Summary of Safety and Effectiveness Data (SSED)

I. GENERAL INFORMATION

Device Generic Name:	LifeStent® FlexStar and FlexStar XL
Device Trade Name:	LifeStent® FlexStar Vascular Stent System LifeStent® FlexStar XL Vascular Stent System
Applicant Name and Address:	Bard Peripheral Vascular, Inc. 1625 W. 3rd Street Tempe, AZ 85281
Premarket Approval Application (PMA) Number:	P070014
Date of Panel Recommendation:	None
Date of Notice of Approval to Applicant:	February 13, 2009
Expedited:	Not applicable

II. INDICATIONS FOR USE

The LifeStent® FlexStar and FlexStar XL Vascular Stent Systems are intended to improve luminal diameter in the treatment of symptomatic *de-novo* or restenotic lesions up to 160 mm in length in native Superficial Femoral Artery (SFA) and/or proximal popliteal arteries with reference vessel diameters ranging from 4.0 – 6.5 mm.

III. CONTRAINDICATIONS

The LifeStent® FlexStar and FlexStar XL Vascular Stent are contraindicated for use in:

- Patients with a known hypersensitivity to Nitinol (nickel, titanium) and/or tantalum.
- Patients who cannot receive recommended anti-platelet and/or anti-coagulation therapy.
- Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or stent delivery system.

IV. WARNINGS AND PRECAUTIONS

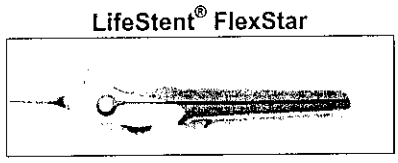
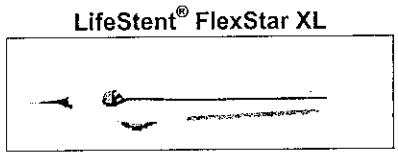
The warnings and precautions can be found in the LifeStent® FlexStar and FlexStar XL Vascular Stent System labeling (Instructions for Use).

V. DEVICE DESCRIPTION

General System Description

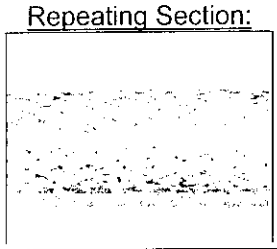
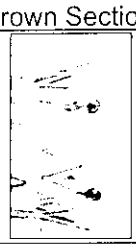
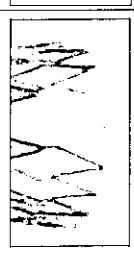
The LifeStent® FlexStar and FlexStar XL Vascular Stent Systems are designed to deliver nitinol self-expanding stents, designed to maintain patency of obstructed peripheral vascular arteries, via a sheathed delivery system.

Table 1: LifeStent® System Family Summary

System	Stent	Deployment Mechanisms
LifeStent® FlexStar 	Ø6mm X 20-80mm Ø7mm X 20-80mm Contains 6 radiopaque tantalum markers	Thumbwheel Rapid Deployment Lever Rapid Deployment Ring
LifeStent® FlexStar XL 	Ø6mm X 100-170mm Ø7mm X 100-170mm No radiopaque markers	Thumbwheel Rapid Deployment Lever

The stents are equivalent in design with only one difference located at the crown section; the LifeStent® FlexStar stent has 6 tantalum radiopaque markers on both the distal and proximal ends of the stent, while the LifeStent® FlexStar XL stent does not have markers.

Table 2: LifeStent® Stent Design

Repeating Section: 	A repeat section of circumferentially distributed struts following a helical pitch/pattern. Rows of struts are connected with bridges placed every fifth strut pair and consists of 19 strut pairs per 360° repeat. Stent length is modified by increasing or decreasing the number of 19 strut pair segments within the repeating section of the stent. This section is the same for both the LifeStent® FlexStar and LifeStent® FlexStar XL stents.
Crown Section: 	FlexStar Stent: Two identical crown sections of circumferentially distributed struts located at each end of the stent. The crown section has a flared outside diameter and consists of 18 strut pairs in each crown section. These segments located at the distal and proximal ends of the stent, contain six (6) links that each terminate into a ring that holds a tantalum, disk-shaped, radiopaque marker.
	FlexStar XL Stent: Two identical crown sections of circumferentially distributed struts located at each end of the stent. The crown section has a flared outside diameter and consists of 18 strut pairs in each crown section. These segments are located at the distal and proximal ends of the stent.

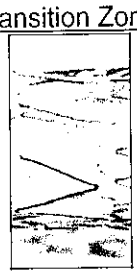
Transition Zone: 	Two identical transition zones of circumferentially distributed struts around 360 degrees. The transition zones are located between the repeat section and the crown sections at both ends of the stent and are connected to the crown sections and the repeat sections of the stent with bridges. This section is the same for both the LifeStent® FlexStar and LifeStent® FlexStar XL stents.

Figure 1: LifeStent® FlexStar Stent Design (20-80mm lengths)

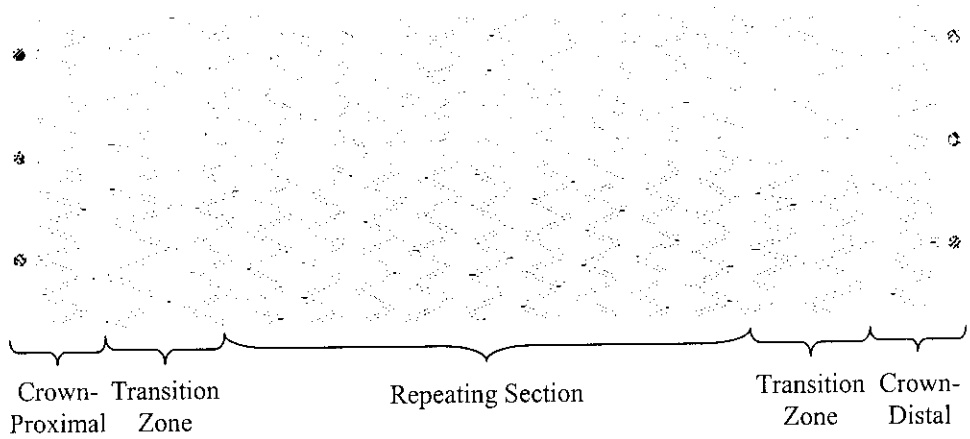
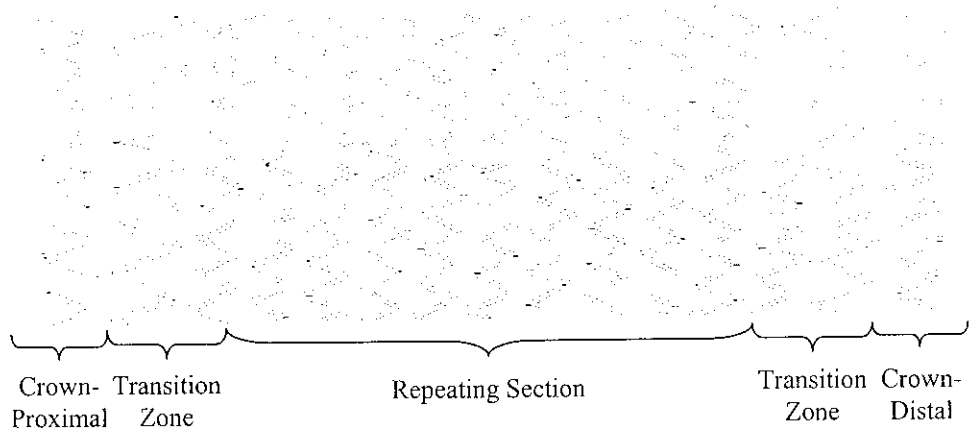


Figure 2: LifeStent® FlexStar Stent Design (100-170mm lengths)



The device is available in the following diameters and lengths:

Table 3: LifeStent® FlexStar and FlexStar XL Lengths									
Diameters	*FlexStar Lengths (mm)*					*FlexStar XL Lengths (mm)*			
6mm	20	30	40	60	80	100	120	150	170
7mm	20	30	40	60	80	100	120	150	170

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of superficial femoral and proximal popliteal artery atherosclerotic disease:

- Non-Invasive Treatment (exercise and/or drug therapy)
- Minimally Invasive Treatment (balloon angioplasty, endovascular stent placement, directional atherectomy)
- Surgical Treatment (surgical by-pass)

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

The LifeStent® FlexStar and FlexStar XL Vascular Stent Systems were introduced into the European Union (EU) market in the winter of 2006. Additionally, the LifeStent® FlexStar and FlexStar XL Stent System have been cleared for use within the Biliary Tree in the United States beginning in December of 2005 and April of 2006, respectively. The stent systems approved for this PMA are identical with the systems cleared for use in the Biliary Tree. In August 2008, the LifeStent® FlexStar Biliary Stent System device was recalled. Specifically, some of the devices exhibited a gap between the tip of the delivery system and the primary sheath such that the guidewire lumen could be visible. The corrective and preventative actions implemented appear to have adequately addressed the tip-to-sheath gap issue. The FlexStar and FlexStar XL delivery systems were evaluated in the E-TAGIUSS confirmatory clinical study.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The potential adverse effects (e.g., complications) that may occur and/or require intervention with the use of this device include, but are not limited to:

- Allergic/anaphylactoid reaction
- Amputation
- Aneurysm
- Angina/coronary ischemia
- Arterial occlusion/thrombus, near the puncture site
- Arterial occlusion/thrombus, remote from puncture site
- Arterial occlusion/restenosis of the treated vessel
- Arteriovenous fistula
- Arrhythmia
- By-pass Surgery
- Death related to procedure
- Death unrelated to procedure
- Embolization, arterial
- Embolization, stent

- Fever
- Hemorrhage/bleeding requiring a blood transfusion
- Hematoma bleed, remote site
- Hematoma bleed at needle, device path: nonvascular procedure
- Hematoma bleed, puncture site: vascular procedure
- Hypotension/hypertension
- Incorrect positioning of the stent requiring further stenting or surgery
- Intimal injury/dissection
- Ischemia/infarction of tissue/organ
- Liver failure
- Local infection
- Malposition (failure to deliver the stent to the intended site)
- Open surgical repair
- Pain
- Pancreatitis
- Pulmonary embolism/edema
- Pneumothorax
- Pseudoaneurysm
- Renal failure
- Respiratory arrest
- Restenosis
- Septicemia/bacteremia
- Stent Fracture
- Stent Migration
- Stroke
- Vasospasm
- Venous occlusion/thrombosis, remote from puncture site
- Venous occlusion/thrombosis, near the puncture site

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Biocompatibility

Toxicology and biocompatibility testing were conducted for materials in the LifeStent® FlexStar and FlexStar XL Stent Systems. Testing was conducted in accordance with applicable Good Laboratory Practices (21 CFR §58) and ANSI/AAMI/ISO 10993-1: 2003 *Biological Evaluation of Medical Devices*. The LifeStent® FlexStar and FlexStar XL Stents were classified per ISO 10993-1 *Biological Evaluation of Medical Devices* as an implant device in permanent contact (> 30 days) with blood. The FlexStar and FlexStar XL Delivery Systems were classified as an externally communicating device in limited contact (< 24 hours) with circulating blood.

Table 3 summarizes the test results for both the FlexStar and FlexStar XL stent. Tables 4 and 5 summarize the test results for the FlexStar and FlexStar XL Delivery System, respectively.

Table 4: Summary of Biocompatibility Testing – LifeStent® FlexStar and FlexStar XL Stent

Test	Purpose	Results	Pass/Fail
Cytotoxicity: Percent Inhibition of Cell Growth	Determine whether test article extract would inhibit cell growth	Test article found to be non-inhibitory to cell growth	Pass
Cytotoxicity: Medium Eluate Method (MEM)	Determine whether test article extracts would cause cytotoxicity and cell lysis	Test article sample was non-cytotoxic. 0% cell lysis was observed with equivalent results to the negative control.	Pass
Cytotoxicity: Agar Overlay (AO)	Determine whether solid samples of test article would cause cytotoxicity and cell lysis	Solid samples of test articles were non-cytotoxic. 0% cell lysis was observed with equivalent results to the negative control.	Pass
Sensitization: Guinea Pig Maximization – Saline	Investigate the potential for delayed dermal contact sensitization	No irritation was present on any of the test or control animals at 24 or 48 hour readings.	Pass
Sensitization: Guinea Pig Maximization – Vegetable Oil	Investigate the potential for delayed dermal contact sensitization	No irritation was present on any of the test or control animals at 24 or 48 hour readings.	Pass
Irritation/Intracutaneous: Rabbit Intracutaneous Reactivity	Determine whether test article extracts would cause s local dermal irritation or toxic effects	No evidence of irritation or abnormal effects over a 72 hour period as compared to negative controls.	Pass
Systemic/Acute Toxicity: USP Mouse Systemic Injection	Determine whether test article extracts would cause acute systemic toxicity	No significant weight differences or observed systemic effects as compared to negative controls over 72 hour test period.	Pass
Subacute/Subchronic Toxicity: Rabbit Intramuscular Implantation	Determine whether the test article would cause systemic toxicity affects after 7, 30, and 90 days implanted	No microscopic evidence of cytotoxicity.	Pass
Genotoxicity: Ames Test – Plate Incorporation	Determine whether test article extracts would cause mutagenic changes in *S. typhimuruim* strains	Test article extracts demonstrated no mutagenic potential under both the activated and non-activated conditions.	Pass
Genotoxicity: Chromosomal Aberration Assay	Determine whether test article extracts would cause genotoxicity in Chinese Hamster ovary cells	Test article extracts demonstrated no mutagenic potential under both the activated and non-activated conditions.	Pass
Genotoxicity: Mouse Micronucleus	Determine whether test article extracts would cause genotoxic changes as determined by induced micronucleated polychromatic erythrocytes	Test article extracts were determined to be non-mutagenic.	Pass
Implantation: Rabbit Intramuscular Implantation	Investigate the potential for toxic response to test articles implanted in direct contact with muscle tissue	No microscopic evidence of cytotoxicity.	Pass
Hemocompatibility: Hemolysis	Determine whether the test article would cause hemolysis *in vitro* and determine the degree of inhibition or promotion of clotting time	No hemolytic effects observed under static conditions for both extract and solid samples. Material's extract did not adversely effect the clotting time and was determined to be compatible with plasma.	Pass

