL	Inference
Stent patent at 12 months (ITT)	54.0% (141/261)	H_0: $p \leq 0.66$ H_A: $p > 0.66$	48.0%, 60.0%	H_0 not rejected
US Stent patent at 12 months (ITT)	51.7% (104/201)			
OUS Stent patent at 12 months (ITT)	61.7% (37/60)			
Sub-Analysis by Set:				
Stent patent at 12 months (mITT)	62.4% (141/226)			
Stent patent at 12 months (PP)	62.6% (139/222)			

A supporting analysis conforming to FDA guidance using Kaplan-Meier (KM) methods avoided this issue by evaluating all available data in a time-to-event format and censoring subjects with missing data at the appropriate times. Although the primary effectiveness endpoint was not met by the protocol-defined analysis, when analyzed using the KM method, the freedom from loss of patency at 12 months was 78.9% (Figure 2).

Additional considerations may also be made using a more contemporary approach to evaluate stent patency using a PSVR $\leq$ 2.4 (modified VIVA criteria). Using this alternative PSVR for the analysis of the 12 month primary patency outcome, the freedom from loss of patency at 12 months was 60.5% and 69.9% in the ITT and mITT cohort, respectively. Furthermore, the KM freedom from loss of patency at 12 months (360 days) estimate was 82.9% using the modified VIVA criteria (Figure 3).

Table 14: Primary Effectiveness Endpoint using Modified VIVA Criteria

Secondary Effectiveness Endpoint, PSVR ≤ 2.4	**% (n/N)**
Stent patent at 12 months based on peak systolic velocity ratio ≤ 2.4 (ITT)	60.5% (158/261)
Sub-Analysis by Set:	
Stent patent at 12 months (mITT)	69.9% (158/226)
Stent patent at 12 months (PP)	69.8% (155/222)

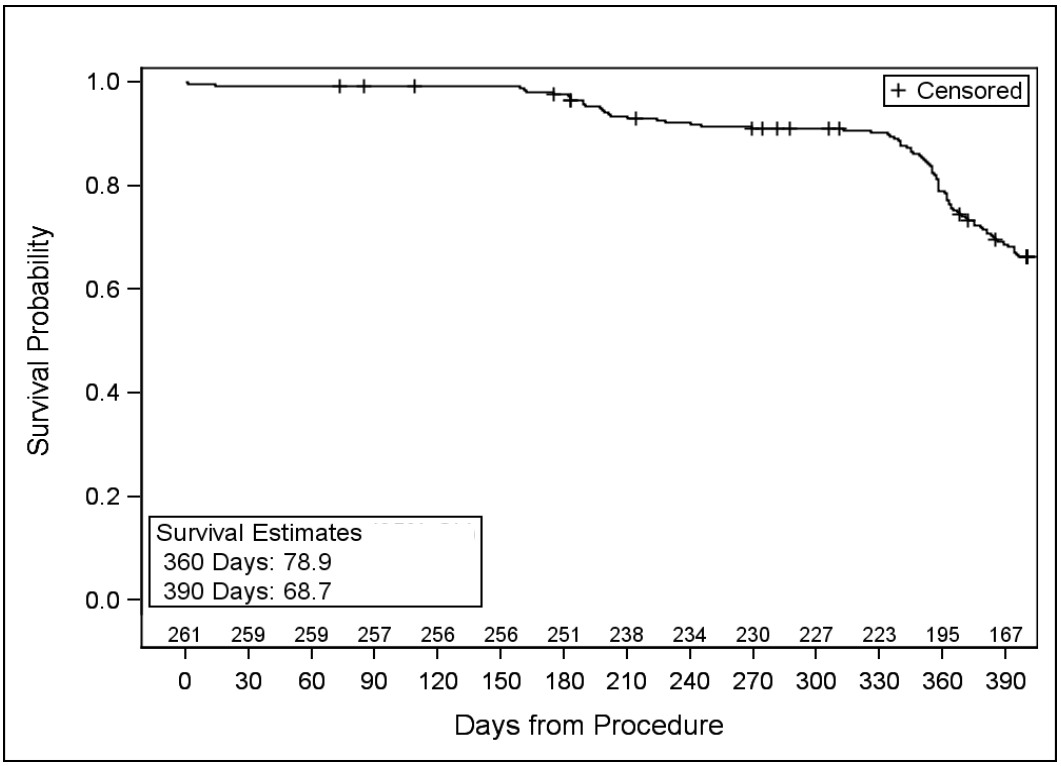


Figure 2. Kaplan-Meier Freedom from Loss of Patency within 12 Months (PSVR ≥ 2.0 or TLR)

