SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Endovascular Graft

Device Trade Name: COVERA™ Vascular Covered Stent

Device Procode: PFV

Applicant's Name and Address: Bard Peripheral Vascular, Inc. (BPV)
1625 West 3rd Street
Tempe, AZ 85281
Registration number: 2020394

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170042

Date of FDA Notice of Approval: July 30, 2018

II. INDICATIONS FOR USE

The COVERA™ Vascular Covered Stent is indicated for use in the treatment of stenoses at the venous anastomosis of ePTFE or other synthetic arterio-venous (AV) access grafts.

III. CONTRAINDICATIONS

There are no known contraindications for the COVERA™ Vascular Covered Stent.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the COVERA™ Vascular Covered Stent labeling.

V. DEVICE DESCRIPTION

The COVERA™ Vascular Covered Stent is a self-expanding covered stent pre-mounted on a delivery system.

Description of Covered Stent

The COVERA™ Vascular Covered Stent is a flexible, self-expanding endoprosthesis comprised of ePTFE encapsulating a nitinol (nickel-titanium) stent framework. The ePTFE on the inner lumen of the covered stent (blood contacting surface) is carbon impregnated.

The COVERA™ Vascular Covered Stent is available in a diameter range of 6 to 10 mm and a length range of 30 to 100mm.

The COVERA™ Vascular Covered Stent is available in a straight (Figure 1) and a flared configuration (Figure 2). The distal (outflow) end of the flared configuration device is approximately 3 mm larger in diameter than the body and begins approximately 15 mm from the distal end of the device. Radiopaque ePTFE encapsulated tantalum markers are evenly distributed around the circumference of the proximal and distal ends of the covered stent.

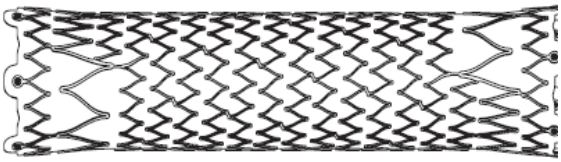

Figure 1: Straight Configuration

Figure 2: Flared Configuration

Description of Delivery System

The delivery system is illustrated in Figure 3. The covered stent is premounted on the delivery system and compressed between the inner catheter and the covered stent delivery sheath at the distal end of the delivery system. The COVERA™ Vascular Covered Stent is an over-the-wire delivery system. The delivery system is compatible with 0.035 inch guidewires, and compatible with 8F and 9F introducer sheaths. The delivery system is available in working lengths of 80 cm and 120 cm.

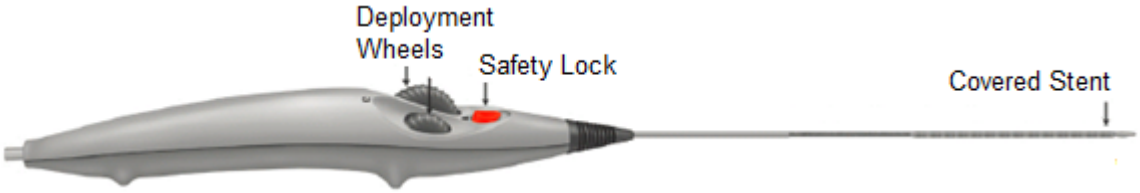

Figure 3: COVERA™ Vascular Covered Stent Delivery System

Retraction of the distal catheter and deployment of the covered stent is initiated by rotating the large wheel on the handle. The large deployment wheel is used for the initiation of deployment and a slower deployment rate whereas the small deployment wheel may be used for faster deployment after initiation. A red safety lock on the handle prevents premature release of the covered stent. Prior to covered stent deployment, the safety lock must be retracted from the locked position into the unlocked position.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of stenoses at the venous anastomosis of ePTFE or other synthetic AV access grafts. Alternative procedures include use of percutaneous transluminal angioplasty (PTA), other commercially available stents

or stent grafts, creation of new fistulas/grafts, different methods for dialysis (peritoneal, catheter placement), and surgical revisions. 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 COVERA™ Vascular Covered Stent has been commercially available outside the United States since October 2015. It was first marketed in the European Union, and additionally has been commercialized in Israel, Saudi Arabia, Iran, Argentina, Bahrain, United Arab Emirates, Kuwait, Qatar, and Oman.