Table 5: Summary of Biocompatibility Testing – LifeStent® FlexStar Delivery System

Test Method	Purpose	Result	Pass/Fail
Cytotoxicity: Medium Eluate Method (MEM)	Determine whether test article extracts would cause cytotoxicity and cell lysis	No significant difference found between test extract and negative control.	Pass
Cytotoxicity: Agar Overlay (AO)	Determine whether solid samples of test article would cause cytotoxicity and cell lysis	Test articles demonstrated 0% cell lysis.	Pass
Sensitization: Guinea Pig Maximization – Saline	Investigate the potential for delayed dermal contact sensitization	No irritation was present on any of the test or control animals at 24 or 48 hour readings.	Pass
Sensitization: Guinea Pig Maximization – Vegetable Oil	Investigate the potential for delayed dermal contact sensitization	No irritation was present on any of the test or control animals at 24 or 48 hour readings.	Pass
Irritation/Intracutaneous: Rabbit Intracutaneous Reactivity	Determine whether test article extracts would cause s local dermal irritation or toxic effects	No evidence of irritation or abnormal effects over a 72 hour period as compared to negative controls.	Pass
Systemic/Acute Toxicity: USP Mouse Systemic Injection	Determine whether test article extracts would cause acute systemic toxicity	No significant weight differences or observed systemic effects noted as compared to negative controls over the 72 hour test period.	Pass
Hemocompatibility: Hemolysis	Determine whether the test article would cause hemolysis *in vitro* and determine the degree of inhibition or promotion of clotting time	No hemolytic effects observed under static conditions for both extract and solid samples. Material's extract did not adversely effect the clotting time and was determined to be compatible with plasma.	Pass
Hemocompatibility: Complement Activation	Evaluate the test article's potential to activate the C3a complement system	Test article was determined to be hemocompatible and not at risk to activate complement at a level of concern in a clinical application.	Pass

Table 6: Summary of Biocompatibility Testing – LifeStent® FlexStar XL Delivery System

Test Method	Purpose	Result	Pass/Fail
Cytotoxicity: Medium Eluate Method (MEM)	Determine whether test article extracts would cause cytotoxicity and cell lysis	No significant difference found between test extract and negative control.	Pass
Cytotoxicity: Agar Overlay (AO)	Determine whether solid samples of test article would cause cytotoxicity and cell lysis	Test articles demonstrated 0% cell lysis.	Pass
Sensitization: Guinea Pig Maximization – Saline	Investigate the potential for delayed dermal contact sensitization	No irritation was present on any of the test or control animals at 24 or 48 hour readings.	Pass
Sensitization: Guinea Pig Maximization – Vegetable Oil	Investigate the potential for delayed dermal contact sensitization	No irritation was present on any of the test or control animals at 24 or 48 hour readings.	Pass

Test Method	Purpose	Result	Pass/Fail
Irritation/Intracutaneous: Rabbit Intracutaneous Reactivity	Determine whether test article extracts would cause s local dermal irritation or toxic effects	No evidence of irritation or abnormal effects over a 72 hour period as compared to negative controls.	Pass
Systemic/Acute Toxicity: USP Mouse Systemic Injection	Determine whether test article extracts would cause acute systemic toxicity	No significant weight differences or observed systemic effects noted as compared to negative controls over the 72 hour test period.	Pass
Systemic/Acute Toxicity: Material Mediated Pyrogenicity	Determine whether test article extracts would induce a pyrogenic response following intravenous injection in rabbits	Both test article and negative control were found to be non-pyrogenic. Each rabbit exhibited a rise in temperature of <0.5°C after a 3 hour monitoring duration.	Pass
Hemocompatibility: Hemolysis	Determine whether the test article would cause hemolysis *in vitro* and determine the degree of inhibition or promotion of clotting time	No hemolytic effects observed under static conditions for both extract and solid samples. Material's extract did not adversely effect the clotting time and was determined to be compatible with plasma.	Pass
Hemocompatibility: Complement Activation	Evaluate the test article's potential to activate the C3a complement system	Test article was determined to be hemocompatible and not at risk to activate complement at a level of concern in a clinical application.	Pass

Justification for omission of chronic toxicity and carcinogenicity was provided due to the extensive clinical history of the device materials and their well-characterized long-term safety profile, as well as information regarding the processing of the final product. Device Thrombogenicity was evaluated as part of other *in vivo* studies conducted to evaluate device safety and effectiveness. The test results demonstrate that the LifeStent® FlexStar and FlexStar XL Vascular Stent Systems are biocompatible and non-pyrogenic.

B. Product Testing

The sponsor conducted comprehensive preclinical bench testing on the LifeStent® FlexStar and FlexStar XL Stent System. The *in vitro* testing was intended to verify that the performance attributes of the LifeStent® FlexStar and FlexStar XL Stent System are sufficient to minimize adverse events under anticipated clinical conditions. This testing included both the stent and the delivery system. All testing was conducted in accordance with national and international standards and guidance documents.

The comprehensive testing detailed in Table 6 verified that the LifeStent® FlexStar and FlexStar XL Stent System (implant and delivery systems) met its product performance and design specifications. Results obtained from *in vitro* testing provided evidence supporting the safety and effectiveness of the LifeStent® FlexStar and FlexStar XL Stent System.

Table 7: Summary of Testing of the LifeStent® FlexStar and FlexStar XL Stent System

Test	Purpose/ Objective	Samples Tested	Specification/ Accept Criteria	Summary Test Results
Corrosion Resistance	To evaluate the susceptibility of implant materials to corrosion via *in vitro* testing and ensure that the implant maintains corrosion resistance following implantation.	(15) 6x60mm stents	Breakdown Potential (Eb)>300mV	The established acceptance criteria was met
Fretting Corrosion		(10) 6x60mm stents overlapped with 7x60mm stents	Eb>300mV	The established acceptance criteria was met
Galvanic Corrosion		(10) 7x100mm stents	Material loss less than 2µm/year	The established acceptance criteria was met
Diameter Verification	To evaluate the stent diameter dimension post-deployment to ensure that the device meets the design specifications.	(225) 6&7mm diameter x 20, 60, 80, 100 & 170mm length stents	6mm size: 6.08 – 6.68mm 7mm size: 7.08 – 7.68mm	The established acceptance criteria was met
Percent Surface Area	To calculate the percent surface area for the expanded stent post-deployment and ensure that the device meets the design specifications.	6&7mm diameter x 20-80mm length models	7-20%	The established acceptance criteria was met
Foreshortening	To analyze the foreshortening of the stent after deployment.	(227) 6&7mm diameter x 20, 60, 80, 100 & 170mm length stents	Less than 5%	The established acceptance criteria was met
Stent Integrity	To evaluate the integrity of the stent following deployment and ensure the implant shows no defects following deployment rendering it unsuitable for the intended use.	(299) 6&7mm diameter x 20, 60, 80, 100 & 170mm length stents	No cracks or fractures at 20X magnification	The established acceptance criteria was met
Radial Stiffness/ Radial Strength	To characterize the force exerted by the implant as a function of implant diameter.	(160) 6&7mm diameter x 20, 40, 80, 100, 120 & 170mm length stents	Chronic Outward Force (COF)<=0.12N/mm Radial Resistive Force (RRF)>=0.07N/mm	The established acceptance criteria was met
Mechanical Properties (Uts, Ys, El_u, E_a, Ups, Lps, E^{se}, E^{le})	To characterize the tensile strength, yield strength, elongation, plateau strength and strain limits of the implantable stent material.	Dog-boned shaped test coupons	Characterization study	All samples demonstrated acceptable variability consistent with implantable grade nitinol
Endurance Limit in Compression/ Compression	To evaluate the endurance limit of the stent design and ensure that the implant will be structurally suitable for the duration of the intended use.	V-shaped test coupons	Characterization study	Limit measured between 0.45% and 0.5%.

Test	Purpose/ Objective	Samples Tested	Specification/ Accept Criteria	Summary Test Results
Stress Analysis: Crimping	To characterize the stress/strain behavior of the implant when subjected to worst-case physiological load and ensure the structural integrity of the stent for the intended use.	6 & 7mm diameter stent models	Predicted strains less than 9%	The established acceptance criteria was met
Stress Analysis: Radial Loading		6 & 7mm diameter stent models	Safety Factor (SF)>1	The established acceptance criteria was met
Stress Analysis: Non-Radial Individual Loading Modes: A) Bending B) Compression C) Twist		7mm diameter stent models	SF>1	The established acceptance criteria was met
Stress Analysis For Popliteal Combined Loading: Bending, Axial Compression, & Radial		7mm diameter stent models	SF>1	The established acceptance criteria was met
Stress Analysis For SFA Combined Loading: Axial Compression, Torsion, & Radial		7mm diameter stent models	SF>1	The established acceptance criteria was met
Radial Fatigue, 400M Cycles	To evaluate the stent integrity after simulated 10-year radial, flexion, compression, elongation and rotational fatigue testing, proving the structural integrity of the stent for the intended use.	(40) 6&7mm diameter x 30 & 40mm length stents	Stents deform as required Intact stents Visual & dimensional tolerances met	The established acceptance criteria was met
Bending/ Flexion Fatigue, Overlapped, 10M Cycles		(44) 6&7mm diameter x 60mm length overlapped stents	Visual & dimensional tolerances met Intact stents & radiopaque (RO) markers	The established acceptance criteria was met
Compression/ Elongation/ Torsion Fatigue, Overlapped, 10M Cycles		(18) 6&7mm diameter x 60mm length overlapped stents	Visual & dimensional tolerances met Intact stents & RO markers	The established acceptance criteria was met
Crush Resistance	To evaluate the ability of the stent to resist permanent deformation and demonstrate the stent's resistance to localized compressive loads.	(80) 6&7mm diameter x 20, 80, 100 & 170mm length stents	Mean stent diam. not decrease more than 5%	The established acceptance criteria was met
Kink Resistance	To evaluate the stent's flexibility and kink resistance following deployment.	(92) 6&7mm diameter x 20, 40 & 60mm length stents	No luminal compromise	The established acceptance criteria was met

Test	Purpose/ Objective	Samples Tested	Specification/ Accept Criteria	Summary Test Results
Magnetic Resonance Imaging (MRI)	To evaluate the MRI safety and compatibility of the implantable stent and ensuring that the stent is not affected by scanning at 1.5 Tesla and 3.0 Tesla field strengths.	7mm diameter x 20, 80 and 170mm length stent samples	The presence of the stent must not pose an additional unacceptable risk to patients when subjected to 1.5T and 3.0T magnetic fields.	Stents determined to be: MR Conditional
Guidewire Compatibility	To evaluate the delivery system's compatibility with a 0.035" guidewire.	(64) 6&7mm diameter x 60, 80, 100, 120, 150 and 170mm length stent systems	A 0.035" guidewire must pass thru the delivery system without restriction	The established acceptance criteria was met
Deployment Accuracy	To characterize the deployment accuracy of the stent system and verify that the delivery system performs adequately for the intended use with respect to deployment accuracy.	(125) 6&7mm diameter x 20, 60, 80, 100, 120, 150 & 170mm length stent systems	The stent must deploy within ± 2.5mm of the target.	The established acceptance criteria was met
Deployment Force	To evaluate the force required to deploy the stent from the delivery system and verify that the deployment force is adequate for the intended use.	(490) 6&7mm diameter x 20, 80, 100, 120, 150 and 170mm length stent systems	Deployment force must be ≤ 6.0lbf	The established acceptance criteria was met
Catheter Bond Strength	To determine the bond joint strength between relevant components of the delivery system and verify the strength of the bond joints are adequate for the intended use.	(58) FlexStar systems & (70) FlexStar XL systems	Various acceptance criteria for primary sheath bond, assembly bond, revolve bond, tip bond and hypotube bond	The established acceptance criteria was met
Crossing Profile	To evaluate the maximum diameter of the delivery system and to verify that the outer diameters of the delivery systems are adequate for the intended use.	(58) FlexStar systems & (70) FlexStar XL systems	FlexStar: 0.0795" max FlexStar XL: 0.0825" max	The established acceptance criteria was met
Delivery System Torsional Strength	To determine the torsional bond strength between relevant components of the delivery system and verify the strength of the bond joints are adequate for the intended use	(10) FlexStar systems & (10) FlexStar XL systems	No breaks or failures	The established acceptance criteria was met

Test	Purpose/ Objective	Samples Tested	Specification/ Accept Criteria	Summary Test Results
Delivery System Kink Testing	To characterize the kink resistance of the stent system and to verify that the delivery system performs adequately for the intended use.	(10) FlexStar systems & (10) FlexStar XL systems	Characterization study	Kink radius found to be 14mm

C. Animal Studies

Preclinical *in vivo* animal testing, using prototypes of the final device design, was conducted in 14 animals to evaluate acute technical success (deployment), stent integrity, and histopathological response of the LifeStent® FlexStar and FlexStar XL Stent System in the porcine femoral and iliac artery models for up to 6 months. The testing results detailed in Table 7 demonstrated the ability to access the target anatomical location, adequate handling and visualization of the delivery system and implant, and deployment accuracy. Stent integrity and histopathological response were acceptable. The results support the safety and expected performance of the LifeStent® FlexStar and FlexStar XL Stent System.