Table 15: Freedom from Loss of Patency (PSVR≥2.0 or TLR)

Timepoint	[0, 90)	[90, 180)	[180, 270)	[270, 360)	[360, 390)
# At Risk[1]	261	257	251	230	195
# Events[2]	2	4	17	30	25
# Censored[2]	2	2	4	5	3
Survival %[3]	99.2	97.7	91.0	78.9	68.7
Standard Error[3]	0.5	0.9	1.8	2.6	2.9

[1]At beginning of interval
[2]Within interval
[3]At end of interval

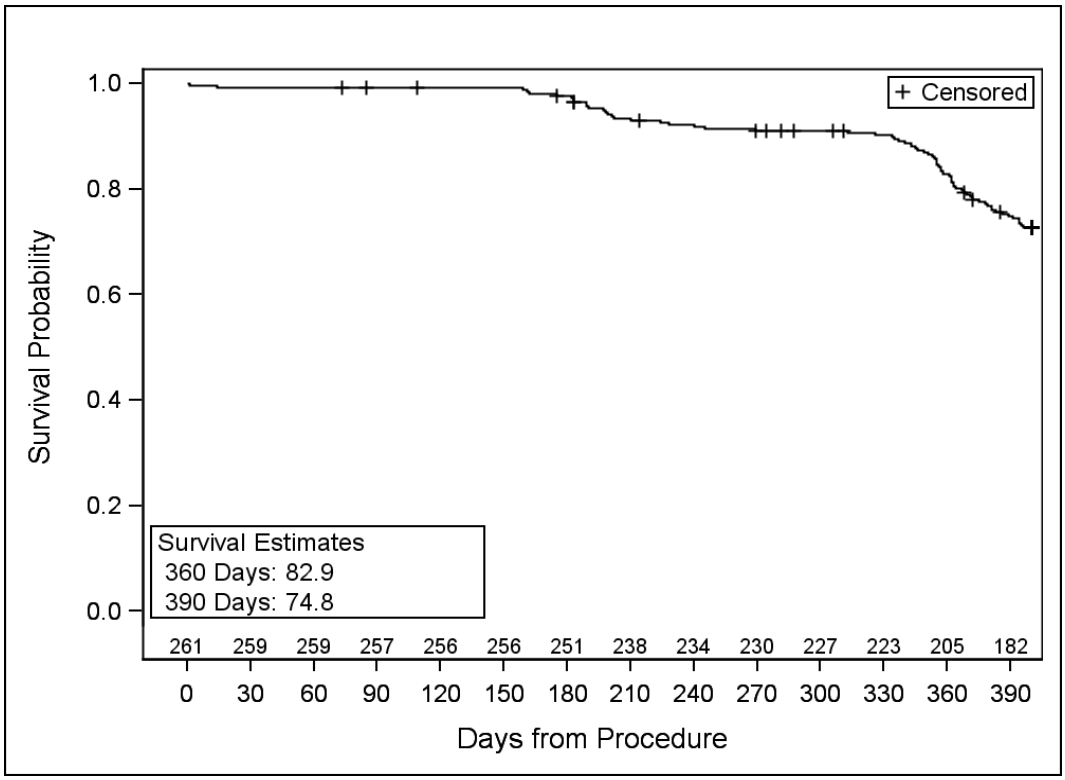


Figure 3. Kaplan-Meier Freedom from Loss of Patency within 12 Months (PSVR > 2.4 or TLR)

Table 16: Freedom from Loss of Patency (PSVR>2.4 or TLR)

Freedom from Loss of Patency (PSVR>2.4 or TLR)					
Timepoint	[0, 90)	[90, 180)	[180, 270)	[270, 360)	[360, 390)
# At Risk[1]	261	257	251	230	205
# Events[2]	2	4	17	20	20
# Censored[2]	2	2	4	5	3
Survival %[3]	99.2	97.7	91.0	82.9	74.8
Standard Error[3]	0.5	0.9	1.8	2.4	2.8

