SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Stent, Superficial Femoral
Device Trade Name:	Astron Pulsar Peripheral Self-Expanding Nitinol System (Astron Pulsar Stent System) and Pulsar-18 Peripheral Self-Expanding Nitinol Stent System (Pulsar-18 Stent System)
Device Procode:	NIP
Applicant's Name and Address:	BIOTRONIK, Inc. 6024 Jean Road Lake Oswego, OR 97035
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P160025
Date of FDA Notice of Approval:	March 23, 2017

II. INDICATIONS FOR USE

The Astron Pulsar and Pulsar-18 stent systems are indicated for use to improve luminal diameter in patients with symptomatic de novo, restenotic or occlusive lesions located in the superficial femoral or proximal popliteal arteries, with reference vessel diameters from 3.0 to 6.0 mm and total lesion lengths up to 190 mm.

III. CONTRAINDICATIONS

The Astron Pulsar and Pulsar-18 stent systems are contraindicated in:

- Patients with known hypersensitivity to nickel or amorphous silicone carbide.
- Patients with uncorrected bleeding disorders and contraindications to antiplatelet and/or anticoagulation therapy.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Instructions for Use documents for Astron Pulsar and Pulsar-18 stent system labeling.

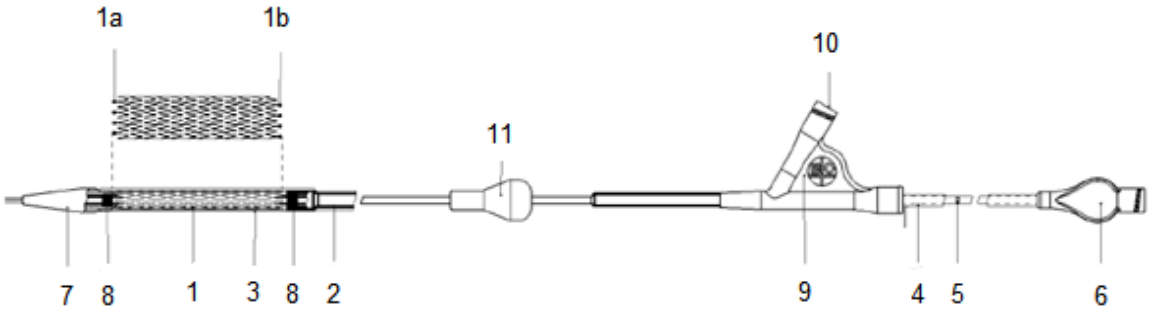
V. DEVICE DESCRIPTION

A. Astron Pulsar Stent System

The Astron Pulsar stent system (**Figure 1**) is a self-expanding stent loaded on an over-the-wire (OTW) delivery system. The stent (1) is laser-cut from a Nitinol tube. It carries six radiopaque marker extensions at each end (1a, 1b) and is completely coated with amorphous silicon carbide (a-SiC:H). The delivery system consists of two coaxially arranged elements: the inner shaft (2) and the outer shaft (3). The inner shaft is made of a thermoplastic polymer. At the proximal end, it is covered with a stainless steel tube. The safety tab (4) that covers the stainless steel tube prevents accidental stent release. The stainless steel tube incorporates a black release marker (5) that indicates the completion of stent deployment and ends with a Luer port (6) at the proximal guide wire exit.

The central guide wire lumen within the inner shaft continues to the radiopaque tip (7). The stent is mounted between the inner shaft and the outer shaft proximal to the tip, between two radiopaque markers (8), which facilitate fluoroscopic visualization and positioning of the delivery system towards and across the lesion. The outer shaft begins within the Y-connector (9) and extends toward the distal tip, covering the stent prior to deployment. A hydrophobic coating is applied to the outside of the inner shaft and the inside and the outside of the entire outer shaft. The annular space between the inner shaft and the outer shaft can be flushed through the Luer port (10) at the Y-connector. The guide wire lumen of the inner shaft is flushed through the Luer port at the proximal guide wire exit. The guide wire lumen permits the use of 0.018" guide wires to facilitate advancement of the delivery system toward and through the lesion to be treated. Astron Pulsar features an "Easy Release" (11) fitted over the proximal outer shaft. The "Easy Release" is intended to be inserted into the hemostatic valve of the introducer to reduce friction between the delivery system and the hemostatic valve during stent release.

Figure 1: Astron Pulsar stent system



The stent system and the “Easy Release” are compatible with an appropriately sized introducer sheath according to the indications on the label.

The stent is advanced to the intended implantation location by means of the over-the-wire delivery system and is deployed by pulling back the outer shaft at the Y-Connector while immobilizing the inner shaft. The stent remains in the vessel as a permanent implant.

The list of commercially available sizes is shown in **Table 1**.

Table 1: Astron Pulsar Available Sizes

Astron Pulsar		Stent length [mm]								
Stent length [mm]		20		30		40		60	80	
Usable length [cm]		72 75	130 135	72 75	130 135	72 75	130 135	72	130	72
Nominal Stent Ø [mm]	4	✓	✓	✓	✓	✓	✓	✓	✓	✓
	5	✓	✓	✓	✓	✓	✓	✓	✓	✓
	6	✓	✓	✓	✓	✓	✓	✓	✓	✓
	7			✓	✓	✓	✓	✓	✓	✓

B. PULSAR-18 STENT SYSTEM

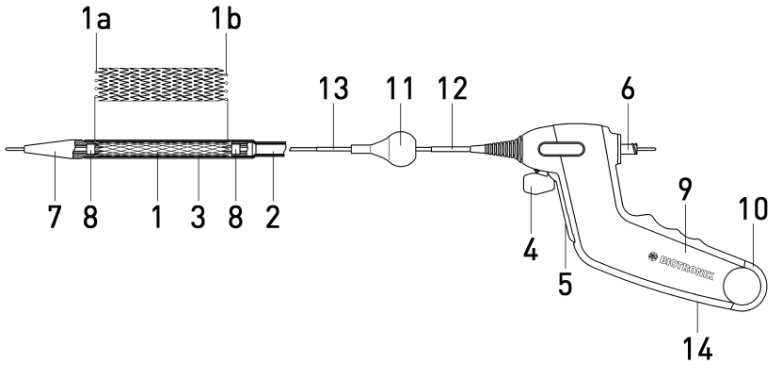
The Pulsar-18 stent system (

Figure 2) is a self-expanding stent loaded on an over-the-wire (OTW) delivery system. The stent (1) is laser-cut from a Nitinol tube. It carries 6 radiopaque marker extensions at each end (1a, 1b) and is completely coated with amorphous silicon carbide (a-SiC:H). The delivery system consists of two coaxially arranged elements: the inner shaft (2) and the outer shaft (3).

The central guide wire lumen within the inner shaft begins with a radiopaque tip (7) at the distal wire exit and ends with a Luer port (6) at the proximal guide wire exit. The stent is loaded between the inner shaft and the outer shaft proximal to the tip, between two radiopaque markers (8), which facilitate fluoroscopic visualization, and positioning of the stent system towards and across the lesion. The outer shaft begins proximally within the handle (9) and extends towards the distal tip, covering the stent. A hydrophobic coating is applied to the outside of the inner shaft and the inside and the outside of the entire outer shaft. The guide wire lumen of the inner shaft and the annular space between the inner shaft and the outer shaft are flushed simultaneously through the Luer port at the proximal guide wire exit. The guide wire lumen permits the use of 0.018" (0.46 mm) guide wires to facilitate advancement of the stent system toward and through the lesion to be treated.
The outer shaft is covered proximally with a blue colored tube (13) that indicates the progress and completion of stent deployment and a transparent tube (12) to protect from kinking.

Prior to deployment, the locking tab (4) must be removed and discarded. The stent is deployed with the trigger (5). In case the trigger release mechanism fails, partial stent deployment can be completed as follows: first, open the handle using the secondary release ring (10) and button (14), then pull directly on the blue tube. Pulsar-18 features an "Easy Release" (11) fitted over the proximal outer shaft. The "Easy Release" is intended to be inserted into the hemostatic valve of the introducer to reduce friction between the stent system and the hemostatic valve during stent release.

Figure 2: Pulsar-18 stent system



The stent system and the "Easy Release" are compatible with an appropriately sized introducer sheath according to the indications on the label.

The stent is advanced to the intended implantation location by means of the over-the-wire delivery system and is deployed by means of the handle and trigger mechanism. The stent remains in the vessel as a permanent implant.

The list of commercially available sizes is shown in Error! Reference source not found..