Table 8: Summary of Pre-Clinical Animal Studies

Study Design	Results
Sub-Chronic (30-Day) Porcine Study	Four swine were implanted in various peripheral vasculature locations to assess the acute and sub-chronic response to the LifeStent® NT. At the 30-day endpoint, the stented vessels were angiographically evaluated, surgically excised and submitted for histopathological analysis. Despite damage to one native vessel consistent with excessive oversizing, the response to the stent was minimal. All remaining results were acceptable.
Chronic (28-Day & 180-Day) GLP Porcine Study	Eight swine were implanted in the femoral and iliac arteries to assess the acute, sub-chronic and chronic response to the LifeStent® NT. At the 30 and 180-day endpoints, the stented vessels were angiographically evaluated, surgically excised and submitted for histopathological analysis. During histological analysis, the vessel patency was high and the vessels response to the stent was minimal.
Acute Porcine Study	Two swine were implanted with a total of four (4) LifeStent® FlexStar XL 170mm stents. Stents were tracked to the contralateral iliac and assessed for deployment accuracy and deployed stent length. All stent deployed accurately and maintained pre-deployed stent lengths. Additionally, stents were imaged and found to have no compromise of the stent structure following deployment.

D. Packaging, Shelf Life, and Sterilization Testing

Sterilization of the stent system (self-expanding stent and delivery system as described in the **Device Description** section) is accomplished with a validated sterilization process using 100% Ethylene Oxide. This process has demonstrated a sterility assurance level of 10^{-6}. Product and package stability testing of the LifeStent® FlexStar and FlexStar XL Stent and Delivery System was performed and validated for a 1-year shelf life.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed two clinical studies (the two-phase RESILIENT study (feasibility and pivotal) and the E-TAGIUSS confirmatory study) to establish a reasonable assurance of safety and effectiveness of using the LifeStent® Vascular Stent System for the treatment of *de-novo* and

restenotic (non-stented) lesions causing arterial narrowing in the superficial femoral artery (SFA) and proximal popliteal artery under the IDE. Data from these clinical studies were the basis for the PMA approval decision.

A. Study Design

RESILIENT Study Overview

Phase I of RESILIENT was a feasibility study intended to demonstrate peri-procedural safety. The RESILIENT feasibility study enrolled 20 subjects at six US sites. This phase of the study was a prospective, single-arm, non-randomized, non-blinded study of the LifeStent® Vascular Stent System.

Phase II of RESILIENT was a prospective, randomized (2:1), non-blinded study comparing the LifeStent® Vascular Stent System to Percutaneous Transluminal Angioplasty (PTA), a well-established therapy for this indication. The study was conducted at 22 US and 2 out-of-US (OUS) sites. Any participating site that had not been involved in the Phase I feasibility trial was required to perform one "roll-in" patient procedure before beginning randomized procedures. A total of 226 subjects were treated: 20 roll-in patients, 134 LifeStent® treatment-arm patients, and 72 PTA control arm patients. Subjects eligible to be enrolled in this study had stenotic or occluded lesions of the SFA and/or proximal popliteal artery and suffered from lifestyle limiting claudication (Rutherford Category 1 – 3). Lesions could be either *de-novo* or restenotic. Subjects with previously stented lesions or target limb vascular by-pass were excluded. Reference vessel diameter (RVD) of the treated subjects was to be 4.0 – 6.5mm in diameter and the collective length of the treated segment was to be 150mm or less. Subjects were to undergo angiographic analysis of the lesion prior to and immediately following treatment. Subjects were followed-up at 30 days, 6 months and annually thereafter. Office visits in the first year of follow-up were to be coupled with duplex ultrasound assessments of the treated segments. X-ray evaluation of the stented lesions was also to be performed. Independent core laboratories were utilized to analyze angiographic, x-ray and duplex imaging. Adverse events were adjudicated by the clinical events committee (CEC), and the data safety monitoring board (DSMB) reviewed the study outcomes to ensure that the benefits of continuing the study outweighed any potential risks.

The RESILIENT trial utilized a Frequentist approach with its statistical plan. The primary objectives were to show the following:

- that the probability of the occurrence of Target Lesion Revascularization (TLR) or Target Vessel Revascularization (TVR) for the subjects treated with the LifeStent® NT (test arm) was significantly lower than (and therefore superior to) that for the subjects treated with PTA-alone (control arm); and,

- that the death rates at 30-days post-procedure were not significantly different between the test arm and the control arm.

Continuous variables were compared using an independent samples t-test. Dichotomous variables were compared using Fisher's exact test. Ordinal variables were compared using a Chi-square test. Time to event was compared using a log-rank test. Interval censored data were analyzed using the Kaplan-Meier method as the primary analysis. A sensitivity analysis for interval censored data was performed using the Weibull distribution. Effectiveness endpoints were analyzed as one-sided tests. Safety endpoints were analyzed as two-sided tests.

The results were evaluated using an Intent-to-Treat (ITT) analysis. In particular, control subjects requiring stent placement to salvage a failed angioplasty remained in the cohort to which they were randomized.

RESILIENT Clinical Inclusion and Exclusion Criteria

Subjects enrolled in the RESILIENT Trial were required to meet the following inclusion criteria:

1. The subject or legal representative provided written informed consent using a form that is reviewed and approved by the Institutional Review Board for the clinical site.

2. The subject was ≥ 18 years old.

3. The subject had lifestyle-limiting claudication defined as: Rutherford Category 1-3 (mild to severe claudication).

4. Female subjects of childbearing potential must have had a negative pregnancy test within 7 days prior to study procedure. Female subjects who were surgically sterile or post-menopausal were exempt from having a pregnancy test.

5. Subject agreed to comply with the protocol-mandated follow-up visits and testing regime.

6. The target lesion(s) must have met the following criteria:

    a. The target lesion(s) is *de-novo* or restenotic (stenosed, occluded, restenosed, or re-occluded) and is located within the native SFA and/or proximal popliteal artery, 3 cm above the knee joint and 1 cm below the origin of the profunda femoris artery. If the lesion(s) is restenosed or re-occluded, prior PTA-only treatment must have occurred > 6 months prior to the study procedure.

    b. The target lesion(s) has angiographic evidence of stenosis or restenosis ≥ 50% or occlusion (by visual estimate) and is amenable to PTA-alone or PTA with primary stenting.

    c. The target vessel reference diameter is ≥ 4.0 mm and ≤ 6.5 mm (by visual estimate) and therefore appropriate for treatment with available stent diameters of 6.0 mm and 7.0 mm.

    d. The total length of the lesion or series of lesions is visually estimated to be ≤ 150 mm.

    e. There is angiographic evidence of at least one vessel runoff to the foot.

    f. Prior to enrollment/randomization, access is obtained to the target vessel and the balloon (un-inflated) is across the most distal target lesion.

Candidates who met any of the following exclusion criteria at the time of the study procedure were not eligible for enrollment in the study:

1. The subject is unable or unwilling to provide informed consent or is unable to conform to the study protocol follow-up procedures and visits.

2. The subject has lifestyle-limiting claudication or critical limb ischemia described as Rutherford Category 4 (rest pain), Category 5 (minor tissue loss) or Category 6 (major tissue loss, functional foot no longer salvageable).

3. The subject has a contraindication (including allergic reaction) to antiplatelet/anticoagulant medications, nickel, titanium, tantalum or sensitivity to contrast media that is not amenable to pretreatment with steroids or/and antihistamines.

4. The subject has a history of bleeding diatheses or coagulopathy.

5. The subject has concomitant renal failure with a creatinine of > 2.0 mg/dL.

6. The subject has concomitant hepatic insufficiency, thrombophlebitis, uremia, systemic lupus erythematosus (SLE), or deep vein thrombosis (DVT) at the time of the study procedure.

7. The subject is receiving dialysis or immunosuppressive therapy.

8. The subject suffered a hemorrhagic stroke ≤ 6 months prior to the study procedure.

9. The subject has had a prior peripheral vascular bypass surgery involving the target limb.

10. The target vessel has been previously stented.

11. The target lesion(s) received angioplasty intervention ≤ 6 months prior to the study procedure.

12. The subject has undergone any non-iliac percutaneous intervention(s) < 7 days prior to the study procedure.

13. The subject is currently participating in an investigational drug or another device study that has not completed the primary endpoint or that clinically interferes with the study endpoints. (Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.

14. The subject has another medical condition, which may cause him/her to be non-compliant with the protocol, confound the data interpretation, or is associated with limited life expectancy of less than two years.

15. The subject has extensive peripheral vascular disease that precludes safe insertion of an introducer sheath.

16. The target lesion(s) is located within an aneurysm or associated with an aneurysm in the vessel segment either proximal or distal to the target lesion(s).

17. There is angiographic evidence of unresolved thrombus at the target lesion(s) or within the target vessel that does not resolve with infusion of thrombolytics and/or mechanical thrombectomy (using an FDA approved device) without adverse events/complications.

18. The subject has angiographic evidence of poor inflow which would be deemed inadequate to support a vascular bypass graft.

19. The subject is diagnosed with septicemia at the time of the study procedure.

20. There are additional percutaneous interventional procedures (cardiac/peripheral) planned ≤ 30 days following the study procedure.

RESILIENT Follow-up Schedule

All subjects were scheduled to return for follow-up examinations at 1 month (± 7 days); and 6, 12, 24, and 36 months (± 30 days) postoperatively. X-ray examinations for stent integrity were performed at 6, 12 and 18 months postoperatively.

Preoperative and postoperative evaluations were conducted according to the table below:

Table 9: RESILIENT Follow-up Schedule

Observation	Baseline (prior to cath)	Intra-Procedure	Hospital Discharge	30 d (± 7d)	6 mo (± 30d)	18 mo (± 30d)	Annual (± 30d)[1]
Informed Consent	✓						
Medical History	✓						
12-Lead ECG	✓						
Pregnancy test HCG (<7d)	✓						
Physical Exam	✓		✓	✓	✓		✓
Angiogram	✓	✓					
Randomize/Enroll		✓					
Complete Blood Count (CBC)	✓		✓				
Serum BUN (Blood, Urine, Nitrogen) & Creatinine	✓		✓				
Electrolytes (Na, K, Cl)	✓		✓				
hs-CRP	✓		✓				
ACT		✓					
Resting ABI	✓		✓	✓	✓		✓
Rutherford	✓			✓	✓		✓
Definition of Improvement				✓	✓		✓
C-DUS				✓	✓		✓[2]
X-RAY					✓	✓	✓
Adverse Event Assessment		✓	✓	✓	✓		✓
SF-8 & WIQ	✓			✓	✓		✓

[1] Subjects will be followed for 3 years.
[2] C-DUS is required at the 1st (12-month) annual visit only, not at year 2 or 3.

Adverse events and complications were recorded at follow-up visits.

RESILIENT Clinical Endpoints

The primary safety endpoint for Phase II of the study was defined as the occurrence of death at 30 days post-procedure. Secondary safety endpoints included the evaluation of 30-day death in conjunction with stroke, myocardial infarction, emergent surgical revascularization, significant distal embolization in target limb, and thrombosis of target vessel at 30-days, 6-, and 12-months post-procedure; and worsening of Rutherford-Becker Category at 6- and 12-months post-procedure.

The primary efficacy endpoint for Phase II of the study was defined as the occurrence of Target Lesion Revascularization (TLR) and/or Target Vessel Revascularization (TVR) at 6 months post-procedure. Secondary efficacy endpoints included:

- Primary patency rate and secondary patency rate at 6 and 12 months post-procedure

- TLR/TVR at 12 months post-procedure
- Acute (peri-procedural) measures of success
    - Anatomic: attainment of ≤ 30% residual stenosis of the target lesion using PTA-alone versus PTA with stenting
    - Lesion: attainment of ≤ 30% residual stenosis of the target lesion using any percutaneous method and/or non-investigational device
    - Hemodynamic: angiographic evidence of improved flow across the treated area immediately post-procedure. Ankle-Brachial Index (ABI) improved from baseline by ≥ 0.10 and not deteriorated by > 0.15
    - Procedure: attainment of ≤ 30% residual stenosis of the target lesion and no peri-procedural complications defined as: death, stroke, myocardial infarction, emergent surgical revascularization, significant distal embolization in target limb, and thrombosis of target vessel
- Chronic (clinical) success: relief or improvement of baseline symptoms by Rutherford categories for chronic limb ischemia. Improvement must be sustained by one clinical category above the pretreatment clinical value during follow-up.
- Quality of Life Measurement: Short Form 8 Question Health Survey (SF-8) and the Walking Impairment Questionnaire (WIQ) comparisons

E-TAGIUSS Study Overview

The E-TAGIUSS trial was a prospective, non-randomized, non-blinded confirmatory study intended to evaluate the LifeStent® FlexStar and FlexStar XL Vascular Stent Systems in the treatment of symptomatic vascular disease of the SFA and proximal popliteal artery. The study was conducted at 7 European sites. A total of 37 subjects were treated with 49 stents deployed. Subjects eligible to be enrolled in this study had to demonstrate the Transatlantic Inter-Society Consensus (TASC) A, B or C lesions. Reference vessel diameter (RVD) of the treated subjects was to be 4.0 – 6.5mm in diameter and the collective length of the treated segment was to be less than 200mm. Subjects underwent angiographic analysis of the lesion prior to and immediately following treatment. Subjects were followed at 30 days with an office visit. Independent core laboratories were utilized to analyze angiographic imaging. Adverse events were adjudicated by the clinical events committee (CEC).