[1]At beginning of interval
[2]Within interval
[3]At end of interval

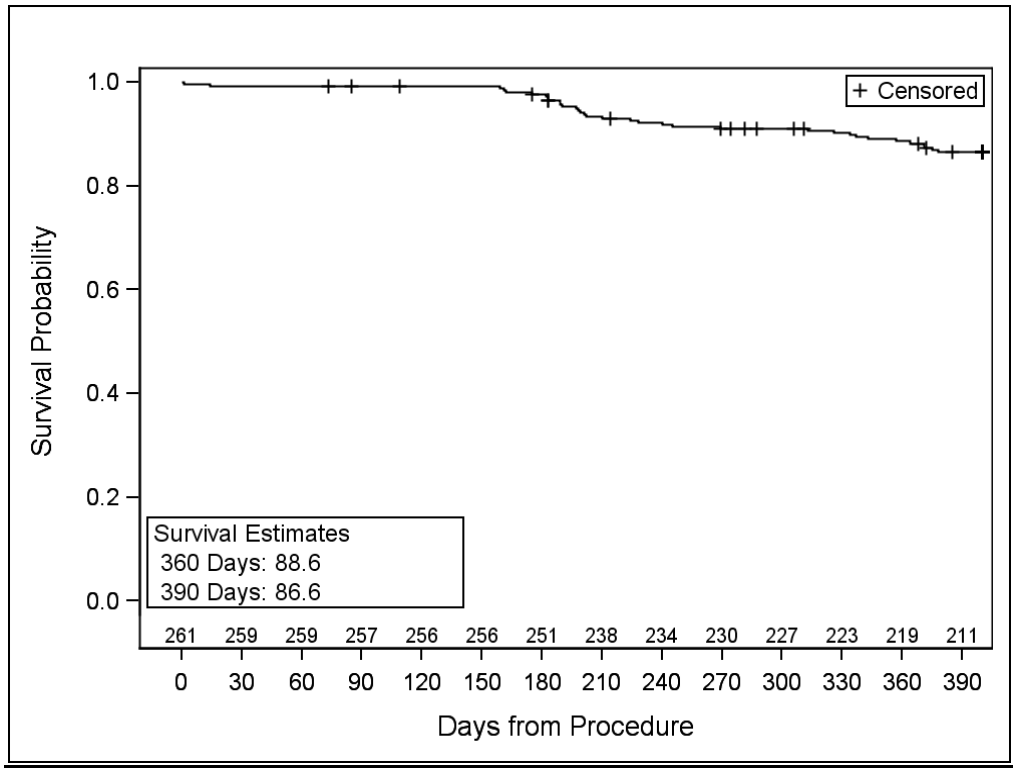


Figure 4. Kaplan-Meier Freedom from TLR within 12 Months of Procedure

Table 17: Freedom from TLR within 12 Months of Procedure

Timepoint	[0, 90)	[90, 180)	[180, 270)	[270, 360)	[360, 390)
# At Risk[1]	261	257	251	230	219
# Events[2]	2	4	17	6	5
# Censored[2]	2	2	4	5	3
Survival %[3]	99.2	97.7	91.0	88.6	86.6
Standard Error[3]	0.5	0.9	1.8	2.0	2.2

[1]At beginning of interval
[2]Within interval
[3]At end of interval

Patency as a Function of Lesion Length:
In the combined study cohort (US and Asian subjects), similar short and mid-length lesion effectiveness was observed (67.6% in lesions ≤ 60 mm, 63.3% in lesions 61-100mm), while patency was reduced in lesions > 100 mm (54.8%). Table 18, 19, and 20 summarize patency by lesion lengths. These tables include the DUS for 23 subjects that were obtained after the 12 month window; these subjects were used in the mITT analysis.