Table 2: Pulsar-18 Available Sizes

Pulsar-18		Stent length [mm]																			
Stent length [mm]		20		30		40		60		80		100		120		150		170		200	
Usable length [cm]		90	135	90	135	90	135	90	135	90	135	90	135	90	135	90	135	90	135	90	135
Nominal Stent Ø [mm]	4	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	5	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	6	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	7	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of peripheral artery disease located in the superficial femoral artery (SFA) and proximal popliteal artery (PPA) including the following:

- Percutaneous transluminal angioplasty (PTA) or atherectomy
- Stenting with another stent for which there is an approved indication
- Surgical treatment (e.g., bypass surgery)
- Lifestyle modifications (e.g., exercise and cessation of tobacco use)
- Medical therapy (e.g., antiplatelet therapy, lipid control, and medicine to manage claudication symptoms)

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

Astron Pulsar stent system has been market released outside the United States (OUS) since September 2005. A list of countries where the Astron Pulsar stent system was distributed in 2014 and 2015 is provided in **Table 3**. The Astron Pulsar stent system was the subject of two Voluntary Field Safety Corrective Actions (FSCAs). The first voluntary action in September 2009 was for removal of one lot due to incorrect labeling of the catheter usable length. The secondary voluntary action in April 2014 was to withdraw three lots following complaints about partial stent release. The issue was determined to be due to a single deviation in the coating process that only affected these three lots. A list of countries affect by the FSCAs is provided in **Table 4**.

Table 3: List of countries where Astron Pulsar stents were distributed in 2014-2015.

Australia	Colombia	Greece	Netherlands	Slovenia
Austria	Croatia	Hungary	Palestine	Spain
Belgium	Cyprus	India	Paraguay	Switzerland
Bosnia-Herz.	Czech Republic	Israel	Poland	Thailand
Brazil	Denmark	Italy	Portugal	Unit.Arab Emir.
Bulgaria	Finland	Jordan	Romania	United Kingdom
Canada	France	Kuwait	Russia	
Chile	Georgia	Latvia	Saudi Arabia	
China	Germany	Macedonia	Slovakia	

Table 4: List of countries affected by Astron Pulsar FSCAs

Incorrect labeling				
Austria Australia	Belgium France	Italy Switzerland		
Partial stent release				
Austria Belgium Croatia	France Germany Hungary	Israel Latvia Macedonia	Netherlands Spain Switzerland	

The Pulsar-18 stent system has been market released OUS since February 2010. A list of countries where the Pulsar-18 stent system was distributed in 2014 and 2015 is provided in **Table 5**. Pulsar-18 has been the subject of three voluntary field safety corrective actions. Two actions were to remove three lots in June and July of 2013 after complaints that some device sizes listed on inner labels, outer labels, and device markings did not match. These two FSCAs affected only the United States and FDA was notified through the IDE. The third FSCA in May 2015 was in response to complaints of partial stent deployment. An evaluation of the complaints determined that this was caused by increased friction during stent deployment of some lots. Possible sources of friction have been identified and addressed by appropriate improvements in the design and manufacturing process. Since the implementation of these improvements the rate of partial stent deployments has been reduced. A list of countries affected by the FSCAs is provided in **Table 5**.

Table 5: List of countries where Pulsar-18 stents were distributed in 2014-2015.

Argentina	Croatia	Guatemala	Mexico	South Africa
Australia	Cyprus	Hong Kong	Netherlands	South Korea
Austria	Czech Republic	Hungary	Paraguay	Spain
Belgium	Denmark	India	Poland	Sweden
Brazil	Estonia	Indonesia	Portugal	Switzerland
Bulgaria	Finland	Israel	Russia	Taiwan
Canada	France	Italy	Saudi Arabia	Thailand
Chile	Georgia	Jordan	Singapore	Unit.Arab Emir.
China	Germany	Latvia	Slovakia	United Kingdom
Costa Rica	Greece	Malaysia	Slovenia	Vietnam

Table 5: List of countries affected Pulsar-18 FSCAs

Incorrect labeling				
USA				
Partial stent deployment				
Argentina	Costa Rica	Hungary	Netherlands	Singapore
Australia	Croatia	Iran	New Zealand	Slovakia
Austria	Cyprus	Ireland	Palestine	Spain
Belgium	Czech Republic	Israel	Poland	Switzerland
Brazil	Denmark	Italy	Portugal	Thailand
Bulgaria	France	Jordan	Russia	United Kingdom
Canada	Georgia	Malaysia	Saudi Arabia	USA
China	Germany	Mexico	South Africa	Vietnam

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The following are possible adverse events that may occur relative to the stenting procedure and chronic implant of the Astron Pulsar or Pulsar-18 stents. These potential adverse events include, but are not limited to, the following:

- Allergic reactions to contrast media, antiplatelet aggregation or anticoagulant medications, amorphous silicon carbide and nitinol and/or its components (e.g. nickel, titanium)
- Bleeding events: Access site bleeding or hemorrhage, hemorrhage requiring transfusion or other treatment
- Death
- Embolization of air, thrombotic or atherosclerotic material
- Emergency surgery to correct vascular complications
- Infection and sepsis
- Stent system events: Failure to deliver stent to intended site, stent misplacement, stent deformation, stent embolization, stent thrombosis or occlusion, stent fracture, stent migration, inadequate apposition or compression of stent/s, withdrawal difficulties, embolization of catheter material
- Tissue necrosis and limb loss due to distal embolization
- Vascular events: Access site hematoma, hypotension/ hypertension, pseudoaneurysm, arteriovenous fistula formation, retroperitoneal hematoma, vessel dissection or perforation, restenosis, thrombosis or occlusion, vasospasm, peripheral ischemia, dissection, distal embolization (air, tissue debris, thrombus)

The BIOFLEX-I clinical trial conducted with the Astron Pulsar and Pulsar-18 stent systems contributed to the analysis of adverse events. For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. *In Vitro* Bench Testing

In vitro bench testing was performed to assess the functional characteristics of the stent systems. Testing was conducted according to the guidelines provided in *FDA Guidance for Industry and FDA Staff-Non-clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems* (April 18, 2010). Additionally, testing followed updated guidelines provided in *Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stent and Associated Delivery Systems – Guidance for Industry and Food and Drug Administration Staff* (August 18, 2015). **Table 7** below summarizes the bench testing performed on both stent systems. The test results are supportive of the device safety and effectiveness of both devices.

Table 7: Non-Clinical Engineering Tests of Stents and Delivery Systems

Test	Test Purpose	Acceptance Criteria	Results

Test	Test Purpose	Acceptance Criteria	Results
Material composition	To verify the composition of the stent nitinol body, X-ray markers and proBIO® coating.	The nitinol stent body material must conform to ASTM F2063. All materials of the X-ray markers and the proBIO® coating must be identified.	Pass
Surface characterization	Characterization of the stent body surface and proBIO® coating.	Characterization study only.	Elemental components of the coating were detected. Coating was confirmed to be uniform.
Determination of the Austenitic final transformation temperature (A_f)	To evaluate the Austenite finish temperature (A_f) of the stent.	Passed test if $A_f = 25 \pm 10°C$.	Pass
Pitting and crevice corrosion resistance – pre-fatigue	To evaluate the susceptibility of the metallic components of the stent to pitting and crevice corrosion pre-fatigue.	The range of stable passivity must be >200 mV, breakdown potential >300 mV vs. saturated calomel electrode (SCE).	Pass
Fretting corrosion resistance following accelerated durability testing in overlapped configuration	To evaluate the potential for fretting corrosion in a simulated physiological environment for the intended implant duration in overlapped configuration.	Characterization test only to document size and number of fretting spots	The size and number of fretting spots were determined.
Galvanic corrosion	To evaluate the susceptibility of the stent to galvanic corrosion in a simulated physiological environment	The stent shall be resistant to corrosion when subjected to physiological conditions at the implantation site. The theoretical calculated corrosion rate in penetration per year must be less than 200 nm/year.	Pass
Dimensional inspection stent	The purpose of this test was to inspect and measure the stent body dimensions before placement onto delivery system.	Astron Pulsar stent unconstrained diameter must be within the following tolerances (mm) of the labeled stent diameters:± 0.15 (Ø4 mm) or ± 0.30 (Ø5, 6, 7 mm) Stent length must be within the following tolerances (mm) of the labeled stent lengths: ± 0.5 (20, 30 mm) or ± 1.0 (40, 60, 80 mm)	Pass
		Pulsar-18 stent unconstrained diameter must be ± 0.3 mm of the labeled stent diameter. Stent length must be within the following tolerances (mm) of the labeled stent lengths: ± 0.5 (20, 30 mm) or ± 1.0 (40, 60, 80 mm) or ± 2.0 (100, 120 mm) or ± 3.0 (150, 170 mm) or ± 4.0 (200 mm)	Pass