E-TAGIUSS Clinical Inclusion and Exclusion Criteria

Subjects enrolled in the E-TAGIUSS Trial were required to meet the following inclusion criteria:

1. The subject or legal representative has been informed of the nature of the evaluation, agrees to its provisions and has signed the informed consent.
2. Subject agrees to comply with the protocol-mandated follow-up visits and testing regime.

3. The subject is ≥ 18 years old.

4. Female subjects of childbearing potential must have a negative pregnancy test within 7 days prior to study procedure. Female subjects who are surgically sterile or post-menopausal are exempt from having a pregnancy test.

5. The subject has lifestyle-limiting claudication and/or critical limb ischemia defined as: Rutherford Category 1-5 (mild to severe claudication).

6. The target lesion(s) has angiographic evidence of stenosis or restenosis ≥ 50% or occlusion (by visual estimate) and is amenable to PTA with primary stenting.

7. Lesion(s) must meet TASC type A, B or C definitions

8. The target vessel reference diameter is ≥ 4.0 mm and ≤ 6.5 mm (by visual estimate) and therefore appropriate for treatment with available stent diameters of 6.0 mm and 7.0 mm.

9. There is angiographic evidence of at least one vessel runoff to the foot (at the level of the malleolus).

Candidates who met <u>any</u> of the following exclusion criteria at the time of the study procedure were <u>not</u> eligible for enrollment in the study:

1. The subject is unable or unwilling to provide informed consent or is unable to conform to the study protocol follow-up procedures and visits.

2. The subject has critical limb ischemia described as Rutherford Category 6 (major tissue loss, functional foot no longer salvageable).

3. The subject has a contraindication (including allergic reaction) to antiplatelet/anticoagulant medications, nickel, titanium, tantalum or sensitivity to contrast media that is not amenable to pretreatment with steroids or/and antihistamines.

4. The subject has a history of bleeding diatheses or coagulopathy.

5. The subject has concomitant renal failure with a creatinine of > 2.5 mg/dL.

6. The subject has concomitant hepatic insufficiency, thrombophlebitis, uremia, systemic lupus erythematosus (SLE), or deep vein thrombosis (DVT) at the time of the study procedure.

7. The subject is receiving dialysis or immunosuppressive therapy.

8. The subject is currently participating in an investigational drug or another device study that has not completed the primary endpoint or that clinically interferes with the study endpoints. (Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.

9. The subject has another medical condition, which may cause him/her to be non-compliant with the protocol, confound the data interpretation, or is associated with limited life expectancy of less than two years.

10. The subject has extensive peripheral vascular disease that precludes safe insertion of an introducer sheath.

11. The target lesion(s) is located within an aneurysm or associated with an aneurysm in the vessel segment either proximal or distal to the target lesion(s).

12. There is angiographic evidence of unresolved thrombus at the target lesion(s) or within the target vessel that does not resolve with infusion of thrombolytics and/or mechanical thrombectomy (using an FDA approved device) without adverse events/complications.

13. The subject has angiographic evidence of poor inflow which would be deemed inadequate to support a vascular bypass graft.

14. The subject is diagnosed with septicemia at the time of the study procedure.

E-TAGIUSS Follow-up Schedule

All subjects were scheduled to return for follow-up examinations at 1 month (± 7 days) postoperatively. Preoperative and postoperative evaluations were conducted according to the table below:

Table 10: E-TAGIUSS Follow-up Schedule

Observation	Baseline	Intra-Procedure	Hospital Discharge	30 Day
CBC, Serum BUN, Creatinine, Electrolytes (Na, K, Cl)	✓		✓	
ACT		✓		
Resting ABI	✓		✓	✓
Rutherford	✓			✓
Definition of Improvement				✓

Adverse events and complications were recorded at follow-up visits.

E-TAGIUSS Clinical Endpoints

The primary safety endpoint for the study was defined as the occurrence of death at 30 days post-procedure. Secondary safety endpoints included the evaluation of death, stroke, myocardial infarction, emergent surgical revascularization, significant distal embolization in target limb, and thrombosis of target vessel at 30-days post-procedure.

The primary efficacy endpoint was to assess deployment success, as defined by post-deployment stent length being within 10% of pre-deployment stent length; length was to be determined

angiographically. Secondary efficacy endpoints included the acute (peri-procedural) measures of success:

- Anatomic: Attainment of ≤ 30% residual stenosis of the target lesion using PTA with stenting.
- Lesion: Attainment of ≤ 30% residual stenosis of the target lesion using any percutaneous method and/or non-study device (i.e., post dilation).
- Procedure: Lesion success and no peri-procedural complications defined as: death, stroke, myocardial infarction, emergent surgical revascularization, significant distal embolization in target limb, and thrombosis of target vessel.

B. Accountability of PMA Cohort

RESILIENT Subject Accountability

Database lock occurred 3 years after the first patient and 15 months after the last patient had enrolled into the randomized phase of the study. At time of database lock, of 246 subjects enrolled in the studies, 95.1% (234) and 91.0% (223) subjects are available for analysis at the specified 30-day primary safety endpoint and 6-month primary effectiveness endpoint, respectively. The tables below document compliance with follow-up visits at 30 days, 6 months, and 12 months:

Table 11: RESILIENT
30-Day Follow-Up Compliance

	Phase I (N=20)	Roll-In (N=20)	Test	Control
Available	18	19	130/134 (97.0%)	67/72 (93.1%)
Not Available	2	1	4/134 (3.0%)	5/72 (6.9%)
Expired	0	0	0/134 (0.0%)	0/72 (0.0%)
Lost to Follow-Up	0	0	1/134 (0.7%)	0/72 (0.0%)
Withdrew Consent	0	0	0/134 (0.0%)	0/72 (0.0%)
Missed Visit	2	1	3/134 (2.2%)	5/72 (6.9%)

Table 12: RESILIENT
6-Month Follow-Up Compliance

	Phase I (N=20)	Roll-In (N=20)	Test	Control
Available	19	20	121/133 (91.0%)	63/72 (87.5%)
Not Available	1	0	12/133 (9.0%)	9/72 (12.5%)
Expired	0	0	2/133 (1.5%)	1/72 (1.4%)
Lost to Follow-Up	0	0	0/133 (0.0%)	0/72 (0.0%)
Withdrew Consent	0	0	3/133 (2.3%)	3/72 (4.2%)
Missed Visit	1	0	7/133 (5.3%)	5/72 (6.9%)

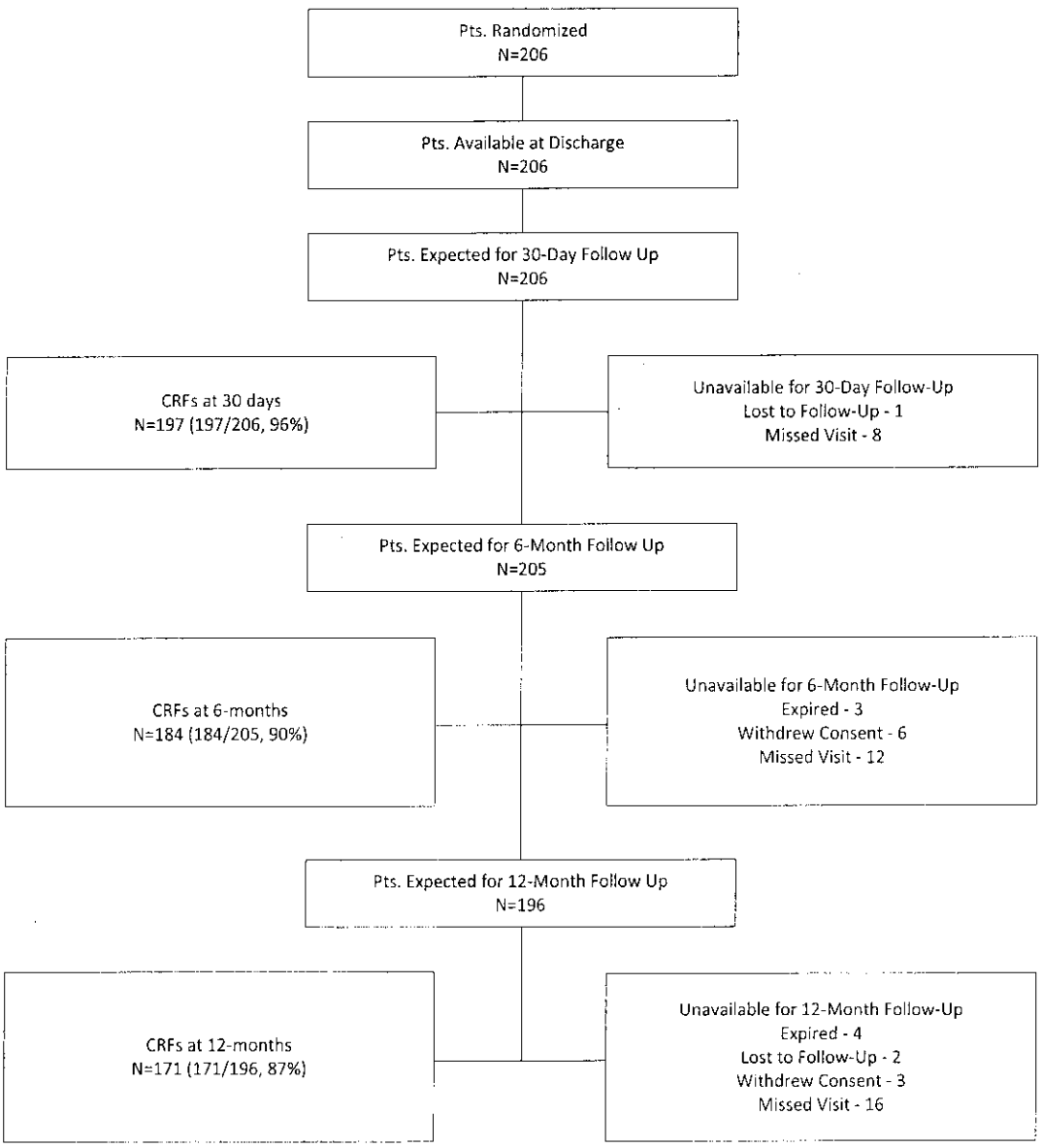
Table 13: RESILIENT
12-Month Follow-Up Compliance

	Phase I (N=20)	Roll-In (N=20)	Test	Control
Available	18	17	112/128 (87.5%)	59/68 (86.8%)
Not Available	2	3	16/128 (12.5%)	9/68 (13.2%)
Expired	0	1	3/128 (2.3%)	1/68 (1.5%)
Lost to Follow-Up	0	0	1/128 (0.8%)	1/68 (1.5%)
Withdrew Consent	1	1	2/128 (1.6%)	1/68 (1.5%)
Missed Visit	1	1	10/128 (7.8%)	6/68 (8.8%)

At 1 month, 11 patients "missed" the follow-up, and 1 patient was permanently lost-to-follow-up.

- At 6 months, 13 patients "missed" the follow-up, 6 patients withdrew from the study, and 3 patients died.
- At 12 months, 18 patients "missed" the follow-up, 2 patients were permanently lost-to-follow-up, 5 patients withdrew from the study, and 5 patients died.

For the Phase II randomized patients, the following flow-diagram further details patient availability for follow-up:



At each follow-up interval, the censoring rates for control and test patients were appropriately similar.

RESILIENT Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an interventional peripheral vascular study performed in the US. Details of the demographics are presented in the tables below.

Table 14: RESILIENT
Baseline Demographics and Clinical Characteristics

Variable	Category	Randomization		
		Test	Control	P-value*
Age at Procedure (Yrs)	N, Mean ± SD	134, 68.4 ± 9.9	72, 66.1 ± 9.2	0.11
Gender, % (n/N)	Female	29.1 (39/134)	33.3 (24/72)	0.53
	Male	70.9 (95/134)	66.7 (48/72)	
Race, % (n/N)	African American	9.0 (12/134)	9.7 (7/72)	0.25
	Caucasian	89.6 (120/134)	84.7 (61/72)	
	Other	1.5 (2/134)	5.6 (4/72)	
Hypertension, % (n/N)		83.6 (112/134)	91.7 (66/72)	0.14
Hypercholesterolemia, % (n/N)		78.4 (105/134)	73.6 (53/72)	0.49
Diabetes, % (n/N)		38.1 (51/134)	38.9 (28/72)	1.00
Smoking (current or past), % (n/N)		71.6 (96/134)	83.3 (60/72)	0.088
Coronary Artery Disease, % (n/N)		56.0 (75/134)	54.2 (39/72)	0.88
Myocardial Infarction, % (n/N)		20.1 (27/134)	26.4 (19/72)	0.38
Target Limb Rutherford Category, % (n/N)	Class 1	3.0 (4/134)	6.9 (5/72)	0.17
	Class 2	35.8 (48/134)	41.7 (30/72)	
	Class 3	61.2 (82/134)	50.0 (36/72)	
	Class 5		1.4 (1/72)	
Target Limb ABI (mm Hg)	N, Mean ± SD	124, 0.71 ± 0.19	66, 0.72 ± 0.19	0.85
Contralateral Limb ABI (mm Hg)	N, Mean ± SD	120, 0.88 ± 0.21	64, 0.84 ± 0.21	0.19

* t-test(s) were used for continuous variables, the Fisher's exact test was used for dichotomized variables, and Chi-square test(s) were used for other categorical variables. All p-values are two-sided.