The device has never been withdrawn from any market for any reason related to its safety or effectiveness.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Thrombotic occlusion
- Restenosis requiring reintervention
- Pseudoaneurysm
- Vessel rupture
- Dissection
- Extravasation
- Perforation
- Pain
- Infection
- Hemorrhage
- Hematoma
- Arm or hand edema
- Steal Syndrome
- Congestive heart failure
- Venous spasm
- Numbness
- Cerebrovascular accident
- Allergic reaction
- Rash
- Reaction to contrast
- Fever
- Sepsis
- Prolonged bleeding
- Ventricular fibrillation
- Face or neck edema

- Bleeding at access site
- Hemoptysis
- Death
- Covered stent: misplacement, migration, embolism, fracture, kinking, and insufficient covered stent expansion
- Delivery system: bond joint failures, detachment of parts, incompatibility with accessory devices, premature deployment, inaccurate deployment, failure to deploy, high deployment forces, delivery system kinking, poor visibility under fluoroscopy, inability to track to target location, and blood leakage from delivery system

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

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Biocompatibility

Biocompatibility testing was performed in accordance with applicable sections of ISO 10993, "Biological evaluation of medical devices – Part 1: Evaluation and testing" and the FDA guidance document, "Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems." Test samples were manufactured in accordance with standard operating procedures, subjected to two cycles of ethylene oxide sterilization, and are representative of finished product.

Components of the covered stent and delivery system were categorized per ISO 10993-1 based on the intended duration and contact with or within the body. The covered stent was categorized as an implant device with permanent exposure to circulating blood (> 30 days), and the delivery system was categorized as an externally communicating device with limited (≤ 24 hours) exposure to circulating blood.

Table 1 provides a listing of the biocompatibility tests performed for both the implant and delivery system along with corresponding results. All studies performed were in strict compliance with the Good Laboratory Practice (GLP) regulations (21 CFR Part 58).

Table 1: Implant & Delivery System Biocompatibility Testing

Test Name	Test Description	Implant	Delivery System	Results
Cytotoxicity	L929 MEM Elution Test – ISO	X	X	Non-toxic
Sensitization	Kligman Maximization – ISO	X	X	Non-sensitizing
Irritation	Intracutaneous Injection Test – ISO	X	X	Non-irritating
Acute Systemic Toxicity	In Vivo Toxicity Study	X*	N/A	Non-toxic
	Systemic Injection Test – ISO	N/A	X	Non-toxic
Material Mediated Pyrogenicity	Rabbit Pyrogen Test (Material Mediated) – ISO	X	X	Non-pyrogenic
Subchronic Toxicity	In Vivo Toxicity Study	X*	N/A	Non-toxic
Implantation	In Vivo Implantation Study	X*	N/A	Non-toxic
Hemocompatibility	Hemolysis – ASTM Direct and Indirect Contact	X	X	Non-hemolytic
	Complement Activation Assay – ISO	X	X	Not a

	Direct Contact			complement activator
	In Vivo Thrombogenicity Study	X*	X*	Non-thrombogenic

*Evaluated as part of the animal study outlined in Section D.

Chemical characterization and toxicological risk assessment were used to assess the endpoints of chronic systemic toxicity, genotoxicity, and carcinogenicity for the implant.

B. Laboratory Studies

In vitro bench testing was conducted as part of the design verification and validation to support the safety and effectiveness of the COVERA™ Vascular Covered Stent. This testing was conducted based on recommendations from risk assessments with consideration of FDA and industry-recognized standards. The bench test results are summarized in Table 2. The testing presented in Table 2 below includes results from both baseline (T=0) and accelerated aged units.