Test	Test Purpose	Acceptance Criteria	Results
Percent surface area	To determine the surface coverage of the stent in the vessel.	The test was used for characterization only to determine percent surface area of the stent.	The percent stent surface area was determined
Foreshortening	To determine the foreshortening of the stent from the catheter constrained diameter to use diameter.	Foreshortening of the Astron Pulsar stent must be ≤7 %.	Pass
		Foreshortening of the Pulsar-18 stent must be ≤5 %.	Pass
Particle count and visual inspection of stent and coating after expansion in simulated use environment of overlapped stents	To investigate the stent integrity and the coating integrity by particle count and visual inspection of the stent during simulated use within an in-vitro model.	Particle count: not more than 6000 particles ≥ 10 µm and not more than 600 particles ≥ 25 µm. Stent coating: No visually detectable coating defects Stent: No stent body defects.	Pass
Radial force	To measure the outward radial force (F_R) exerted by the self-expanding stent on the vessel in the deployed state.	Within the recommended use range, the length normalized outward radial force of the stents must be >0.02 N/mm.	Pass
Mechanical properties of the raw materials	To determine the mechanical properties of the raw materials of the stent.	Mechanical properties of the raw materials must meet the following parameters: Upper Plateau Stress (UPS): ≥ 400 MPa Ultimate Tensile Strength (UTS): 1000-1500 MPa Uniform Elongation: ≥ 13 % Residual Elongation after 6% strain: ≤0.3%	Pass
Mechanical properties post-processing: tensile testing	To evaluate post processing material properties of nitinol material.	The following mechanical properties of the post processed materials must be met: Astron Pulsar Loading plateau UPS: >350 N/mm^2 Pulsar-18 Loading plateau UPS: >330 N/mm^2 Tensile Strength (TS): > 1000 MPa Uniform Elongation: > 12 % Residual Elongation: < 0.3 %	Pass
Stress/ strain analysis / fatigue analysis	To locate and determine the critical stresses and/or strains within the stent due to manufacture, deployment and worst case *in vivo* loading by means of a Finite Element Analysis. Calculation of Safety Factor (SF). Determination of worst case conditions for accelerated durability testing.	Worst case strains and load history shall be determined and Safety Factors calculated. Test passed if the following specification was met: SF > 1	Pass

Test	Test Purpose	Acceptance Criteria	Results
Accelerated durability testing radial pulsatile load	To determine the fatigue resistance of the expanded stent in overlapped configuration after 380 million physiological load cycles (radial pulsatile load / equivalent to 10 years of service life).	Stent integrity is demonstrated if: • No serious loss in stent integrity where the implanted stent is considered no longer able to keep the lumen of a vessel open.No significant surface defects or wear • No strut fractures of grade IV and V	Pass
Accelerated Durability testing: combined loading modes (bending, torsion and axial)	To evaluate the fatigue resistance of Pulsar stents when subjected to the worst case combined SFA fatigue loading modes of axial compression, bending, and torsion. Stents will be tested in the overlapped configuration for a duration equivalent to 10 years walking followed by 10 years stair-climbing.	After 10 million cycles of walking and 650k cycles of stair-climbing: • No serious loss in stent integrity where the implanted stent is considered no longer able to keep the lumen of a vessel open • No significant surface defects or wear • No strut fractures of type IV and V	Pass
MRI safety and compatibility	To evaluate the safety and compatibility of the stents used within magnetic resonance environments and to define label recommendations for scanning conditions.	The test was passed if: • Displacement and torque results met criteria of ASTM F2052 • MRI related heating remained under recommended label conditions (i.e. 6°C for 15 minutes) Artifacts were characterized	Pass
X-ray visibility	To determine the X-ray visibility of the stent system and stent.	Passed test if the stent system and the stent were X-ray visible.	Pass
Crush resistance	To determine the crush resistance of the stent.	Passed test if the mean stent diameter per stent section evaluated prior to and after the test did not deviate more than 5 %. Stent straightness: no visible stent deformation	Pass
Accelerated local compression	To evaluate the fatigue resistance of Pulsar stents when subjected to local compression loading. Stents will be tested in the overlapped configuration for a duration equivalent to 10 years.	After 10 million cycles of local compression: • No serious loss in stent integrity where the implanted stent is considered no longer able to keep the lumen of a vessel open • No strut fractures of type IV and V	Pass
Kink resistance peripheral stents	To characterize the kink resistance of the stent.	The test was for characterization only. This test determines the smallest radius of curvature that the stent can withstand without kinking and recovers its original size and shape.	The smallest radius of curvature was determined.
Dimensional and visual inspection of the final product	To inspect the physical and dimensional properties of the stent system.	Passed test if the delivery system met the design specifications for length, diameter, etc.	Pass

Test	Test Purpose	Acceptance Criteria	Results
Crossing profile	To measure the crossing profile of the stent system.	Passed test if the distal part of the stent system could pass through a ring hole gauge of min. Ø: 0.057" and max. Ø: 0.061".	Pass
Tensile strength catheter	To determine the bond strength of the joints and/or fixed connections of the stent system after pre-conditioning in a simulated use model.	Passed test if the minimum tensile force fulfills the product specification..	Pass
Flexibility and Kink	To demonstrate the flexibility and the resistance to kinking of the stent systems by tracking through a radius gauge over a guide wire.	The delivery system must not kink and must maintain guide wire movement, and the stent must not be damaged, while the system is passed through an anatomically relevant radius curve.	Pass
Adhesive strength of catheter coating	To evaluate the adhesive strength of the hydrophobic surface coating on the outer sheath of the stent system.	Passed if there was no visible indication of delaminating of the coating under 20X and 50X microscopic magnification.	Pass
Delivery, deployment and retraction	To evaluate if the delivery system can reliably deliver the stent to the intended location in a simulated use model.	Passed test if the delivery system delivers the stent to the intended location without damage to the stent	Pass
Release force	To measure the stent release force during deployment. Test is performed in a simulated use model.	Astron Pulsar: Passed test if the maximum release force was ≤ 12 N.	Pass
		Pulsar-18: Passed test if the maximum release force by trigger and secondary release was ≤ 60 N.	Pass
Accuracy of stent placement	To demonstrate that the stent can be accurately placed in a simulated use model.	Passed test if the stent ends were within ± 4 mm of the target deployment area.	Pass
Torque testing	To evaluate the torsional bond/torque strength of the delivery system. Test is performed in a simulated use model.	Passed test if all bonds of the device remained undamaged after multiple rotations with the tip kept in place.	Pass
Package Integrity	To assess the integrity of the device packaging.	The packaging must withstand the hazards of the distribution and the environment and maintain sterility of the device.	Pass

B. Biocompatibility

As per ISO 10993-1: 2009, *Biological Evaluation of Medical Devices*, the stent systems were evaluated for biocompatibility. Tests were conducted separately on sterilized products to support the biocompatibility of (1) the delivery systems and (2) the stents. The delivery systems were categorized as externally communicating devices with limited contact duration (<24 hours) with vascular tissue and circulating blood. The stents were categorized as implant devices with permanent contact (> 30 days) with vascular tissue and circulating blood. Biocompatibility evaluation is summarized in **Table 8**. The results from the biocompatibility evaluation support the overall conclusion that the Astron Pulsar and Pulsar-18 stent systems are biologically safe for their intended use and duration.

Table 8: Biocompatibility Evaluation

Endpoint/Test	Test Method	Stent	Delivery System	Results
Cytotoxicity	ISO MEM Elution Cytotoxicity	✓	✓	Non-cytotoxic
Sensitization	ISO Maximization Sensitization (Guinea Pig Maximization Test, (GPMT))	✓	✓	Non-sensitizing
Irritation	ISO Intracutaneous Reactivity	✓	✓	Non-irritating
Acute Systemic Toxicity	ISO Acute Systemic Toxicity (4 Extracts)	✓	✓	Non-toxic
Pyrogenicity	ISO Material Mediated Rabbit Pyrogen Test	✓	✓	Non-pyrogenic
Implantation	ISO Intramuscular Implantation 14 days	✓[a]	N/A	Non-irritant
Subchronic/Chronic Toxicity/Implantation	Implantation 90 days (combined with subchronic/chronic systemic toxicity)	✓[a]	N/A	Non-toxic
Hemocompatibility	ASTM In vitro Hemolysis (indirect and direct contact)	✓	✓	Non-hemolytic
	ISO In vitro Hemocompatibility	✓	✓	Hemocompatible
	ISO Lee and White Coagulation	✓	✓	Hemocompatible
	Complement Activation C3a & SC5b-9	✓	✓	Non-activator
	In vivo Thrombogenicity	✓[b]	✓[b]	Non-thrombogenic
Ion-release	Immersion up to 63 days in Phosphate Buffered Saline (PBS) at 37°C. Extract analyzed by ICP-MS.	✓	N/A	Ni-ion release below 20 µg / day.
Genotoxicity and Carcinogenicity	Chemical Characterization with Exhaustive extraction in water or saline solution, isopropyl alcohol, and hexane. Extracts analyzed by ICP-MS (saline solution), GC-MS and UPLC-MS. A Toxicological Risk Assessment was performed based on results of the chemical characterization.	✓	N/A	Extractables not a concern for genotoxicity or carcinogenicity.

a-This endpoint was also supported by results from the GLP animal studies, as outlined in Section E below
b-This endpoint was evaluated as part of the GLP animal studies, as outlined in Section E below

C. Sterilization

The Astron Pulsar and Pulsar-18 stent systems are sterilized with ethylene oxide (EO) gas to a sterility assurance level (SAL) of $1x10^{-6}$ in compliance with 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*. The product has also been shown to meet the endotoxin limit of 20 EU/device in FDA 2012 Pyrogen/Endotoxin Guidance.

D. Shelf Life Testing

Performance testing was conducted following 3 years of real-time aging to demonstrate that the device and packaging within product specifications for a labeled shelf-life of 3 years.