Table 15: RESILIENT
Baseline Lesion Characteristics

Variable	Category	Randomization		
		Test	Control	P-value*
Number of Lesions, % (n/N)**	1 Lesion(s)	85.8 (115/134)	87.5 (63/72)	0.83
	2 Lesion(s)	14.2 (19/134)	12.5 (9/72)	
Target Side, % (n/N)***	Left	47.7 (73/153)	54.3 (44/81)	0.41
	Right	52.3 (80/153)	45.7 (37/81)	
Lesion Location, % (n/N)***	Distal 1/3 Of SFA	50.3 (77/153)	45.7 (37/81)	0.44
	Middle 1/3 Of SFA	32.0 (49/153)	38.3 (31/81)	
	Proximal 1/3 Of SFA	13.1 (20/153)	14.8 (12/81)	
	Proximal Popliteal	4.6 (7/153)	1.2 (1/81)	
Lesion Classification, % (n/N)***	*De-Novo*/Stenosed	80.4 (123/153)	79.0 (64/81)	0.96
	Occlusion	17.0 (26/153)	18.5 (15/81)	
	Restenosed	2.6 (4/153)	2.5 (2/81)	
Target Vessel RVD (mm)***	N, Mean ± SD	153, 5.2 ± 0.8	81, 5.2 ± 0.8	0.96
Lesion % Diameter Stenosis (%)***	N, Mean ± SD	153, 86.3 ± 12.5	80, 87.8 ± 11.5	0.38
Lesion Length (mm)***	N, Mean ± SD	153, 61.8 ± 42.5	81, 57.2 ± 36.8	0.42
Total Lesion Length per Subject (mm)**	N, Mean ± SD	134, 70.5 ± 44.3	72, 64.4 ± 40.7	0.33

* t-test(s) were used for continuous variables, the Fisher's exact test was used for dichotomized variables, and Chi-square test(s) were used for other categorical variables. All p-values are two-sided.
Variables identified with (**) are evaluated by per subject while variables identified with (***) are evaluated by per lesion.

Approximately one-quarter of study subjects were enrolled at the two OUS study centers; these centers represented only 8% of the total number of study sites. The sponsor provided an analysis that demonstrated the clinical similarities between US and OUS patients.

Table 16: US and OUS Patient Clinical Similarities
Baseline Demographics and Lesion Characterization – Literature Summary

Region	No. of Patients	Mean Age (yr)	Percent Males (%)	Percent Smokers (%)	Percent Diabetics (%)	Percent Occlusion (%)	Percent Hyper-Tension (%)	Percent Hyper-Lipidemia (%)
Europe	979	68	65	41	38	46	70	69
US	391	67	66	66	44	40	76	83

Baseline Demographics and Lesion Characterization – Literature & RESILIENT Summary

Data Sets	No. of Patients	Mean Age (yr)	Percent Males (%)	Percent Smokers (%)	Percent Diabetics (%)	Percent Occlusion (%)	Percent Hyper-Tension (%)	Percent Hyper-Lipidemia (%)
EU RESILIENT Cohort Data	55	66	82	51	35	19	93	64
US RESILIENT Cohort Data	151	68	65	85	40	17	84	81
RESILIENT Pivotal Cohort	206	68	69	76	38	18	86	77
Entire RESILIENT Population	246	68	69	76	39	15	86	77

A poolability analysis compared effectiveness results between US and OUS patients:

Table 17: RESILIENT Poolability Analysis – Success Measures

Variable	--US--		--OUS--		P-value*
	Test % (n/N)	Control % (n/N)	Test % (n/N)	Control % (n/N)	
Lesion Success	95.5 (84/88)	86.7 (39/45)	96.8 (30/31)	75.0 (12/16)	0.58
Hemodynamic Success	67.9 (55/81)	58.3 (21/36)	86.7 (26/30)	50.0 (7/14)	0.12
Procedure Success	95.5 (84/88)	86.7 (39/45)	96.8 (30/31)	75.0 (12/16)	0.58
6 Month Clinical Success	71.3 (62/87)	20.0 (10/50)	67.7 (21/31)	44.4 (8/18)	0.12
12 Month Clinical Success	70.4 (57/81)	31.3 (15/48)	71.0 (22/31)	41.2 (7/17)	0.71

* The p-values are based on the exact test of homogeneity of odds ratios calculated by STATXACT 8.

Table 18: RESILIENT Poolability Analysis – Chronic Effectiveness

Event	--US--		--OUS--		P-value*
	Test %	Control %	Test %	Control %	
Freedom From Loss Of Primary Patency at 6-mo	93.2	41.3	96.9	68.4	0.86
Freedom From Loss Of Primary Patency at 12-mo	77.1	34.1	85.2	45.6	
Freedom From Loss Of Secondary Patency at 6-mo	100.0	97.8	100.0	100.0	**
Freedom From Loss Of Secondary Patency at 12-mo	100.0	97.8	100.0	100.0	
Freedom From TLR at 6-mo	99.0	46.2	97.1	75.0	0.49
Freedom From TLR at 12-mo	87.0	40.2	87.0	61.1	
Freedom From TLR/TVR at 6-mo	93.9	46.2	97.1	75.0	0.81
Freedom From TLR/TVR at 12-mo	82.0	40.2	87.0	61.1	

The rates are estimated by Kaplan-Meier analysis.
* The p-values are based on the test of interaction between treatment and region (US/OUS) from a Cox regression model.
** The number of events is too small to perform a meaningful test of interaction.

Table 19: RESILIENT Poolability Analysis - Safety Measures				
Variable	--US--		--OUS--	
	Test % (n)	Control % (n)	Test % (n)	Control % (n)
30-Day Mortality	0.0 (0/99)	0.0 (0/52)	0.0 (0/35)	0.0 (0/20)
30-Day MACE	0.0 (0/99)	1.9 (1/52)	0.0 (0/35)	0.0 (0/20)
Freedom From 6-Month MACE**	92.9	90.1	93.6	100.0
Freedom From 12-Month MACE**	84.1	81.0	90.2	100.0
** The rates are estimated by Kaplan-Meier analysis.				

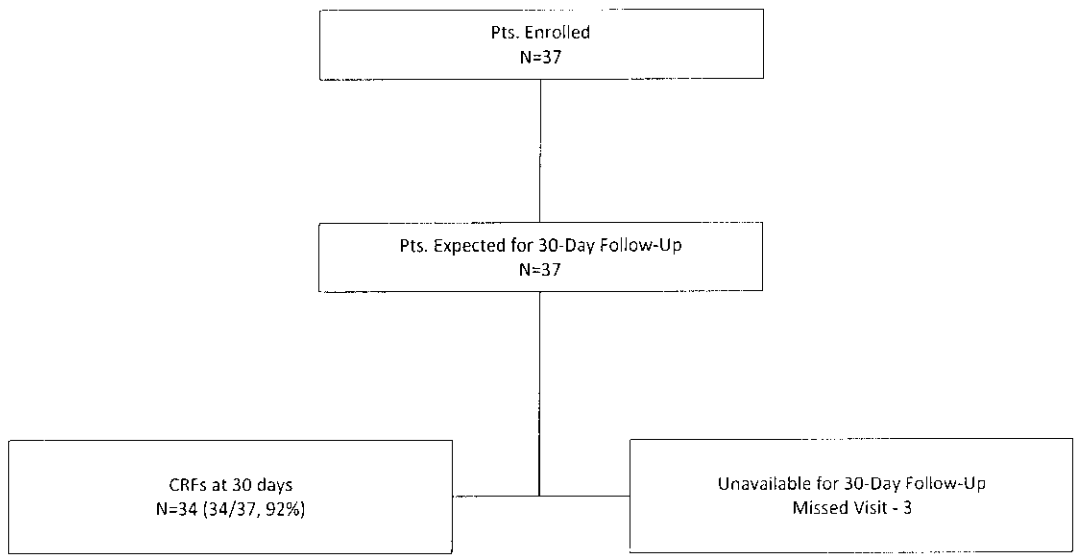
Although the post-hoc analysis did not find any statistically significant differences between US and OUS safety measures, this sub-group analysis was not powered adequately to identify any differences that may have existed. In this regard, the control group rates of 6- and 12-month for Clinical Success and Freedom from TLR/TVR exhibit qualitative clinical differences between the OUS and US cohorts.

E-TAGIUSS Subject Accountability

Database lock occurred 9 months after the first patient and 8 months after the last patient had enrolled into the randomized phase of the study. At time of database lock, of the 37 subjects enrolled in the studies, 92% (34) subjects are available for analysis at the specified 30-day primary safety endpoint. The tables below document compliance with the 30-day follow-up visits:

Table 20: E-TAGIUSS 30-Day Follow-Up Compliance	
Available	34/37 (92%)
Not Available	3/37 (8%)
Expired	0/37 (0%)
Lost to Follow-Up	0/37 (0%)
Withdrew Consent	0/37 (0%)
Missed Visit	3/37 (8%)

- At 1 month, 3 patients "missed" the follow-up.
- The following flow-diagram further details patient availability for follow-up:



E-TAGIUSS Study Population Demographics and Baseline Parameters

Although performed outside the U.S., the demographics of the study population are typical for an interventional peripheral vascular study performed in the US. Details of the demographics are presented in the tables below.

Table 21: E-TAGIUSS
Baseline Demographics and Clinical Characteristics

Variable	Category	Total
Age at Procedure (Yrs)	N, Mean ± SD	37, 71.1 ± 7.8
Gender, % (n/N)	Female	29.7 (11/37)
	Male	70.3 (26/37)
Race, % (n/N)	Caucasian	97.3 (36/37)
	Other	2.7 (1/37)
Hypertension, % (n/N)		83.8 (31/37)
Hypercholesterolemia, % (n/N)		56.8 (21/37)
Diabetes, % (n/N)		24.3 (9/37)
Smoking, % (n/N)		48.6 (18/37)
Coronary Artery Disease, % (n/N)		32.4 (12/37)
Myocardial Infarction, % (n/N)		13.5 (5/37)
Target Limb Rutherford Category, % (n/N)	Class 1	5.4 (2/37)
	Class 2	35.1 (13/37)
	Class 3	45.9 (17/37)
	Class 4	5.4 (2/37)
	Class 5	8.1 (3/37)
Target Limb ABI (mm Hg)	N, Mean ± SD	35, 0.6 ± 0.2
Contralateral Limb ABI (mm Hg)	N, Mean ± SD	31, 0.9 ± 0.2

Table 22: E-TAGIUSS
Baseline Lesion Characteristics

Variable	Category	Total
Number of Lesions, % (n/N)	1	86.5 (32/37)
	2	13.5 (5/37)
Target Side, % (n/N)	Left	47.6 (20/42)
	Right	52.4 (22/42)
Lesion Location, % (n/N)	Popliteal	2.4 (1/42)
	SFA	95.2 (40/42)
	SFA & Popliteal	2.4 (1/42)
Lesion Classification, % (n/N)	Occlusion	42.9 (18/42)
	Reoccluded	7.1 (3/42)
	Restenosed	2.4 (1/42)
	Stenosed	47.6 (20/42)
Target Vessel RVD (mm)	N, Mean ± SD	42, 5.3 ± 0.6
Lesion % Diameter Stenosis (%)	N, Mean ± SD	42, 89.3 ± 15.1
Lesion Length (mm)	N, Mean ± SD	42, 89.2 ± 69.8
Lesion Severity TASC Grade, % (n/N)	TASC A	45.9 (17/37)
	TASC B	24.3 (9/37)
	TASC C	29.7 (11/37)

The variables presented in this table are from investigational site evaluation

Table 23: E-TAGIUSS Baseline Lesion Characteristics (Quantitative Angiographic Analysis)		
Variable	**Category**	**Total**
Target Vessel RVD (mm)	N, Mean ± SD	38, 5.5 ± 0.7
Target Vessel MLD (mm)	N, Mean ± SD	38, 0.7 ± 0.9
Lesion % Diameter Stenosis (%)	N, Mean ± SD	38, 87.0 ± 16.6
Target Lesion Length (mm)	N, Mean ± SD	24*, 65.4 ± 35.1
Lesion Calcification, % (n/N)	None/Mild	55.3 (21/38)
	Moderate	13.2 (5/38)
	Severe	31.6 (12/38)
Vessel Run-off, % (n/N)	1 Vessel	10.5 (4/38)
	2 Vessel	15.8 (6/38)
	Not Evaluable	73.7 (28/38)
* Lesion length is typically measured from still films. For 14 of the 38 lesions assessed by the angiographic core lab lesion length could not be assessed. This was primarily for the long lesions that required a cine loop to capture the entire lesion. A more accurate representation of the population lesion length can be found in the table above.		