Table 18: 12 Month Effectiveness (no TLR and PSVR < 2.0 and ≤ 2.4) by Core Lab Assessed Lesion Length Terciles – Combined Cohort *

	Lesion Length Terciles (Core Lab)		
	Lower (≤ 60) N=83	**Mid (61-100) N=104**	**Upper (> 100) N=74**
Pre-Procedure Lesion Length (mm) (core lab assessed)			
N	83	104	74
Mean ± SD	40.7 ± 12.6	80.3 ± 12.2	137.1 ± 26.1
Median	41.6	78.8	133.1
Min, Max	12.2, 60.0	61.2, 100.0	101.0, 227.5
Primary Effectiveness Endpoint (mITT)			
Primary Patency	67.6% (50/74)	63.3% (57/90)	54.8% (34/62)
PSVR < 2.0	71.8% (51/71)	75.9% (63/83)	60.3% (35/58)
No clinically driven TLR	90.4% (75/83)	84.6% (88/104)	86.5% (64/74)
Secondary Effectiveness Endpoint (mITT)			
Secondary Patency	73.0% (54/74)	71.1% (64/90)	64.5% (40/62)
PSVR ≤ 2.4	77.5% (55/71)	84.3% (70/83)	70.7% (41/58)
No clinically driven TLR	90.4% (75/83)	84.6% (88/104)	86.5% (64/74)

* Results based on core lab reported lesion length and includes DUS data collected outside the 12 month visit window

Table 19: 12 Month Effectiveness (no TLR and PSVR<2.0 and ≤ 2.4) by Core Lab Assessed Lesion Length – Combined Cohort*

	Lesion Length by Core Lab Read Angiography	
	≤ 150 N=241	**> 150 N=20**
Primary Effectiveness Endpoint (mITT)		
Primary Patency	63.4% (135/213)	46.2% (6/13)
PSVR < 2.0	71.9% (143/199)	46.2% 6(/13)
No clinically driven TLR	86.3% (208/241)	95.0% (19/20)
Secondary Effectiveness Endpoint (mITT)		
Secondary Patency	70.9% (151/213)	53.8% (7/13)
PSVR ≤ 2.4	79.9% (159/199)	53.8% (7/13)
No clinically driven TLR	86.3% (208/241)	95.0% (19/20)

* Results based on core lab reported lesion length and includes DUS data collected outside the 12-month visit window

Table 20: 12 Month Effectiveness (no TLR and PSVR<2.0 and ≤ 2.4) by Core Lab Assessed Lesion Length – Combined Cohort*

	% (n/N)
Primary Effectiveness Endpoint (mITT)	
Core Lab Lesion Length	
≤ 60	67.6% (50/74)
61-100	63.3% (57/90)
101-150	57.1% (28/49)
> 150	46.2% (6/13)
Secondary Effectiveness Endpoint (mITT)	
Core Lab Lesion Length	
≤ 60	73.0% (54/74)
61-100	71.1% (64/90)
101-150	67.3% (33/49)
> 150	53.8% (7/13)

* Results based on core lab reported lesion length and includes DUS data collected outside the 12-month visit window

A variety of secondary effectiveness endpoints were defined for this study. Table 21 summarizes the secondary effectiveness endpoints and subjects meeting each endpoint.

Table 21: Secondary Effectiveness Endpoints

Secondary Effectiveness Endpoint	Mean ± SD or % (n/N)
Technical Success	100.0% (261/261)
Successful delivery of stent at lesion site	100.0% (261/261)
Stent deployed in lesion with adequate lesion coverage	100.0% (261/261)
Procedural Success	93.5% (244/261)
Clinical Success: relief or improvement from baseline symptoms as measured by the Rutherford score for chronic limb ischemia at 30 days as compared to baseline	90.0% (234/260)
Ankle-Brachial Index change from baseline to Day 30 post-procedure	0.3 ± 0.2
Ankle-Brachial Index change from 30 days to12 Months post-procedure	-0.1 ± 0.2
Rutherford sustained (without increase of one or more in the score) at 12 months post-procedure from 30 days post-procedure	80.2% (190/237)
Clinically driven target lesion revascularization through 12 months post-procedure	13.0% (34/261)
Patency of target vessel based on systolic velocity ratio ≤ 2.4 and absence of TLR	69.9% (158/226)
Target lesion revascularization through 30 days	0.8% (2/261)
Target lesion revascularization through 12 months	13.0% (34/261)

Rutherford Becker (RB)

The majority of subjects had moderate-severe claudication (Rutherford Becker 2-3) at baseline. At 1 and 12 months post procedure, a majority of subjects were asymptomatic (see Table 22).