E. Animal Studies

Three pre-clinical animal studies were conducted on the Astron Pulsar stent systems to evaluate the acute and chronic *in vivo* response, as further detailed in **Table 9**. The animal studies were conducted using the healthy swine model and were performed in accordance with the Good Laboratory Practice (GLP) for Non-clinical Laboratory Studies requirements outlined in 21 CFR Part 58. The results of the animal studies support the safety and performance of the device.

The purpose of the 28-day and 90-day studies was to evaluate *in vivo* safety of the Astron Pulsar stent systems. This was done by examination of the vascular response (i.e., amount of intimal area, degree of inflammation, thrombosis) and mechanical integrity (evaluation of strut fractures) of overlapped stents in comparison to a marketed control device.

The purpose of the acute thrombogenicity study was to evaluate the risk of acute thrombosis of Astron Pulsar delivery systems in peripheral arteries after an exposure of 1 hour ± 5 minutes in swine, in comparison to the marketed control device.

The results of the Astron Pulsar animal study were leveraged to support the Pulsar-18 stents due to the similarity in the Astron Pulsar and Pulsar-18 stent materials and designs.

Table 9: Summary of animal studies conducted on the peripheral stent systems

28-day safety study			
Number of Animals	**Implant location**	**# Stents**	
5 swine	Femoral arteries* / carotid approach	10 Astron Pulsar (5 overlapping stent pairs) stent Ø: 7mm stent lengths: 80mm + 40mm	10 control stents (5 overlapping stent pairs) stent Ø: 7mm stent lengths: 80mm + 40mm
Testing Summary			
Results support safety and vascular compatibility for Astron Pulsar. No evidence of dissection, thrombosis, or aneurysms was observed by angiography. Devices were easy to position and deploy in the femoral arteries except one control stent. All other device performance parameters were rated as good for the tested devices. At histomorphometry evaluation, Astron Pulsar stents showed a trend of lower lumen narrowing than the control. Intimal area was significantly lower for Astron Pulsar in the single stent sections. Astron Pulsar stents and the control stents showed overall low and similar inflammation and fibrin scores. Endothelialization scores tended to be lower for Astron Pulsar stents than for the control stents but were overall high in both groups. No evidence of thromboembolism was noted in this study. No strut fracture was observed in any of the groups.			
90-day safety study			
Number of Animals	**Implant location**	**# Stents**	
5 swine	External femoral and iliac arteries / carotid approach	8 Astron Pulsar (4 overlapping stent pairs) stent Ø: 7mm stent lengths: 40mm + 40mm	8 control stents (4 overlapping stent pairs) stent Ø: 7mm stent lengths: 40mm + 40mm
Testing Summary			
All device performance parameters were rated as good. No evidence of dissection, thrombosis, or aneurysms was observed angiographically. Astron Pulsar stents tended to show better lumen patency. Histomorphometry analysis demonstrated significantly smaller intimal area in the single stented sections of Astron Pulsar stents and a trend towards lower area stenosis and mean intimal thickness compared to control stents. No significant difference was present in the overlapped segments between Astron Pulsar and control stents. Astron Pulsar stents and control stents showed overall low and similar inflammation and fibrin scores. Endothelialization was complete in both groups. No evidence of thromboembolism was noted in this study and fibrin scores were all very low showing that the healing process was advanced. No strut fracture was observed in any of the groups.			

Acute thrombogenicity study of the delivery system			
Number of Animals	**Implant location**	**# Delivery systems**	
2 swine	Ilio-femoral arteries/ femoral approach	2 Astron Pulsar delivery system usable length: 130 cm	2 control delivery system usable length: 130 cm
Testing Summary			
All devices were inserted in the artery as per protocol with the exception of the control devices which were inserted further than required. However as they were not in contact with the device inserted in the contra-lateral vessel, any potential thrombus that may have been formed could not reach the second device. No deposits of thrombus-like material were observed on any of the devices or the arteries in which they were introduced. Therefore this study revealed no evidence of adverse thrombogenic potential of the devices tested.			

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant conducted a clinical study (BIOFLEX-I) to establish a reasonable assurance of safety and effectiveness of stenting with the Astron Pulsar or Pulsar-18 stent systems for the treatment of atherosclerotic lesions found in the superficial femoral artery (SFA) or proximal popliteal artery (PPA) with reference vessel diameter ranging from 2.5 to 6 mm and lesion length ≤190 mm if de novo or restenotic or ≤100 mm if occluded. The trial was conducted under Investigational Device Exemption (IDE) #G100002. A summary of the clinical trial is presented below.

A. Study Design

Patients were treated between July 19, 2011 and September 15, 2014. The database for this PMA reflected data collected through April 6, 2016 and included 302 patients. There were 38 investigational sites (29 in US, 2 in Canada, and 7 in Europe) that treated patients.

The BIOFLEX-I study was a prospective, non-randomized, multi-center study with two treatment cohorts, iliac lesion treatment and SFA/PPA lesion treatment. Only the SFA and PPA lesion treatment cohort is applicable to the Pulsar stent group, comprised of the Astron Pulsar and Pulsar-18 stents.

Overall, the BIOFLEX I study included 302 subjects enrolled at 38 sites located in the United States, Canada and Europe for the SFA/PPA cohort. Subjects were considered eligible for Astron Pulsar or Pulsar-18 stent implantation if they had de novo or restenotic, atherosclerotic (≤190 mm long) or occlusive (≤100 mm long) lesions in either the SFA or PPA with reference vessel diameters ranging from 2.5 to 6 mm. Evaluable subjects are subjects that underwent an investigational stent implant procedure where the stent system entered the introducer sheath.

The primary safety endpoint for the Pulsar stent group was the freedom from procedure- or stent-related major adverse events (MAEs) at 30 days post-index procedure. The MAE rate included 30-day mortality, clinically-indicated target lesion revascularization (TLR) and index limb amputation. The primary effectiveness endpoint for the Pulsar stent group was the primary patency rate at 12 months (395 days) post-index procedure. Primary patency was defined as freedom from more than 50% restenosis.

For the primary safety endpoint, the null hypothesis was rejected if the lower limit on the one-sided 95% confidence interval calculated using an Exact binomial test on the 30 day freedom from MAE rate exceeded the performance goal (PG) of 88%. For the primary PMA effectiveness endpoint, the null hypothesis was rejected if the lower limit of the one-sided 95% confidence interval calculated using an Exact binomial test on the 12 month patency rate exceeded the PG of 66%.

A final one-sided p-value of 0.048 or less was considered evidence that the primary endpoints had met the associated performance goal. Primary patency in the first 12 months was also summarized in a Kaplan-Meier survival analysis. Secondary endpoints were not tested with formal hypotheses and were reported with descriptive statistics, including means, standard deviations and ranges. Exploratory analyses evaluating the interaction of covariates that may influence the primary effectiveness outcomes was completed. Categorical variables were summarized by the number of observations and the number and percentage of participants falling into each category. Continuous variables were summarized by the number of observations, number of missing values, mean, standard deviation, median, minimum, maximum and interquartile range.

For the SFA/PPA treatment cohort, the sample sizes were based on a Fisher's Exact Test with an overall Type I error of 0.05 (one-sided) and a statistical power of 80%, as used by the VIVA investigators in establishing the recommended performance goals and evaluations. Estimates were calculated with the commercially available software package StatXact (Version 8, Cytel Software). The sample size required to demonstrate that the primary safety endpoint of the freedom from MAEs at 30 days, with an expected rate of 94%, to meet the performance goal of 88% was 159 evaluable study subjects. The sample size required to demonstrate the primary effectiveness endpoint of the primary patency rate at 12 months, with an expected value of 73.2%, and a performance goal minimum of 66% was 266 evaluable study subjects. To adjust for a potential loss to follow-up of 10% due to non-study related reasons (e.g., withdrawal of informed consent or co-morbidities), the estimated number of subjects required to receive a stent in the SFA/PPA cohort was 296 (266/0.9).

Following enrollment/baseline and the index procedure, all evaluable subjects were assessed at 1, 6, and 12 months post-index procedure for the primary endpoint evaluation phase. Additional long-term follow-up assessments were to be completed at 24 and 36 months post-index procedure.

The study utilized independent angiographic and vascular ultrasound core laboratories and an independent clinical events committee (CEC) to evaluate and adjudicate study primary endpoint data. The core laboratories and CEC were composed of experts in their field.

1. <u>Clinical Inclusion and Exclusion Criteria</u>

Subjects enrolled in the BIOFLEX-I SFA/PPA study group were required to meet the

clinical and angiographic inclusion criteria. Potential study subjects who met any of the clinical and angiographic exclusion criteria were not eligible for enrollment in the study. **Table 10** lists the final Inclusion and Exclusion Criteria according to protocol version dated August 19, 2013.