C. Safety and Effectiveness Results

RESILIENT Outcomes

For consideration of the safety and effectiveness endpoints, the sponsor provided analyses dependent upon available data as well as dependent upon the available data supplemented with imputed data reflecting worse-case scenarios (i.e., imputing failure values for the test procedures and success values for the control procedures). In general, the worst-case scenarios corroborated the statistical results of the available-data analyses.

RESILIENT Safety Outcomes

The primary safety endpoint compared 30-day mortality rates. No 30-day deaths were seen in either arm of the study, and therefore no formal statistical comparison was performed. The 95% confidence intervals were -5.0% and 3.0%. The worst-case analysis, in which 1 death was attributed to the test arm, yielded a 30-day mortality difference of 0.7% (95% CI -4.1%, 4.4%). This result was consistent with the primary analysis's result.

Since the 30 day mortality rates were 0%, the secondary safety endpoints became the composite rate of stroke, myocardial infarction, emergent surgical revascularization, significant distal embolization in target limb, and thrombosis of target vessel (major adverse clinical events or MACE) at 30-days post-procedure; and MACE + worsening of Rutherford-Becker Category at 6 and 12 months.

At 30 days, the difference in observed MACE rates was neither clinically nor statistically significant:

Table 24: RESILIENT Primary Safety – 30 Days					
Variable	Randomization				
	Test % (n/N)	Control % (n/N)	Difference (%)	95% CI for Difference	P-value*
Composite Safety Outcome at 30 Days**	0.0 (0/134)	1.4 (1/72)	-1.4	(-7.5, 1.6)	0.35
Death at 30 Days	0.0 (0/134)	0.0 (0/72)	0	(-5.0, 3.0)	
Stroke	0.0 (0/134)	0.0 (0/72)			
Myocardial Infarction	0.0 (0/134)	0.0 (0/72)			
Significant Distal Embolization	0.0 (0/134)	1.4 (1/72)			
Emergent Surgical Revascularization	0.0 (0/134)	0.0 (0/72)			
Thrombosis	0.0 (0/134)	0.0 (0/72)			
* The p-value is based on a Fisher's Exact test. The exact 95% confidence interval for the difference is calculated using StatXact 8. ** The composite safety outcome is defined as any event of death, stroke, myocardial infarction, significant distal embolization, emergent surgical revascularization of target limb, and thrombosis by 30 days post procedure					

For the 6- and 12-month secondary safety endpoints, the sponsor provided Kaplan-Meier estimates for freedom from MACE. Freedom from MACE was essentially identical in both arms (~93% [6 months] and ~86% [12 months]).

Table 25: RESILIENT Percent Free of Major Adverse Clinical Events (MACE) with 30-Day Mortality					
Event	Randomization				
	Test %	Control %	Dif. %	95% CI for the Difference	P-value*
Freedom From MACE at 6 Months	93.1	92.8	0.3	(-7.23, 7.73)	0.95
Freedom From MACE at 12 Months	85.6	85.9	-0.3	(-10.93, 10.32)	0.96
The MACE rates are estimated from the Kaplan-Meier curves at specific time intervals (6-month or 12-month). * The p-values are based on a two-sided test with normal approximation.					

The worst-case analyses yielded similar, statistically insignificant differences in the MACE rates.

Table 26: RESILIENT Secondary Endpoints (Safety Measures) - Worst Case Analysis					
Variable	Test % (n/N)	Control % (n/N)	Dif (%)	95% CI for Difference	P-value
Combined Events at 30 Days*	0.7 (1/134)	1.4 (1/72)	-0.6	(-6.6, 3.0)	1.00
Freedom From MACE At 6 Months**	89.43	93.01	-3.59	(-11.48, 4.31)	0.37
Freedom From MACE At 12 Months**	78.39	86.99	-8.60	(-19.27, 2.07)	0.11
* "Combined events" is defined as any event of death, stroke, myocardial infarction, significant distal embolization, emergent surgical revascularization of target limb, and thrombosis by 30 days post procedure. The p-value for 30 day combined events is based on Fisher's Exact test. The exact 95% confidence interval for this variable is calculated by StatXact 8. ** Six months and 12 month freedom from MACE (death within 30-days, and interval specific (6-month or 12-month) stroke, myocardial infarction, significant distal embolization, emergent surgical revascularization of target limb, thrombosis, and worsening Rutherford category) are estimated by Kaplan-Meier analysis. The p-values are based on a two-sided test with normal approximation.					

RESILIENT Adverse Events

12 patient deaths occurred throughout the course of the randomized portion of the trial; 11 of the 12 deaths occurred more than 3 months after the stent implantation procedures. Review of all patient deaths did not identify any evident relationship to the LifeStent®. Survival curves comparing test and control groups did not reveal statistically significant differences at 12 months (p=0.71) or throughout the term of the study (p=0.66).

Figure 3: Survival Curve

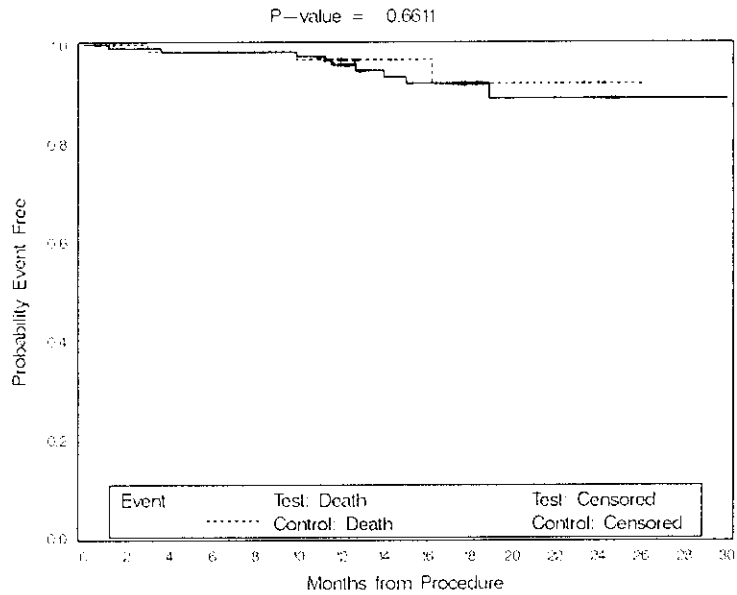


Table 27: Probability Alive -- Test / Control --						
Month	**# Pts at Risk**	**Cumulative # Events**	**Cumulative Censored**	**Probability Event Free**	**Difference (95% CI)**	**P-value (log-rank)**
0	134 / 72	0 / 0	0 / 0	1.000 / 1.000	0.000 (0.00, 0.00)	0.66
1	133 / 71	0 / 0	1 / 1	1.000 / 1.000	0.000 (0.00, 0.00)	
6	128 / 65	2 / 1	4 / 6	0.985 / 0.985	-0.000 (-0.04, 0.03)	
12	99 / 46	5 / 2	30 / 24	0.959 / 0.970	-0.010 (-0.06, 0.04)	
18	48 / 16	8 / 3	78 / 53	0.921 / 0.921	0.000 (-0.11, 0.11)	
24	16 / 6	9 / 3	109 / 63	0.892 / 0.921	-0.030 (-0.16, 0.10)	
The nominal 95% confidence intervals for the difference at each time point were calculated using the Kaplan Meier estimates and Greenwood's formula. The Kaplan-Meier analysis uses the date of the last reported contact (e.g., follow-up, lab test result or non-death AE) as the censored date. Therefore subjects who missed a specified follow-up (e.g., 6-months), but were confirmed to be alive at either a future follow-up (e.g., 12-months) or through contact with the site, were not censored in the interval that includes the specified follow-up.						

The table below provides a summary of the adverse events rates for test and control groups.

Table 28: RESILIENT Cumulative Adverse Events Summary (Test vs. Control)		
Variable	**Test % (n/N) [events]**	**Control % (n/N) [events]**
All Adverse Event	74.6** (100/134) [303]	86.1 (62/72) [175]
Myocardial Infarction	5.2 (7/134) [9]	2.8 (2/72) [2]
Death	6.7 (9/134) [9]	4.2 (3/72) [3]
Significant Distal Embolization	0.7 (1/134) [1]	1.4 (1/72) [1]
Amputation	1.5 (2/134) [2]	2.8 (2/72) [2]
Injury to the target vessel / dissection during PTA*	3.0 (4/134) [4]	20.8 (15/72) [16]
Acute thrombosis in target vessel during PTA		1.4 (1/72) [1]
TLR/TVR of target limb (Bailout Procedure) during PTA*	1.5 (2/134) [2]	20.8 (15/72) [15]
Other target vessel events during PTA* (AE 2.8)		4.2 (3/72) [3]
Injury to the target vessel / dissection during Stenting	1.5 (2/134) [2]	
Abrupt closure / total occlusion of target vessel during Stenting	0.7 (1/134) [1]	
Arterial spasm	0.7 (1/134) [1]	
Abrupt closure/total occlusion		1.4 (1/72) [1]
Acute thrombosis	3.0 (4/134) [5]	
False aneurysm		4.2 (3/72) [3]
AV fistula		1.4 (1/72) [1]
Other non-target vessel events (AE 4.8)	28.4 (38/134) [46]	29.2 (21/72) [28]
TLR/TVR during follow-up	21.6 (29/134) [33]	19.4 (14/72) [20]
Cardiac arrest	1.5 (2/134) [2]	
Allergic reaction	1.5 (2/134) [2]	
Other cardio-vascular adverse events (AE 6.11)	29.1 (39/134) [77]	20.8 (15/72) [26]
Severe prolonged hypotension	0.7 (1/134) [1]	1.4 (1/72) [1]
Severe prolonged hypertension	0.7 (1/134) [1]	
Prolonged cardiac chest pain	1.5 (2/134) [2]	5.6 (4/72) [4]
Cardiac arrhythmia	1.5 (2/134) [3]	5.6 (4/72) [4]
Blood loss requiring transfusion	3.0 (4/134) [7]	4.2 (3/72) [3]
Hematoma >5 cm	1.5 (2/134) [2]	1.4 (1/72) [1]
Retroperitoneal bleed	1.5 (2/134) [2]	
TIA (transient ischemic attack)	0.7 (1/134) [1]	
Other neurological event (AE 7.3)	5.2 (7/134) [8]	
Allergic reaction	0.7 (1/134) [1]	
Renal failure	0.7 (1/134) [1]	
Pulmonary Complication	3.0 (4/134) [4]	1.4 (1/72) [1]
Shock	0.7 (1/134) [1]	
Other systemic event (AE 8.7)	28.4 (38/134) [65]	31.9 (23/72) [39]
Delivery System Malfunction	1.5 (2/134) [2]	
Other device malfunction (DM 9.9)	3.0 (4/134) [6]	
Adverse Events utilized by investigators to document control bailout cases. As multiple AEs could lead to a bailout procedure, the total number of identified AEs is greater than the number of control bailout procedures (N=29) ** test vs. control p = 0.074		

The most clinically noticeable difference occurred in rates of target vessel injury/dissection (20.8% control vs. 1.5% treatment). The control group's target vessel injury/dissection rate led to a higher-than-predicted need for bailout procedures in the control group. This rate also figured prominently in the primary efficacy measure of freedom from TVR/TLR.

RESILIENT Effectiveness Outcomes

The primary efficacy endpoint compared the occurrence of target lesion revascularization (TLR) and/or target vessel revascularization (TVR) at 6 months post-procedure. Freedom from TLR/TVR was significantly different between test and control groups (94.6% vs. 54.1%).

Table 29: RESILIENT
Primary Effectiveness Estimated From Survival Analysis

Event	Test %	Control %	Diff %	95% CI for the Difference	P-value*
Follow up at 6 Months					
Freedom From TLR	98.5	54.1	44.4	(32.7, 56.1)	**<0.0001**
Freedom From TLR/TVR	94.6	54.1	40.5	(28.4, 52.7)	**<0.0001**

The rates are estimated by Kaplan-Meier analysis.
* The p-values are two-sided and were based on a normal approximation with no adjustment for multiplicity.