Table 22: Rutherford Becker Scale Analysis (Combined Cohort)

	Baseline % (n/N)	**30 day**	**12 Month**
Mean±SD	3.6 ± 0.6	1.6 ± 1.0	1.6 ± 0.9
Rutherford – 0	0.0% (0/261)	62.7% (163/260)	61.6% (146/237)
Rutherford – 1	0.0% (0/261)	19.6% (51/260)	22.4% (53/237)
Rutherford – 2	48.3% (126/261)	11.9% (31/260)	10.5% (25/237)
Rutherford – 3	47.1% (123/261)	4.6% (12/260)	5.5% (13/237)
Rutherford – 4	4.6% (12/261)	0.8% (2/260)	0.0% (0/237)
Rutherford – 5	0.0% (0/261)	0.0% (0/260)	0.0% (0/237)
Rutherford – 6	0.0% (0/261)	0.4% (1/260)	0.0% (0/237)

Ankle-Brachial Index (ABI)

There was an overall improvement in ABI from a mean of 0.7 at baseline to 0.9 at 12 Months (see Table 23).

Table 23: ABI and Change from Baseline in Combined Cohort Through 12 Months

ABI on Target Limb	Baseline	1 Month	6 Month	12 Month
Mean + SD (N)	0.70 ± 0.15 (259)	0.98 ± 0.16 (260)	0.92 ± 0.18 (253)	0.91 ± 0.17 (236)
Median	0.71	0.99	0.94	0.93
Min, Max	0.13, 1.12	0.39, 1.63	0.00, 1.42	0.43, 1.60

3. <u>Subgroup Analyses</u>

There were no subgroup analyses preformed on the study data.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 42 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data

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

In accordance with the provisions of Section 515©(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems 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. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint was defined as stent patency at 12 months as evidenced by a peak systolic velocity ratio < 2.0 from DUS obtained within the 12 month visit window, including DUS data collected outside the 12 month visit window; it also regarded missing data as loss of patency under the ITT analysis. The ITT cohort included all 261 subjects, the mITT cohort had 226 subjects (excluded subjects with unknown primary effectiveness endpoint) and the PP cohort had 222 subjects (excluded subjects that failed to meet all eligibility criteria). In the ITT analysis 54.0% (141/261) of subjects met the primary effectiveness endpoint and were noted to have patent stents at 12 months as evidenced by peak systolic velocity ratio < 2.0 and freedom from a target lesion revascularization (TLR) event. The primary effectiveness endpoint was met in 141/226 subjects (62.4%) in the mITT cohort and in 139/222 subjects (62.6%) in the PP cohort. The lower bound of the two-sided 95% confidence interval was 48.0% in the ITT cohort. The primary effectiveness objective was not met and a 12 month patency rate of 66% or less could not be ruled out.

The primary effectiveness analysis was a conservative approach but was subject to bias in estimates of 12 month patency since failure of patency can be recorded regardless of whether 12-month data are available (such as cases of TLR prior to 12 months). Moreover, the assumption that subjects without a DUS measurement within the 12 month window were not patent was overly conservative. A supporting

analysis conforming to FDA guidance using Kaplan-Meier methods avoided this issue by evaluating all available data in a time-to-event format and censoring subjects with missing data at the appropriate times. Kaplan-Meier freedom from loss of patency had a 12-month (360 day) estimate of 78.9%.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described below.

The primary safety endpoint for this study was freedom from major adverse events (MAE) at 30 days post-procedure. MAE was defined as a target lesion revascularization (TLR), amputation of the treated limb, or death. Study success was based on the proportion of patients with freedom from MAE at 30 days post-procedure when tested against a performance goal of 88% using the lower bound of the 95% confidence interval. In both the ITT and mITT cohorts, 99.2% (259/261) met the primary safety endpoint; it was met by 99.5% (255/257) of subjects in the PP cohort. The lower bound of the 95% two-sided confidence limit was 97.1% in both the ITT and mITT cohorts and 97.0% in the PP cohort. In both cohorts, the lower confidence interval exceeded the prespecified performance goal indicating the study met its primary safety endpoint.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefits of the Misago® RX Self-expanding Peripheral Stent of improving the patient symptoms and quality of life outweigh the probable risks associated with use of the device.