Table 10: Inclusion and Exclusion Criteria

Clinical Inclusion Criteria	1. Age ≥ 18 years 2. Willingness to comply with study follow-up requirements. 3. Candidate for PTA. 4. Life-style limiting claudication or rest pain with an ABI ≤ 0.9 (resting or exercise). Thigh brachial index (TBI) may be used / performed if ABI is inadequate. Written informed consent.
Angiographic Inclusion Criteria	1. One de novo, restenotic or occluded lesion representing a femoropopliteal indication OR 2. Two de novo, restenotic or occluded lesions representing one femoropopliteal indication and one iliac indication on contralateral limbs - (i.e. one lesion per limb). 3. Lesions may be one solid lesion or a series of multiple, smaller lesions to be treated as one lesion. 4. Subjects with bilateral, SFA/PPA disease (i.e. one SFA/PPA lesion per limb) are eligible for enrollment into the study. The target lesion will be selected at the investigator's discretion based on study eligibility criteria. The contralateral SFA/PPA intervention may be performed at the time of the index procedure; however, the use of an investigational treatment is prohibited. If the contralateral SFA/PPA intervention is not performed at the time of the index procedure, the intervention must be performed at least 30 days after the index procedure. The use of an investigational treatment for the subsequent contralateral intervention is also prohibited. 5. Femoropopliteal lesions must be located at least 1 cm distal to the profunda femoris artery and at least 3 cm above the knee joint (radiographic joint space). 6. Lesions must be treatable with a maximum of two stents. 7. Angiographic evidence of ≥70% stenosis or occlusion (operator visual assessment). 8. Lesion length ≤190 mm (if de novo or restenotic) or ≤100 mm (if occluded) 9. Target vessel reference diameter: 2.5 to 6 mm (SFA/PPA) by visual estimate 10. Angiographic evidence of at least one distal vessel runoff to the foot. Patent is defined as <50% stenosis. 11. For SFA/PPA intervention, a significant stenosis (> 70%) or occlusion of an ipsilateral, inflow artery (e.g. aortoiliac, common femoral) must be successfully treated (use of investigational treatment prohibited) just prior to treatment of the target lesion. Successful treatment is defined as no complications and less than 30% residual stenosis following intervention.
Clinical Exclusion Criteria	1. Subjects pregnant or planning to become pregnant during the course of the study 2. Life expectancy of less than one year. 3. Rutherford-Becker category 5 or 6. Subjects with ulcers caused by venous

	disease may be enrolled in the study. 4. Previously stented lesion(s) in the target vessel. 5. Target lesion(s) received previous treatment within 30 days prior to enrollment 6. Prior peripheral vascular bypass surgery involving the target limb(s). 7. Thrombophlebitis or deep vein thrombosis within the past 30 days 8. Known allergy to nitinol (nickel and/or titanium). 9. Participation in any other clinical investigational device or drug study. Subjects may be concurrently enrolled in a post-market study, as long as the post-market study device, drug or protocol does not interfere with the investigational treatment or protocol of this study. 10. Previous stroke or transient ischemic attack within the last three months prior to enrollment. 11. Previous coronary or peripheral bypass surgery (non-target limb) within 30 days prior to enrollment. 12. Intolerance to contrast agents that cannot be medically managed and/or intolerance to anti-platelet, anti-coagulant or thrombolytic medications. 13. Refuses blood transfusions. 14. Any medical condition that in the opinion of the investigator, poses an unacceptable risk for implant of a stent according to the study indications.
Procedure-related / Angiographic Exclusion Criteria	1. INR ≥ 1.6. 2. Concomitant renal failure with serum creatinine level >2.5 mg/dL. 3. Unresolved neutropenia (white blood cell count <3,000/μL) or thrombocytopenia (platelet count <80,000/μL) at the time of the index procedure. 4. Unresolved bleeding disorder (INR ≥ 1.6) at the time of the index procedure. 5. Presence of other ipsilateral, arterial lesions distal to the target lesion requiring treatment within 30 days of the index procedure (either before or after) or at the time of the index procedure. 6. Additional percutaneous interventional procedures (cardiac and/or peripheral) planned within 30 days after the index procedure (either before or after). 7. Presence of a complication following pre-dilation of target lesion. 8. Presence of a target vessel/lesion that is excessively tortuous or calcified or is adjacent to an acute thrombus that is unresponsive to anti-thrombotic therapies. 9. Target lesion is located within an aneurysm or associated with an aneurysm in the vessel segment either proximal or distal to the target lesion. 10. Target lesion requires the use of cutting balloons, atherectomy or ablative devices. Subjects with less than single vessel runoff to the foot.

2. Follow-up Schedule

The required schedule of visits and assessments with the key timepoints for the SFA/PPA cohort of the BIOFLEX-I study are provided in **Table 11**. These visits included baseline evaluation (including subject screening and enrollment), Index procedure, and office

follow up exams. All patients were scheduled to return for follow-up examinations at 1, 6, 12, 24, and 36 months post index procedure. Adverse events and complications were recorded at all visits.

Table 11: Study Visit Assessment Schedule

	Baseline	Index Proc	1-Mo Visit ±7 days	6-Mo Visit ±30 days	12-Mo Visit ±30 days	24-Mo Visit ±60 days	36-Mo Visit ±60 days	Unsch Visit
Informed consent (enrollment)	X							
Subject demographics / risk factors	X							
Blood pressure	X							
ABI measurement	X			X	X			
Subjective claudication status	X			X	X			
Six-minute walk test	X			X	X			
WIQ	X			X	X			
Concomitant medications	X	X	X	X	X	X	X	X
Creatinine measurement		X						
INR measurement		X						
Complete blood count		X						
Angiogram to assess pre- and post-procedure lesion characteristics		X						
Arterial access information		X						
Highest/lowest ACT (heparin only)		X						
Procedure length		X						
Duplex ultrasound			X	X	X			
Stent X-ray					X	X	X	
Adverse event assessment		X	X	X	X	X	X	X

3. Clinical Endpoints

Primary Endpoints

The primary safety endpoint for the Pulsar stent group was the freedom from procedure- or stent-related major adverse events (MAEs) at 30 days post-index procedure. The MAE rate includes all-cause 30-day mortality, clinically-indicated TLR, and index limb amputation. All potential MAEs related to the Astron Pulsar or Pulsar-18 stents were adjudicated as to their relationship to the procedure or stent and whether they were clinically indicated by an independent CEC composed of physicians knowledgeable in the treatment of peripheral artery disease.

The primary effectiveness endpoint for the Pulsar stent group was the primary patency rate at 12 months post-index procedure. Primary patency was defined as freedom from more than 50% restenosis based on the duplex ultrasound (DUS) peak systolic velocity ratio (PSVR), comparing data within the treated segment to the proximal normal segment or based on a clinically-indicated TLR with angiographic evidence of >50% stenosis. A PSVR greater than 2.4 with a final determination of patency made by the core laboratory

was used to diagnose a stenosis greater than 50% in diameter. A clinically-indicated TLR was defined as any repeat, percutaneous intervention or bypass surgery of the target lesion driven by clinical findings (ischemic symptoms). TLR events within 395 days were reviewed and adjudicated by the CEC as to whether the event was clinically-indicated.

The primary endpoints to demonstrate the safety and efficacy of the Pulsar stent group were designed based on prior published literature. The endpoints follow published recommendations by the VIVA physician group on endpoint assessment for clinical trials of femoropopliteal, bare, nitinol stents. A performance goal of 88% freedom from major adverse events at 30 days post-index procedure was specified as the primary safety endpoint based on the literature review and recommendations outlined in the VIVA physicians' manuscript.

A performance goal for the primary effectiveness endpoint primary patency rate of 66% was specified based on the VIVA physicians' manuscript published in 2007, along with published literature from femoro-popliteal stent studies in similar subject populations based on standard lesion lengths. The VIVA manuscript included subjects with lifestyle limiting claudication and lesion lengths from 40 to 150mm, where the recommended expected primary patency rate at 12 months was 66%.

Secondary Endpoints

Secondary effectiveness endpoints for the Pulsar stent group were as follows:

- Determination of the contribution of each individual MAE to the primary safety endpoint
- MAE rate at 12 months
- Stent fracture rate at 12 months
- Primary assisted patency at 12 months
- Secondary patency at 12 months
- Acute procedural success
- 30-day clinical success
- Ankle-brachial indices (ABI) at baseline and 12 months
- Walking Impairment Questionnaire (WIQ) scores at baseline and 12 months
- Six-minute walk distance at baseline and 12 months
- Rates of all adverse events not included in the evaluation of the primary endpoints
- Comparison of primary and secondary endpoint results between standard length lesions (20 mm to 140 mm) and long length lesions (141 mm to 190 mm)
- Comparison of all primary and secondary endpoints between occlusive lesions (100% stenosis) and non-occlusive lesions (70% - 99% stenosis)

The definition for MAEs follows the recommendations given in the FDA guidance issued April 18, 2010, *Guidance for Industry and FDA Staff - Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems*.

There were no formal hypotheses associated with the evaluation of the secondary endpoints.

The primary analyses were performed on an intent-to-treat basis. Secondary analyses using multiple imputation were performed to address the impact of missing data on the primary study endpoints.

All site-reported MAEs or possible MAEs, including deaths, were adjudicated as to their relationship to the procedure or stent by an independent Clinical Events Committee (CEC) composed of physicians knowledgeable in the treatment of Peripheral Artery Disease (PAD).