The probability of freedom from TLR/TVR remained significantly different throughout the duration of the study, based upon Kaplan-Meier estimates:

Figure 4: Freedom from TLR/TVR

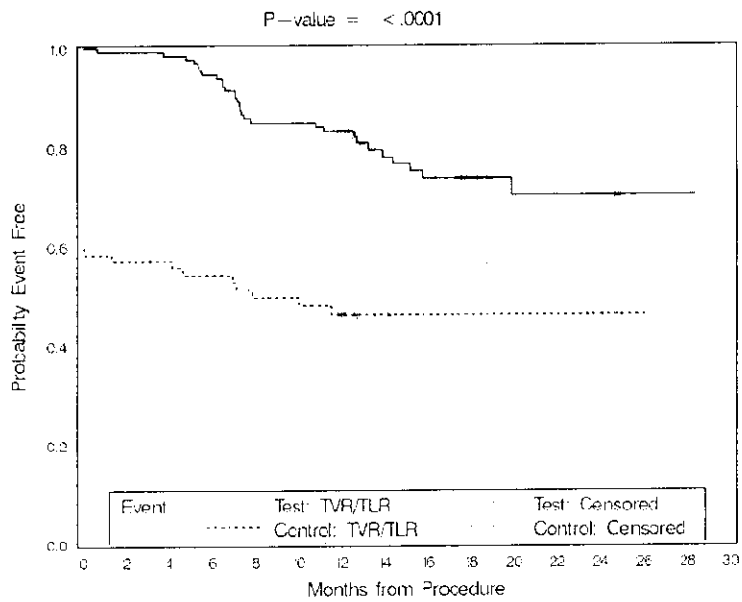


Table 30: Probability of Freedom from TLR/TVR						
-- Test / Control --						
Month	# Pts at Risk	Cumulative # Events	Cumulative Censored	Probability Event Free	Difference (95% CI)	P-value
0	134 / 72	0 / 29	0 / 0	1.000 / 0.597	0.403 (0.29, 0.52)	<.0001
1	133 / 42	1 / 30	0 / 0	0.993 / 0.583	0.409 (0.29, 0.52)	
6	122 / 37	7 / 33	5 / 2	0.946 / 0.541	0.405 (0.28, 0.53)	
12	84 / 20	21 / 38	29 / 14	0.832 / 0.462	0.370 (0.24, 0.50)	
18	40 / 5	28 / 38	66 / 29	0.737 / 0.462	0.275 (0.13, 0.42)	
24	14 / 3	29 / 38	91 / 31	0.702 / 0.462	0.240 (0.08, 0.40)	
The nominal 95% confidence intervals for the difference at each time point were calculated using the Kaplan Meier estimates and Greenwood's formula. The Kaplan-Meier analysis uses the date of the last reported contact (e.g., follow-up, lab test result or non-TLR/TVR AE) as the censored date. Therefore subjects who missed a specified follow-up (e.g., 6-months), but were confirmed to be TLR/TVR-free at either a future follow-up (e.g., 12-months) or through contact with the site, were not censored in the interval that includes the specified follow-up.						

It is important to note that 40% (29/72) of the control patients underwent a bailout procedure (a rate higher than had been predicted by the sponsor (4-16%)) and that these bailout procedures constituted 90% of the control patients' need for TLR/TVR through 6 months. If these intra-procedure TLR/TVR events are excluded, and the results analyzed outside the guidelines dictated by the approved study protocol, it is assumed that the 6 month freedom from TLR/TVR rate for the control group could near 90%, which is more comparable with the test group (94.6%).

A worst-case scenario analysis for freedom from TLR/TVR, in which an additional 4 test group patients were imputed to have undergone TLR/TVR, confirmed the finding of superiority for the test device:

Table 31: RESILIENT Worst Case Analysis – Probability of Freedom from TLR/TVR					
	-- Test / Control --				
Month	# Pts at Risk	Cumulative # Events	Cumulative Censored	Probability Event Free	Difference (95% CI)
0	134 / 72	0 / 29	0 / 0	1.000 / 0.597	0.403 (0.289, 0.516)
1	133 / 42	1 / 30	0 / 0	0.993 / 0.583	0.409 (0.294, 0.524)
6	**121 / 38**	**11 / 33**	**2 / 1**	**0.917 / 0.541**	**0.376 (0.252, 0.500)**

Tables comparing results for the worst-case scenarios of the secondary efficacy endpoints are presented below:

Table 32: RESILIENT Worse Case Analysis - Time Until TLR/TVR					
	-- Test / Control --				
Month	# Pts at Risk	Cumulative # Events	Cumulative Censored	Probability Event Free	Difference (95% CI)
0	134 / 72	0 / 29	0 / 0	1.000 / 0.597	0.403 (0.289, 0.516)
1	133 / 42	1 / 30	0 / 0	0.993 / 0.583	0.409 (0.294, 0.524)
6	121 / 38	11 / 33	2 / 1	0.917 / 0.541	0.376 (0.252, 0.500)
12	**84 / 24**	**31 / 38**	**19 / 10**	**0.765 / 0.468**	**0.296 (0.160, 0.433)**

Table 33: RESILIENT Worst Case Analysis – Probability of Freedom from Loss of Primary Patency					
	-- Test / Control --				
Month	# Pts at Risk	Cumulative # Events	Cumulative Censored	Probability Event Free	Difference (95% CI)
0	134 / 72	0 / 29	1 / 0	1.000 / 0.597	0.403 (0.289, 0.516)
1	122 / 40	11 / 32	1 / 0	0.917 / 0.556	0.362 (0.238, 0.486)
6	107 / 35	23 / 36	4 / 1	0.827 / 0.499	0.328 (0.196, 0.461)
12	**46 / 16**	**44 / 42**	**44 / 14**	**0.648 / 0.409**	**0.240 (0.096, 0.383)**

Table 34: RESILIENT Success Measures – Worst Case Analysis					
Variable	Test % (n)	Control % (n)	Diff %	95% CI for the Difference	P-value*
Lesion Success	85.1 (114/134)	86.1 (62/72)	-1.0	(-10.7, 10.3)	1.00
Hemodynamic Success	60.4 (81/134)	69.4 (50/72)	-9.0	(-22.2, 5.2)	0.23
Procedure Success	85.1 (114/134)	86.1 (62/72)	-1.0	(-10.7, 10.3)	1.00
6 Month Clinical Success	61.9 (83/134)	30.6 (22/72)	31.4	(17.3, 44.3)	**<0.0001**
12 Month Clinical Success	59.0 (79/134)	40.3 (29/72)	18.7	(4.3, 32.4)	**0.013**
The p-values are based on the Fisher's exact test for binomial variables. The p-values are two-sided. The exact 95% confidence interval of the difference of rates is calculated by STATXACT 8.					

The test group was statistically superior at 6- and 12-months, under worst-case assumptions, for the endpoints of:

- freedom from TLR/TVR
- freedom from loss of primary patency
- clinical success

In the worst-case analysis, there were no significant differences noted for rates of secondary patency in test (100%) and control (98.4%) groups. Additionally, no superiority was demonstrated for lesion, hemodynamic, or procedure success, or for quality of life evaluations using the worst-case assumptions.

Subgroup analyses did not identify an impact of lesion morphology (i.e., stenosed vs. occluded) on safety and efficacy results, although the study was not statistically powered for this determination. Too few popliteal lesions (compared to SFA lesions) were treated to enable an appropriate subgroup analysis based upon lesion location. The subgroup analysis of stent integrity (rate of fracture) was discussed above.

RESILIENT - Stent Integrity

Of 287 implanted stents for which radiographic data were available, 11 stents in 10 patients demonstrated some form of stent fracture; five (5) stents in 5 subjects, demonstrated single-strut (Type 1) fractures and 5 stents in 4 subjects, demonstrated multiple strut fractures with displacement (Type 4). A single stent placed, off protocol, across the point of flexion in the mid-popliteal region was characterized with both a Type 1 and Type 4 fracture. 40% (4/10) of the fractures occurred in patients where multiple (≥ 2) stents were deployed in an overlapping fashion. 73% (8/11) of the fractures were identified within 7 months of implantation. All of the Type 4 fractures (occurring in 5 patients) were associated with stent elongation during implantation; thus 38% (5/13) of patients with >10% elongation went on to develop Type 4 fractures in less than 1 year.

The following table summarizes the fractures according to Allie, Hebert, and Walker.

Table 35: RESILIENT Fracture Analysis

Type	Count (stents/subjects)
Type 1	5/5
Type 4	5/4
Type 1 & 4	1/1
Total	11/10

The sponsor noted the following safety measures as evidence that the presence of fractures did not adversely affect patients:

Table 36:RESILIENT Safety Measures

Event	No Fracture % (n/N)	Fracture % (n/N)
30-Day Mortality	0.0 (0/183)	0.0 (0/10)
30-Day MACE	0.5 (1/183)	0.0 (0/10)
Freedom From 6-Month MACE	93.4	100.0
Freedom From 12-Month MACE	85.5	100.0
The "Freedom From" outcomes are estimated by Kaplan-Meier (K-M) analysis.		

The sponsor did not identify a negative impact on effectiveness measures in patients with fractures:

Table 37: RESILIENT Effectiveness at 6-months

Event	No Fracture (%)	Fracture (%)	Dif (%)	95% CI for the Difference
Freedom From Loss Of Primary Patency	91.6	100.0	8.5	(4.4, 12.5)
Freedom From Loss Of Secondary Patency	100.0	100.0	0.0	(0.0, 0.0)
Freedom From TLR	95.6	100.0	4.4	(1.4, 7.3)
Freedom From TLR/TVR	92.9	100.0	7.1	(3.4, 10.8)
The rates are estimated by Kaplan-Meier analysis.				

Table 38: RESILIENT Effectiveness at 12-months				
Event	No Fracture (%)	Fracture (%)	Dif (%)	95% CI for the Difference
Freedom From Loss Of Primary Patency	73.2	100.0	26.8	(19.8, 33.8)
Freedom From Loss Of Secondary Patency	100.0	100.0	0.0	(0.0, 0.0)
Freedom From TLR	78.8	100.0	21.2	(15.2, 27.2)
Freedom From TLR/TVR	76.1	100.0	23.9	(17.7, 30.2)
The rates are estimated by Kaplan-Meier analysis.				

It is important to note, however, that this study was not powered to identify differences in this, or any other subgroup analysis. The sponsor reasonably asserts that the occurrence of stent elongation has been mitigated by the FlexStar delivery system, as opposed to the original LifeStent® NT delivery system used in the RESILIENT trial, and by the availability of longer XL stents that should reduce the incidence of overlapped stent implantation. Fracture rates following deployment with the LifeStent® FlexStar and FlexStar XL study will be further characterized in the post-marketing CONTINUUM study.

E-TAGIUSS Outcomes

This confirmatory study was designed to investigate the acute (30-day) safety and effectiveness of the redesigned LifeStent® (FlexStar) delivery system and the longer FlexStar XL stents. Twenty-eight (28) of the 49 implanted stents (57%) were XL stents.

E-TAGIUSS Safety Outcomes

The primary safety endpoint of E-TAGIUSS characterized 30-day mortality. There were no deaths reported within this timeframe (0%), a result similar to RESILIENT.

Since the 30 day mortality rates were 0%, the secondary safety endpoint became a composite rate of stroke, myocardial infarction, emergent surgical revascularization, significant distal embolization in target limb, and thrombosis of target vessel (MACE) at 30-days post-procedure. There was one event, yielding a MACE event rate of 2.7%. This single event (digit amputation) had been anticipated prior to the stent implantation.

Table 39: E-TAGIUSS Safety Events		
Variable	In Hospital	30-Days
	Total % (n/N)	Total % (n/N)
Death	0.0 (0/37)	0.0 (0/37)
Stoke	0.0 (0/37)	0.0 (0/37)
Myocardial Infarction	0.0 (0/37)	0.0 (0/37)
Significant Distal Embolization	0.0 (0/37)	0.0 (0/37)
Emergent Surgical Revascularization	0.0 (0/37)	0.0 (0/37)
Thrombosis	0.0 (0/37)	0.0 (0/37)
Amputation of the target limb	2.7 (1/37)	2.7 (1/37)
Combined Events	**2.7 (1/37)**	**2.7 (1/37)**

E-TAGIUSS Adverse Events

A total of 6 adverse events occurred in the 37 study patients, yielding a rate of 16.2%. None of the events, adjudicated by the CEC, were deemed device-related.

Table 40: E-TAGIUSS Adverse Events	
Event Description	**Total % (N pts) [N events]**
All Adverse Event	16.2 (6/37) [6]
Allergic reaction	2.7 (1/37) [1]
Target limb amputation	2.7 (1/37) [1]
Cardiac arrhythmia	2.7 (1/37) [1]
Hematoma >5 cm	2.7 (1/37) [1]
Non-target vessel events (embolization)	2.7 (1/37) [1]
Non-target vessel revascularization	2.7 (1/37) [1]

E-TAGIUSS Effectiveness Outcomes

The primary efficacy endpoint was to assess deployment success, as defined by post-deployment stent length being no greater than 110% of pre-deployment stent length; length was to be determined angiographically. As noted above, 25 (51%) of the 49 stents implanted during E-TAGIUSS lacked paired angiographic length measurements. Three of the 49 stents lacked post-implantation measurements, and the sponsor excluded these stents from data analysis; the sponsor imputed pre-implantation length measurements for the remaining 22 unpaired stents. Average length change (with and without the use of imputed values) was within 10% of pre-implantation length.

Table 41: E-TAGIUSS Percent Length Change						
Data Sets	**N**	**Mean**	**SD**	**Minimum**	**Maximum**	**Central 99.9th Percentiles***
Stent with observed pre-deployment stent length	24	-0.14%	0.63%	-2.66%	0.87%	(-2.2%, 1.9%)
Stents with observed and imputed pre-deployment stent length	46	-0.03%	2.39%	-6.67%	6.95%	(-7.9%, 7.8%)
* The 0.0005th and 0.9995th percentiles are calculated from normal distribution						

The sponsor thus identified a 100% deployment success rate. Comparing this result to the 90% OPC using a one-sided exact binomial test, the sponsor concluded that there was a significantly better deployment success rate with the FlexStar and FlexStar XL delivery system.

Table 42: E-TAGIUSS Deployment Success			
Variable	**Total % (n/N)**	**P-value***	**95% Confident Limit**
Deployment Success	100.0 (46/46)	0.0079	0.922 , 1.000
* P value is based on binomial comparison with success rate of 90% (one-sided)			

Tables of the results for the secondary efficacy endpoints are presented below.