Additional factors that were considered in determining probable risks and benefits for the Misago® RX Self-expanding Peripheral Stent included:

- Patient follow-up was satisfactory and with limited missing data. Follow-up for the PMA was 12 months but follow-up will continue for 3 years to evaluate the longer term device performance, such as the duration of the benefit and long term adverse event rates.

- The pivotal study was a multi-center study conducted in the United States and other international sites. The results obtained should not differ from the post-market performance. Additional long-term data will be obtained.

- Most patients with the disease have symptoms only, but some patients may have more extensive disease involvement. The device treats the hemodynamic consequences of the disease to improve perfusion and function. The disease is chronic and affects the mobility of the patient and the quality of life. It is treatable but not curable.

- There are alternative treatments available, but this treatment is highly valued by patients and preferred to the alternatives because it improves their quality of life with lesser need for repeat procedures compared to a performance goal based upon angioplasty results without stenting.

- Patient risk is minimized by limiting use to operators who have the necessary training to use the device safely and effectively and by adherence to recommended periprocedural medications regimens.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for using the device for improve luminal diameter in symptomatic patients with de novo or restenotic native lesions or occlusions of the superficial femoral artery (SFA) and/or proximal popliteal artery with reference vessel diameters ranging from 4mm to 7mm and lesion length up to 150mm.

D. Overall Conclusions

The clinical and non-clinical data in this application provide a reasonable assurance that the device is safe and effective. While the pre-specified effectiveness endpoint was not met, the study results are similar to the results of other US marketed stents intended for use in patients with SFA artery lesions. Overall, the results of the non-clinical and clinical evaluations provide reasonable assurance that the Misago® RX Self-expanding Peripheral Stent is safe and effective. The benefits of the Misago® RX Self-expanding Peripheral Stent outweigh the risks when the device is used as indicated in accordance with the labeling and Instructions for Use (IFU).

XIII. CDRH DECISION

CDRH issued an approval order on May 22, 2015. The final conditions of approval cited in the approval order are described below.

1. *OSPREY Extended Follow-Up Study:* This study will be conducted per Protocol TIS2009-02 Version 13.0 (Amendment 9) dated February 2, 2015 and Statistical Analysis Plan Version 6 dated February 2, 2015. This study is a multi-center, single arm, prospective continued follow-up of the OSPREY pivotal US study. It will evaluate the long-term safety and effectiveness of the Misago stent. All 198 remaining patients (15 patients exited due to death) of the 216 OSPREY pivotal study US patients enrolled from 31 investigational sites will be followed annually through 36 months post-procedure with no more than 20% attrition, not including attrition due to death.

   The primary endpoint is freedom from clinically-driven target lesion revascularization (TLR) assessed at 36 months post-procedure as compared to a performance goal of 55%. The co-primary endpoint is freedom from clinically driven

TLR assessed at 24 months post-procedure as compared to a performance goal of 60%. A minimum of 173 subjects at 36 months are required to provide >80% power assuming an underlying freedom from event proportion of at least 66% and two-sided 0.05 alpha.

The endpoints to be assessed through 36 months post-procedure are: (1) freedom from the composite endpoint of acute death (within 30 days), amputation of the target limb, or clinically driven TLR; (2) clinical success defined as relief or improvement from baseline symptoms by Rutherford score for chronic limb ischemia; (3) quality of life assessed by the Quality of Life Survey (SF-36) and the walking impairment questionnaire (WIQ); major adverse event (TLR, amputation of the treated limb, or death); (4) all-cause mortality; (5) device-related complications; (6) adverse events; and (7) device-related adverse events (TLR, amputation of the target limb, all-cause mortality, distal embolization, thrombosis of target vessel, arterial dissection/perforation/rupture/injury, hemorrhage, hypotension, arterial spasm, arteriovenous fistula, bradycardia/palpitation, arterial embolism/thrombosis/occlusion, stent fracture, and leg pain/claudication).

The applicant's manufacturing facility has been 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.

XV. REFERENCES

none