B. Accountability of PMA Cohort

At the time of database lock, of 302 patients enrolled in the SFA/PPA cohort of the PMA study, 89% (268/302) patients are available for analysis at the completion of the study, the 395-day post-operative visit.

Of the 302 evaluable subjects in the SFA/PPA cohort, 100.0% (302/302) had a stent implanted during the index procedure. Subject status was available for all 302 subjects at 30 days post-index procedure for evaluation of the primary safety endpoint. The primary effectiveness endpoint assessment of patency at 12 months was available for 268 subjects. The 34 subjects that were not included in the primary effectiveness endpoint assessment included 19 subjects that exited prior to 395 days without failure of patency and six (6) subjects that missed the 12-month visit without a subsequent assessment of patency. Subjects that had a study visit without an evaluable duplex ultrasound, due to the assessment being missed (2 subjects), non-diagnostic (2 subjects), or outside of 395 days (5 subjects), were not included in the analysis at 12 months (395 days). Subjects that had a subsequent confirmation of patency on duplex ultrasound or angiography without a revascularization procedure performed after 12 months were included in the primary patency analysis.

C. Study Population Demographics and Baseline Parameters

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

Table provides a summary of the subject demographics and clinical characteristics enrollment/baseline visit for all evaluable subjects in the Pulsar stent group.

Table 12: Pulsar Stent Group Baseline Demographics and Clinical Characteristics

Parameter	Pulsar Evaluable n = 302	
Age in years at enrollment		
Mean ± SD	67.3 ± 10.3	
Range (Min/Max)	41.5 to 95.9	
Gender (n,%)		
Male	205	67.9%
Female	97	32.1%
Race (n,%)		
White	273	90.4%
Black or African American	22	7.3%
Asian	7	2.3%
American Indian or Alaska Native	0	0.0%
Native Hawaiian or other Pacific Islander	0	0.0%
Hispanic Ethnicity (n,%)		
Hispanic	21	7.0%
Non-Hispanic	281	93.0%
General Medical History (n,%)		
Diabetes	123	40.7%
Hypertension*	255	84.4%
Hyperlipidemia*	245	81.1%
Smoking status		
Current	122	40.4%
Within last 5 years	46	15.2%
Never/not within last 5 years	134	44.4%
Cerebrovascular disease*	48	15.9%
History of congestive heart failure*	27	8.9%
History of ischemic heart disease*	124	41.1%
History of coronary revascularization*	110	36.4%
Renal insufficiency*	17	5.6%

***Definitions:** Hypertension and Hyperlipidemia - requiring treatment with a prescription medication; cerebrovascular disease - carotid artery disease and history of stroke or TIA; congestive heart failure - ejection fraction < 40% or heart failure diagnosis; ischemic heart disease - myocardial infarction, angina pectoris, percutaneous or surgical coronary revascularization, positive exercise test or anti-anginal therapy; renal insufficiency - creatinine ≥ 1.5 mg/dL (last measurement prior to baseline).

Table 13 summarizes the baseline lesion characteristics for all evaluable subjects obtained from the baseline angiogram at the index procedure.

Table 13: Pulsar Stent Group Baseline Lesion Characteristics – Core Lab

Lesion Characteristic	Category	Pulsar Stent Group n =302*	
Lesion location (n, %)	Ostial SFA	2	0.7%
	Proximal SFA	38	12.6%
	Mid SFA	156	51.7%
	Distal SFA	99	32.8%
	Proximal popliteal	7	2.3%
Lesion calcification (n, %)	None	82	27.2%
	Moderate	91	30.1%
	Severe	129	42.7%
Lesion length (mm)	Mean ± SD	82.0 ± 46.9	
	Range	9.1 to 228.0	
Pre-deployment minimum lumen diameter (mm)	Mean ± SD	1.0 ± 0.9	
	Range	0 to 3.5	
Post-deployment minimum lumen diameter (mm)	Mean ± SD	4.1 ± 0.7	
	Range	2.2 to 6.2	
Reference vessel diameter (mm)	Mean ± SD	5.0 ± 0.9	
	Range	3.0 to 7.5	
Distal vessel runoff (n, %)	Not Available	32	10.6%
	0 vessel	19	6.3%
	1 vessel	74	24.5%
	2 vessel	93	30.8%
	3 vessel	84	27.8%
TASC II Type (n, %)	Type A	166	55.1%
	Type B	106	35.2%
	Type C	26	8.6%
	Type D	3	1.0%

*Core lab baseline angiography data was not available for one subject. Site reported data was substituted where available.

D. Safety and Effectiveness Result

1. Safety Results

Overall, the Astron Pulsar and Pulsar-18 stent systems demonstrated low observed rate of procedure- or stent-related MAEs. In the 302 intent-to-treat (ITT) subjects, the freedom from MAE rate at 30 days was 99.7% (301/302), representing one procedure-related MAE, with a 95% confidence interval of (98.2%, 100.0%). These results exceeded the defined safety goal of 88% and were statistically significant. The null hypothesis that the Pulsar stent system freedom from MAEs at 30 days was less than or equal to the pre-specified performance goal of 88% was rejected in the intent-to-treat and per protocol populations (both p-values were <0.001, one-sided, Exact binominal test). **Table 14** summarizes the freedom from MAE rate for the Pulsar stent group at 30 days post index procedure. The MAE rates are presented based on CEC adjudicated event data.

Table 14: Pulsar Stent Group Primary Safety Endpoint Results

Category	Rate (%) [95% CI], p-value
Freedom from procedure or device-related MAE	99.7% (301/302) [98.2%, 100.0%], p<0.001

The single MAE event was adjudicated as a cardiovascular death due to fatal coronary heart disease and myocardial infarction and occurred approximately two weeks after a cardiac resynchronization therapy (CRT-D) device was removed, at 27 days post-index procedure. The event was assessed by the CEC to be unrelated to the study device but possibly related to the procedure. No stent-related MAEs were reported during the 30-day period. No clinically-indicated TLR events or study limb amputations occurred within the 30-day period.

The analysis of safety was based on the ITT cohort of 302 patients/procedures, etc. available for the 12 month evaluation (up to 395 days). Adverse effects are reported in **Table 15**.

No unanticipated adverse device effects (UADE) have been reported during the course of the BIOFLEX-I study. There have been 1793 adverse events, including 729 serious adverse events reported for patients with a mean study follow-up duration of 2.3 ± 0.7 years/ patient.

Serious Adverse Events (SAEs) occurring within 12 months (395 days) of the procedure are summarized in **Table 65** below listed in order of category event frequency for SAEs. Further details of sub-categories occurring in at least five subjects were also included. Overall, 59.6% (180/302) of subjects experienced 450 SAEs during the 395 day follow-up period.

Table 65: Serious Adverse Events Through 12 Months (395 Days)

Category*	Number of Evaluable Subjects with Event	Percentage of Evaluable Subjects n=302
Vascular event Total	**79/302**	**26.2%**
Carotid stenosis	7/302	2.3%
Hematoma - Non-index procedure related	5/302	1.7%
Planned PVI in contralateral extremity	10/302	3.3%
Stenosis or occlusion in contralateral extremity	43/302	14.2%
Stenosis or occlusion in target extremity outside of stent segment	21/302	7.0%
Cardiovascular Total	**59/302**	**19.5%**
Angina	7/302	2.3%
Atrial arrhythmia	5/302	1.7%
Cardiac arrest	5/302	1.7%
Chest pain	6/302	2.0%
Coronary artery disease	14/302	4.6%

Category*	Number of Evaluable Subjects with Event	Percentage of Evaluable Subjects n=302
Hypotension	5/302	1.7%
Myocardial infarction	8/302	2.6%
Worsening heart failure	8/302	2.6%
Stent event Total	**50/302**	**16.6%**
Stenosis or occlusion of target lesion within stent segment	49/302	16.2%
Infection Total	**28/302**	**9.3%**
Pneumonia	8/302	2.6%
Musculoskeletal Total	**19/302**	**6.3%**
Musculoskeletal pain	10/302	3.3%
Gastrointestinal Total	**16/302**	**5.3%**
Bleeding	5/302	1.7%
Neurological/Nervous system Total	**12/302**	**4.0%**
Cancer Total	**10/302**	**3.3%**
Procedure-related event Total	**9/302**	**3.0%**
Endocrine Total	**8/302**	**2.6%**
Other medical event Total	**8/302**	**2.6%**
Renal Total	**8/302**	**2.6%**
Respiratory Total	**6/302**	**2.0%**
Genitourinary Total	**5/302**	**1.7%**
Hematological event Total	**5/302**	**1.7%**
Anemia	5/302	1.7%
Ophthalmological event Total	**3/302**	**1.0%**
Electrolyte Imbalance Total	**2/302**	**0.7%**
Dermatological Total	**1/302**	**0.3%**
Total	**180/302**	**59.6%**

* Subcategory included in cases with 5 of more subjects with event or category

The most prevalent SAEs observed were vascular events either for the contralateral extremity and/or the target extremity outside of the stented segment, followed by cardiovascular disease events and stent events.