Table 43: E-TAGIUSS Lesion Success	
Variable	**Total % (n/N)**
Lesion Success per Lesion	92.1 (35/38)
Lesion Success per Subject	90.9 (30/33)

Table 44: E-TAGIUSS Procedure Success	
Variable	**Total % (n/N)**
Procedure Success	90.9 (30/33)

Due to the amount of missing data, consideration of the secondary efficacy endpoint of anatomic success is not appropriate. It is important to note that the anatomic success endpoint was intended to evaluate the efficacy of the self-expanding stent without the need for ancillary interventions such as post-implantation balloon angioplasty (i.e. PTA) of the stent. However, during the RESILIENT study, 95% of LifeStent® implantations were augmented with post-stent deployment PTA. Accordingly, use of the FlexStar system includes the recommendation to perform post-implantation PTA.

LifeStent® Chronic Assessments

The E-TAGIUSS confirmatory study was also intended to supplement the data obtained in RESILIENT. In particular, the sponsor sufficiently justified that the safety and efficacy of the 100mm, 120mm, 150mm, and 170mm XL stents could be reasonably expected to provide identical or improved results when compared to those of overlapping stents. In this regard, the sponsor performed a subgroup analysis of RESILIENT data comparing 103 patients implanted with stents < 80mm length with those 98 patients implanted with overlapping stents with total implanted length > 80mm. The patient demographics and lesion characteristics for these two groups were clinically similar, with the expected differences in number and length of lesions to be treated.

Table 45: RESILIENT
Baseline Demographics and Clinical Characteristics
Stent Length Subgroups

Variable	Category	Greater Than 80mm	Less Than 80mm
Age At Procedure (Yrs)	N, Mean ± SD	98, 69.68 ± 10.81	103, 67.42 ± 9.47
Gender, % (n/N)	Female	33.7 (33/98)	29.1 (30/103)
	Male	66.3 (65/98)	70.9 (73/103)
Race, % (n/N)	African American	10.2 (10/98)	7.8 (8/103)
	Caucasian	86.7 (85/98)	91.3 (94/103)
	Other	3.1 (3/98)	1.0 (1/103)
Hypertension, % (n/N)		88.8 (87/98)	81.6 (84/103)
Hypercholesterolemia, % (n/N)		85.7 (84/98)	72.8 (75/103)
Diabetes, % (n/N)		40.8 (40/98)	35.9 (37/103)
Smoking, % (n/N)		74.5 (73/98)	74.8 (77/103)
Coronary Artery Disease, % (n/N)		59.2 (58/98)	54.4 (56/103)
Myocardial Infarction, % (n/N)		27.6 (27/98)	18.4 (19/103)
Target Limb Rutherford Category, % (n/N)	Class 1	3.1 (3/98)	3.9 (4/103)
	Class 2	45.9 (45/98)	34.0 (35/103)
	Class 3	51.0 (50/98)	62.1 (64/103)
Target Limb ABI (mm Hg)	N, Mean ± SD	91, 0.71 ± 0.21	95, 0.73 ± 0.19
Contralateral Limb ABI (mm Hg)	N, Mean ± SD	89, 0.86 ± 0.22	94, 0.90 ± 0.18

Table 46: RESILIENT Baseline Lesion Characteristics Stent Length Subgroup			
Variable	**Category**	**Greater than 80mm**	**Less Than 80mm**
Number of Lesions, % (n/N) *	1 Lesion(s)	77.6 (76/98)	92.2 (95/103)
	2 Lesion(s)	22.4 (22/98)	7.8 (8/103)
Target Side, % (n/N) **	Left	53.3 (64/120)	48.6 (54/111)
	Right	46.7 (56/120)	51.4 (57/111)
Lesion Location, % (n/N) **	Distal 1/3 Of SFA	50.0 (60/120)	47.7 (53/111)
	Middle 1/3 Of SFA	33.3 (40/120)	32.4 (36/111)
	Proximal 1/3 Of SFA	11.7 (14/120)	15.3 (17/111)
	Proximal Popliteal	5.0 (6/120)	4.5 (5/111)
Lesion Classification, % (n/N) **	*De-Novo*/Stenosed	85.0 (102/120)	82.0 (91/111)
	Occlusion	12.5 (15/120)	14.4 (16/111)
	Restenosed	2.5 (3/120)	3.6 (4/111)
Target Vessel RVD (mm) **	N, Mean ± SD	119, 5.4 ± 0.9	111, 5.3 ± 0.8
Lesion % Diameter Stenosis (%) **	N, Mean ± SD	120, 85.9 ± 12.6	111, 85.9 ± 12.4
Lesion Length (mm) **	N, Mean ± SD	120, 86.1 ± 44.7	111, 41.9 ± 24.7
Total Lesion Length per Patient (mm) *	N, Mean ± SD	98, 105 ± 35.9	103, 45.2 ± 25.6
The variables presented in this table are from investigational site evaluation, evaluated by per patient (*) or by lesion (**)			

RESILIENT-defined safety and efficacy outcomes for the two groups were in general not statistically different; a slight trend toward an increase loss in primary patency at 12 months was noted, but further elucidation of this potential issue will be performed in the post-marketing CONTINUUM study.

Table 47: RESILIENT Safety Outcomes Stent Length Subgroup			
Variable	**Greater Than 80mm**	**Less Than 80mm**	**P-value [Difference] (95% CI for Difference)**
Death at 30 Days, % (n/N)	0.0 (0/98)	0.0 (0/103)	--
MACE* at 30 Days, % (n/N)	0.0 (0/98)	1.0 (1/103)	1.00 [-1.0] (-2.9, 0.9)
Freedom from MACE* at 6 Months (%)	91.47	95.09	0.31 [3.62] (-3.43, 10.66)
Freedom from MACE* at 12 Months (%)	81.80	86.65	0.37 [4.85] (-5.73, 15.44)
* MACE defined as the occurrence of any of the following events: death within 30 days, stroke, myocardial infarction, significant distal embolization, emergent surgical revascularization of target limb, thrombosis, or worsening Rutherford category post procedure.			

Figure 5: Freedom from TLV/TVR

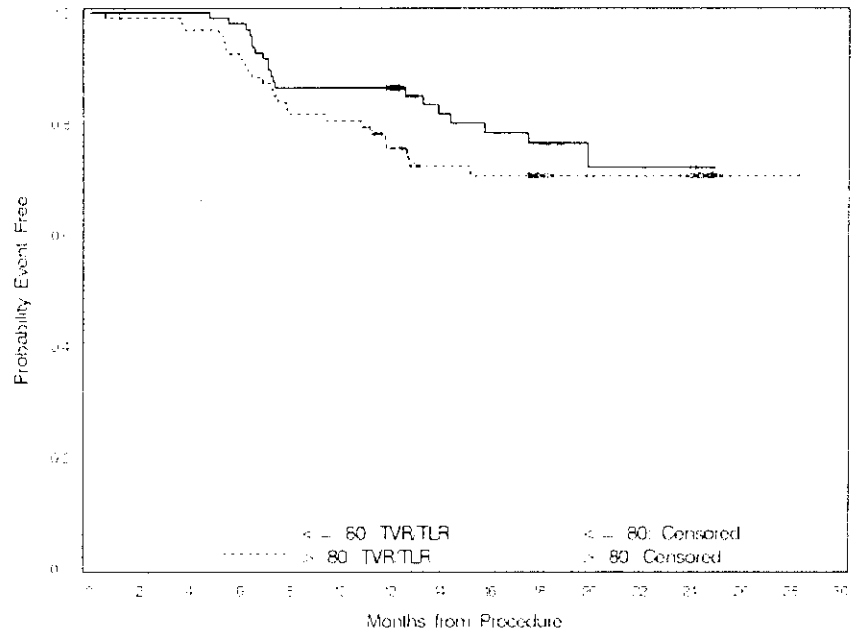


Table 48: Probability of Freedom From TLR/TVR --Less Than 80 / Greater Than 80 --						
Month	# Pts at Risk	Cumulative # Events	Cumulative Censored	Probability Event Free	Difference (95% CI)	P-value
0	103 / 98	0 / 0	0 / 0	1.000 / 1.000	0.000 (0.000, 0.000)	0.27
1	103 / 97	0 / 1	0 / 0	1.000 / 0.990	0.010 (-0.010, 0.030)	
6	97 / 85	2 / 8	4 / 5	0.980 / 0.916	0.064 (0.002, 0.126)	
12	71 / 56	13 / 22	19 / 20	0.865 / 0.756	0.109 (-0.003, 0.222)	
18	37 / 32	19 / 25	47 / 41	0.765 / 0.707	0.058 (-0.081, 0.197)	
24	11 / 21	20 / 25	72 / 52	0.722 / 0.707	0.015 (-0.142, 0.173)	

Figure 6: Freedom from Loss of Primary Patency

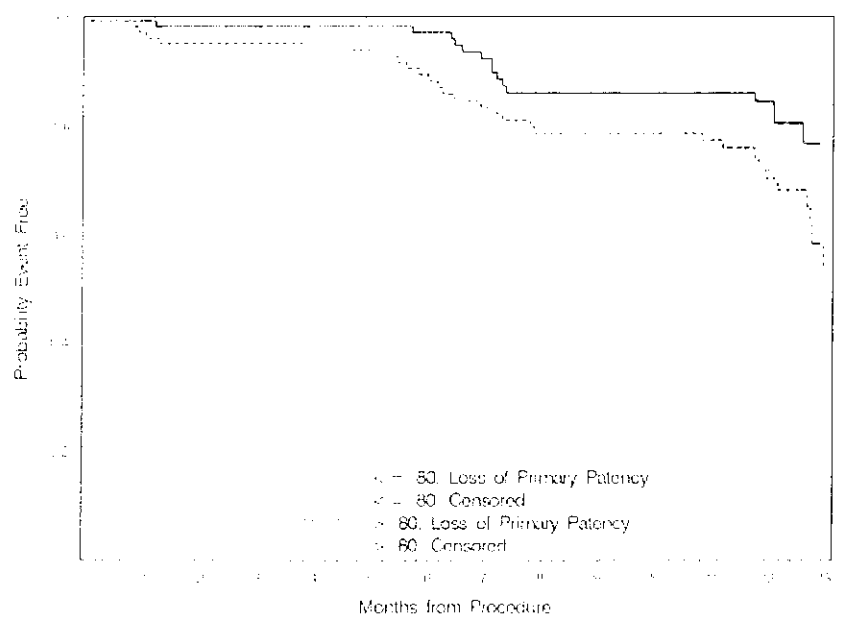


Table 49: Probability of Freedom from Loss of Primary Patency --Less Than 80 / Greater Than 80 --						
Month	# Pts at Risk	Cumulative # Events	Cumulative Censored	Probability Event Free	Difference (95% CI)	P-value
0	103 / 98	0 / 0	5 / 4	1.000 / 1.000	0.000 (0.000, 0.000)	0.14
1	96 / 88	0 / 3	7 / 7	1.000 / 0.968	0.032 (-0.004, 0.068)	
6	85 / 74	2 / 10	16 / 14	0.978 / 0.888	0.091 (0.019, 0.163)	
12	45 / 34	12 / 23	46 / 41	0.850 / 0.707	0.143 (0.013, 0.274)	

Table 50: RESILIENT Effectiveness Outcomes-Stent Length Subgroup			
Variable	Greater Than 80mm	Less Than 80mm	P-value* [Difference] (95% CI for Diff.)
Lesion Success per Lesion	93.1 (94/101)	97.1 (99/102)	0.21 [-4.0] (-9.9, 2.0)
Lesion Success per Patient	91.4 (74/81)	96.8 (92/95)	0.19 [-5.5] (-12.5, 1.6)
Hemodynamic Success	60.5 (49/81)	70.4 (57/81)	0.25 [-9.9] (-24.4, 4.7)
Procedure Success	91.4 (74/81)	96.8 (92/95)	0.19 [-5.5] (-12.5, 1.6)
Clinical Success at 6-months	61.7(50/ 81)	74.2(69/ 93)	0.10 [-12.5] (-26.3, 1.4)
Clinical Success at 12-months	65.1(54/ 83)	72.6(61/ 84)	0.32 [-7.6] (-21.6, 6.4)
Fisher's exact test, two-sided p-value. The exact 95% confidence interval of the difference is calculated by StatXact 8.			

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

All of the issues associated with the long-term results of the clinical studies and long-term follow-up have been addressed in the preceding section.

XII. PANEL MEETING RECOMMENDATION

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 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.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The primary safety and effectiveness data drawn from the pivotal RESILIENT clinical study demonstrated that the LifeStent® was reasonable assurance of safety and effectiveness when used in accordance with the inclusion and exclusion criteria, for the intended patient population. The 30-day results of the confirmatory E-TAGIUSS study demonstrated that the LifeStent® FlexStar and FlexStar XL systems perform as anticipated. The observed rates of adverse events were within expectations.

XIV. CDRH DECISION

CDRH issued an approval order on February 13, 2009. The final conditions of approval cited in the approval order are described below.

The applicant's manufacturing facilities were inspected and found to be in compliance with the Quality System Regulation (21 CFR 820).

XV. APPROVAL SPECIFICATION

Directions for Use: See device labeling.

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

Post Approval Requirements and Restrictions: See approval order.