Procedure or device related events occurring at a rate of > 1% included symptoms common in subjects with PAD such as Edema (2.3%), Leg pain and/or cramping (1.3%) and Musculoskeletal pain (1.0%). Procedure-related complications such as Hematoma (4.3%), Vessel dissection during PTA (3.0%) and Pseudoaneurysm (1.0%) occurred at expected rates. Stent events through 395 days such as Stenosis or occlusion of target lesion within stent segment (23.5%) and site-reported (unconfirmed) Stent fracture (12.6%), as well as Vascular events such as Stenosis or occlusion in target extremity outside of stent segment (2.6%), Stenosis or occlusion in contralateral extremity (2.6%) and Thrombosis (1.3%) were also reported.

The frequency and nature of adverse events observed in the BIOFLEX-I trial were similar to those observed for other self-expanding bare metal nitinol SFA/PPA stents approved in the United States. No adverse events led to a design modification during the clinical study nor have led to a change in the instructions for use.

No adverse events led to a design modification during the clinical study nor have led to a change in the insructions for use.

2. Effectiveness Results

The primary patency rate at 395 days was 66.8% (179/268, 95% confidence interval [60.8%, 72.4%]. While the point estimate of the effectiveness rate was greater than the pre-specified performance goal of 66%, the null hypothesis for the primary effectiveness endpoint was not rejected as the lower 95% confidence bound of 60.8% was below the pre-specified performance goal of 66%. Primary endpoint effectiveness results are summarized in **Table 76**.

Table 76: Pulsar Stent Group Primary Effectiveness Endpoint Results – ITT Group - All Lesion Lengths

Category	Rate (%) [95% CI]
Primary patency rate (0 to 395 days)	66.8% (179/268) [60.8%, 72.4%]

The **Figure 3** and **Table 87** show the Kaplan Meier (KM) analysis for primary patency through 395 Days censoring at the last patency confirmation for each subject with missing data.

Figure 3: Kaplan-Meier Analysis for Primary Patency at 395 Days - ITT

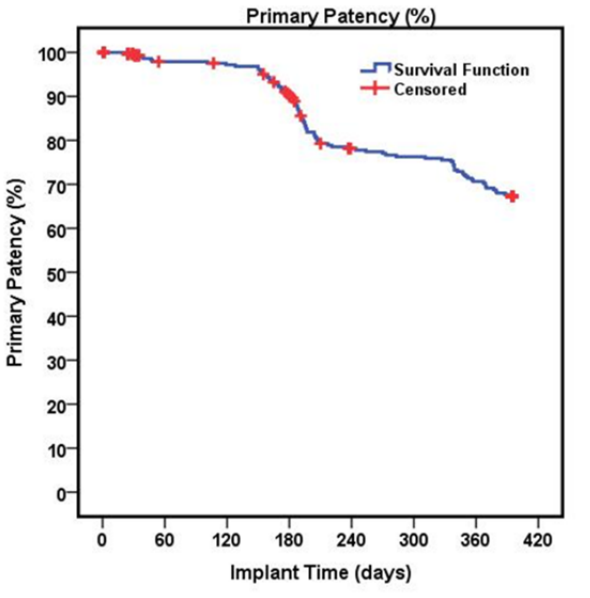


Table 87: Tabulated Kaplan-Meier Analysis for Primary Patency at 395 Days - ITT

Time from Implant (Days)	Primary Patency Rate	Standard Error	95% Confidence Interval	Events	At Risk
0 days	100.0%	0	---	0	302
30 days	99.7%	0.3%	[99.1%, 100.0%]	1	286
90 days	97.9%	0.9%	[96.2%, 99.6%]	6	275
180 days	90.4%	1.8%	[86.9%, 93.9%]	27	249
270 days	77.0%	2.6%	[72.0%, 82.0%]	63	206
365 days	70.6%	2.8%	[65.1%, 76.1%]	80	188
395 days	67.3%	2.9%	[61.7%, 72.9%]	89	179

The majority of primary patency failures were solely due to duplex ultrasound (DUS) findings. There were 54 subjects (out of 89 subjects, 60.7%) who did not have a reported intervention prior to 395 days, but had a loss of primary patency solely based on the core lab assessment of the duplex ultrasound at or prior to 395 days. Of these subjects, 51 had subjective claudication status data available at the study visit corresponding to the DUS patency loss. More than half of these subjects (28/51 subjects, 54.9%) had either no or mild claudication status based on the site assessment of the subject at the time of patency loss. In summary, loss of patency on DUS alone was not always accompanied with clinical symptoms or intervention. The prevalence of DUS patency loss without significant clinical symptoms was further supported by the low rate of TLR intervention. However, a post-hoc analysis using these considerations would also fail to result in the rejection of the null hypothesis for the primary effectiveness endpoint since the lower 95% confidence interval of 61.7% at 395 days is numerically lower than the pre-specified performance goal of 66%.

3. Secondary Endpoints

Secondary endpoints were reported based on the number of subjects assessed at the specified time pointsKey secondary endpoint safety results for the ITT population are summarized in Error! Reference source not found.**8**.

Key Secondary Safety Endpoint Results

Table 98: Secondary Endpoint Safety Results

Secondary Endpoints, Safety	
1. MAE rate at 12-months % (n/n), [95%CI]	12.7% (36/283) [9.1%, 17.2%]
2. 30-day mortality % (n/n)	0.4% (1/283)
3. TLR (clinically-indicated) % (n/n)	12.4% (35/283)
4. Index limb amputation % (n/n)	0.4% (1/283)
5. Stent fracture at 12 months % (n/n stents)	3.1% (9/293)
6. Grade I % (n/n)	0.0% (0/293)
7. Grade II % (n/n)	1.0% (3/293)
8. Grade III % (n/n)	0.7% (2/293)
9. Grade IV % (n/n)	1.4% (4/293)
10. Grade V % (n/n)	0.0% (0/293)

The overall procedure- or stent- related MAE rate at 12 months was 12.7% (36/283 subjects) in the ITT population. The primary driver of the overall rate was the rate of clinically-driven TLR, which was 12.4% (35/283 subjects) in the ITT population. One subject death (within 30 days) and one instance of subject index limb amputation (in subject that had a prior TLR) were reported within 395 days that were procedure- or stent-related and included in the overall MAE rate.

The stent integrity assessment observed a confirmed stent fracture rate of 3.1% in stents (9/293 stents) based on core lab assessment and adjustment for stents with baseline stent deformation occurring during the index procedure. The presence of fractures did not adversely affect patients based on the 12-month MAE rates and their components, nor was it identified as correlating with loss of patency. The rate of stent fracture was within the range of stent fracture rates reported for other self-expanding nitinol stents and provides reasonable assurance of the safety of the Astron Pulsar and Pulsar-18 stents.

The 12-month MAE and stent integrity rates were comparable with rates observed in clinical trials evaluating similar nitinol self-expanding peripheral stents in the SFA/PPA.

Key Secondary Effectiveness Endpoint Results

The analysis of effectiveness was based on the ITT cohort of 302 subjects implanted and as assessed at the specified time points below. In addition to the primary effectiveness endpoint results, secondary effectiveness endpoint outcome measures were reported based on the number of subjects assessed at the specified time points and are included in **Table 109**.

Table 109: Secondary Endpoint Effectiveness Results

Secondary Endpoints, Effectiveness	
1. Primary assisted patency rate at 12 months[a, b] % (n/n)	98.9% (272/275)
2. Subjects free from repeat endovascular procedure on study limb outside of study lesion % (n/n)	98.9% (272/275)
3. Subjects free from repeat surgical procedure on study limb outside of study lesion % (n/n)	100% (275/275)
4. Secondary patency rate at 12 months[b, c] % (n/n),	98.2% (271/276)
5. Subjects free from bypass on study limb % (n/n)	99.6% (275/276)
6. Subjects free from amputation on study limb % (n/n)	98.6% (272/276)
7. Acute procedural success [b, d] % (n/n)	98.0% (296/302)
8. 30-day clinical success [b, e] % (n/n)	97.7% (294/301)
9. ABI Change from Baseline to 12-month, Paired Data (Mean ± SD), n=266	0.22 ± 0.21
10. Six Minute Walk Test Change from Baseline to 12 months Paired Data (Mean feet ± SD), n=247	213.6 ± 412.7
11. WIQ Score Changes from Baseline to 12 months Paired Data	
12. WIQ PAD Specific Score (Mean ± SD), n=265	39.1 ± 40.4
13. WIQ Walking Distance Score (Mean ± SD), n=264	32.6 ± 37.4
14. WIQ Walking Speed Score (Mean ± SD), n=263	18.3 ± 28.1
15. WIQ Stair Climbing Score (Mean ± SD), n=255	20.1 ± 36.0

a) Freedom from a repeat procedure (endovascular or surgical) outside of the initially treated lesion to maintain patency of the target vessel. The treated lesion includes the stented segment plus 5 mm proximal and distal to the

stent.

b) One subject death prior to 30 days was included in this count.
c) Freedom from treated lesion abandonment (bypass) or amputation on the target limb.
d) Completion of the procedure and the stented lesion having less than 30% residual stenosis determined by angiography immediately after stent placement and no MAEs before hospital discharge.
e) Completion of the procedure and the stented lesion having less than 30% residual stenosis determined by angiography immediately after stent placement and no MAEs within 30 days of the index procedure.

The secondary endpoints evaluating the effectiveness of the Pulsar stent group demonstrated similar results to those reported for other similar devices. The primary assisted patency (freedom from remote TVR) at 12-months in the ITT population was 98.9% (272/275 subjects) and the secondary patency rate at 12 months was 98.2% (271/276 subjects).

The overall rate of acute procedural success was 98.0% (296/302 subjects), with an observed 30-day Clinical Success rate of 97.7% (294/301 subjects). The acute procedural success rate and 30-day Clinical Success rate both further support the safety and effectiveness of the Astron Pulsar and Pulsar-18 delivery systems and stents.

A mean increase in subjects' ABI score of 0.22 ± 0.21 between paired baseline and 12-month visits was observed. The majority of subjects (85.0%, 226/266 subjects) showed improvement in their ABI value. The overall mean increase in ABI may correlate with improved lower extremity arterial perfusion post-procedure in the Pulsar stent group, which may be clinically meaningful for patients suffering from PAD.
Clinical measures of a mean six-minute walk distance increased by 213.6 ± 412.7 feet between paired baseline and the 12-month visit. The majority of subjects (70.9%, 175/247 subjects) showed improvement in their six-minute walk distance. Increased walking distances may be clinically meaningful in individual subjects and in general for patients with PAD. Furthermore, subjects demonstrated improvement in their WIQ scores from baseline to 12-month post-index procedure, with 74.0% showing improvement in their WIQ PAD Specific Score (196/265 subjects, range 25 to 100, mean of 58), 76.9% showing improvement in their WIQ Walking Distance Score (203/264 subjects, range 1 to 100, mean of 46), 72.2% showing improvement in their WIQ Walking Speed Score (190/263 subjects, range 2 to 94, mean of 30) and 63.9% showing improvement in their WIQ Stair Climbing Score (163/255 subjects, range 4 to 96, mean of 40). Improvement in WIQ may correlate with improvement in PAD symptoms and increased mobility.

4. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes:

- The heterogeneity of the primary endpoints between males and females was tested with a Fisher's Exact Test. An unadjusted p-value of 0.05 or less was considered evidence of a possible gender difference. The comparison of the primary endpoint MAE rates in subjects with available data was not significant. The only secondary endpoint that reached a statistically significant difference was the MAE rate at 12 months (p = 0.031), with a MAE rate observed for male subjects of 9.6% (19/197) and a MAE rate for female subjects of 19.8% (17/86). The female subjects that experienced a TLR at 12-months had higher rates of occlusive and longer lesion

lengths, as well as proportion of smaller vessels than observed in the primary female cohort and overall study population. This sub-group analysis was not statistical powered, and therefore, no conclusions can be made.

- The use of overlapping stents was evaluated in regards to the primary endpoints. There was a numerical difference in 12-month primary patency rates between overlapped stents of 56.0% (28/50) compared to 69.3% (151/218) in single stents. The results were not statistically significant, and no significant difference was noted for the primary safety endpoint.
- Race, diabetes, hypertension, hyperlipidemia, smoking status, cerebrovascular disease, congestive heart failure, ischemic heart disease, and renal insufficiency were all assessed for association with primary patency at 12 months. No significant association was found for any of the covariates.
- Occlusive and non-occlusive lesions had similar primary patency rates, although numerically higher in the non-occlusive lesions with 59.8% (49/82) in occlusive lesions and 69.9% (130/186) in non-occlusive lesions ($p = 0.122$).
- Observed primary patency rate was numerically higher in standard lesion lengths ($\leq$ 140 mm), although the difference between standard lesion lengths ($\leq$ 140 mm) of 68.5% (161/235) and long lesion lengths (> 140 mm) of 54.5% (18/33) did not reach statistical significance ($p=0.118$).

5. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population. Peripheral artery disease is not typically found in pediatric populations. The Astron Pulsar and Pulsar 18 stent systems are not indicated for use in pediatric patients. The BIOFLEX I study did not evaluate safety and effectiveness in the pediatric population.

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 204 investigators of which none were full-time or part-time employees of the sponsor and three (3) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 3
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. 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(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The BIOFLEX-I multi-center clinical study evaluated the safety and effectiveness of the Astron Pulsar and Pulsar-18 stent systems in the treatment of subjects with atherosclerotic disease of the SFA and PPA. The primary effectiveness endpoint was defined as stent patency at 12 months as evidenced by PSVR<2.4 from DUS. The observed primary effectiveness endpoint of primary patency rate was numerically above the performance goal value of 66% (66.8%, 179/268 subjects); however the 95% lower confidence bound (95% CI [60.8%, 72.4%]) of the pre-specified endpoint was not met. Therefore, the null hypothesis could not be rejected. The Kaplan Meier analysis and imputed analysis to account for missing data at 395 days supported primary patency rates similar to the observed rate, with results of 67.3%, 95% CI [61.7%, 72.9%] and 66.8%, respectively. The trial included longer length lesions (>140 mm) without adjustment of the performance goal which was derived from standard length trials. Patency loss on DUS did not always translate into TLR events, as the primary mode of patency loss was DUS alone, with an overall 12.4% rate of TLR at 12-months. TLR was defined as any repeat, percutaneous intervention or bypass surgery of the target lesion drive by clinical findings (ischemic symptoms). Some of the secondary effectiveness endpoints included primary assisted patency rate at 12 months, subjects free from repeat endovascular procedure on study limb outside of study lesion, and 30-day clinical success.

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 above. In the BIOFLEX-I study, the performance goal assessment (primary safety endpoint) for the Pulsar stent group (Astron Pulsar and Pulsar-18 stents) was the freedom from a composite rate of procedure- or stent-related MAEs at 30 days post-index procedure. The MAE rate included 30-day mortality, along with rates of clinically-indicated TLR and index limb amputation. Overall, in the 302 Intention-to-Treat (ITT) subjects, the freedom from procedure- or stent-related MAE rate was 99.7% (301/302 subjects), with a 95%

confidence interval of (98.2%, 100.0%), which was higher than the performance goal of 88% ($p<0.001$).

C. Benefit-Risk Determination

The probable benefits of the devices are based on the data collected in the clinical study conducted to support PMA approval as described above. The results of the BIOFLEX-I study show positive clinical outcomes in terms of the primary and secondary endpoints (benefits) and outweigh risks when used as intended according to the Instructions for Use, as determined by the product risk analysis.

Additional factors to be considered in determining probable risks and benefits for the Astron Pulsar and Pulsar-18 stent systems 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 the long term adverse event rates. The benefits and risks are expected to be similar to currently marketed devices.
- 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. Furthermore, these are the only SFA stent systems that are compatible with 4Fr sheaths.
- 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.

Patient Perspectives: This submission did not include specific information on patient perspectives for this device.

Given the available information above, the data support that the probable benefits outweigh the probable risks for using the device to improve luminal diameter in symptomatic patients with de novo, restenotic, or occlusive lesions or occlusions of the SFA and/or PPA.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. 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 and PPA lesions. Overall, the results from non-clinical and clinical evaluations demonstrate that the Astron Pulsar and Pulsar-18 stent systems provide reasonable assurance of safety and effectiveness when used as indicated and according to the Instructions for Use.

XIII. CDRH DECISION

CDRH issued an approval order on March 23, 2017.

The final conditions of approval cited in the approval order are described below.

ODE Lead PMA Post-Approval Study: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. This study must be conducted per protocol BIOFLEX-I (dated December 5, 2016) and the Post-Approval Study Analysis Plan (provided in P160025). This study is a prospective, non-randomized, multi-center follow-up of the BIOFLEX-I pivotal study (G100002). It will evaluate the long term safety and effectiveness of the Biotronik Astron Pulsar and Pulsar-18 Stent Systems. All 77 remaining subjects (203 subjects have completed or discontinued the study) of the 280 original study subjects enrolled in the BIOFLEX-I study active at the end of the 12-month evaluation from 38 investigational sites will continue to be followed annually through 36 months. The primary endpoint to be assessed is freedom from a composite of clinically-driven target lesion revascularization (TLR) and index limb amputation at 36 months, as defined by the protocol. The secondary endpoints to be assessed include the following:

- Freedom from a composite of clinically-driven TLR and index limb amputation at 24 months.
- Major adverse event (MAE) rate (30-day mortality, clinically-driven TLR, and index limb amputation) and their components at 24 months.
- MAE rate (30-day mortality, clinically-driven TLR, and index limb amputation) and their components at 36 months.
- Target lesion revascularization (TLR) rate at 24 months.
- Target lesion revascularization (TLR) rate at 36 months.
- Stent fracture rate at 24 months.
- Stent fracture rate at 36 months.
- Adverse events rates at 36 months.

The applicant's manufacturing facilities have 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