Table 2: Summary of *In Vitro* Bench Testing

Test	Purpose	Acceptance Criteria	Results
IMPLANT			
Material Composition	To verify the chemical composition of the implant.	Material composition must comply with ASTM F2633, ASTM F2063, and ASTM B365.	The stent materials conform to implant material standards.
Shape Memory and Superelasticity of Intravascular Stents	To verify the transition temperature of the nitinol implant.	The A_f temperature for the nitinol implant, measured in accordance with ASTM F2082, must permit the covered stent to expand to its intended shape and size at body temperature. Therefore, the A_f temperature must be below body temperature.	PASS
Stent Corrosion Resistance	To verify the implant's ability to resist corrosion (pitting).	Implants must be evaluated for pitting corrosion following 10 years of pulsatile accelerated durability testing at physiological loads. The pitting corrosion evaluations, performed in accordance with ASTM F2129, must yield a breakdown potential greater than or equal to 300mV.	PASS
Dimensional Verification*	To verify that critical implant dimensions (implant diameter and length in the unconstrained expanded condition) are met.	6, 7, 8, 9, and 10 mm in implant outer diameter Flared configuration only: 9, 10, 11, and 12 mm in implant outflow outer diameter 30, 40, 60, 80, and 100 mm implant length	All measurements pass the applicable requirement for implant dimensions.
Foreshortening*	To quantify the percent decrease in length of the implant from between its crimped and deployed states.	Stent foreshortening must be reported in the labeling. Testing was for characterization only.	Covered stent length change ranges from -2% to 3% depending upon covered stent diameter selection.

Test	Purpose	Acceptance Criteria	Results
Stent Integrity*	To evaluate the integrity of the implant post-deployment and verify the implant shows no defects that would render it unsuitable for the intended use.	Implants must maintain structural integrity (e.g. no holes, tears and splitting through ePTFE, no ePTFE or strut protrusion into the inner lumen) upon visual inspection post deployment.	PASS
Radial Outward Force*	To characterize the force exerted by the implant as a function of implant diameter.	Chronic Outward Force (COF) ≤ 0.15 N/mm at maximum recommended oversizing. Radial Resistive Force (RRF) ≥ 0.06 N/mm at minimum recommended oversizing.	PASS
Mechanical Properties	For characterization purposes only to determine uniaxial tensile strength and fatigue strength to support Stress/Strain and Fatigue Analyses.		
Stress/Strain Analysis	For characterization purposes only to determine maximum stresses and strains within the device to support Fatigue Analysis.		
Fatigue Analysis	For characterization purposes only to assess durability of the device to support Accelerated Durability Testing.		
Accelerated Durability Testing	To evaluate the durability (maintenance of structural integrity) of the implant under arterial pulsatile fatigue conditions simulating 10 years of use.	Implants must withstand an equivalent of 10 years of accelerated durability testing. Upon completion of testing, implants must maintain structural integrity following fatigue evaluation per ISO 25539-1.	PASS The tested implants showed no strut fractures, no covering disruption and no strut protrusion into the lumen after 10 years of accelerated durability testing.
Particulate Evaluation*	Characterize particulate following implant expansion to evaluate integrity of the covered stent.	Implants must be visually inspected for implant integrity (refer also to Stent Integrity test). Delivery system must have no dislodged parts or entanglement during withdrawal.	PASS
MRI Safety and Compatibility	To evaluate MRI safety and compatibility.	For characterization purposes only, the conditions under which the device can be safely scanned are provided in the product labeling.	The implant is MR Conditional at a field strength of 1.5 T and 3.0 T.
Radiopacity	To evaluate the radiopacity of the implant under fluoroscopy.	The visibility of the implant under fluoroscopy during and after deployment as well as after placement must be rated as clinically acceptable by physician experts in an animal model.	PASS
Crush Resistance/ Local Compression*	To evaluate the ability of the implant to resist permanent deformation following collapse.	After local compression and compression between parallel plates, the stent graft must maintain structural integrity (refer also to Stent Integrity test) and return to its original shape.	PASS

Test	Purpose	Acceptance Criteria	Results
Kink Resistance*	To evaluate the implant's flexibility in its deployed configuration.	Resistance to kink must be evaluated in an anatomically relevant landing zone, applicable to the intended indication. The covered stent must be kink resistant and the radius of the stent must be characterized at the point at which the stent starts to kink.	PASS No kinking was observed at 15 mm radius. In addition, of the 209 hand deployed covered stents, all were found to conform to the wall of the worst-case anatomical model with no kinking observed.
Porosity	To characterize porosity of the stent covering.	The internodal distance (IND) of the implant covering was evaluated and required to be within a specified range (10-40 μm).	PASS
Migration Resistance*	To verify that the covered stent adequately resists displacement during use.	The force required to displace the covered stent must be ≥ 0.025 N/mm.	PASS
Strength of Stent/ Attachment System to Graft Bond	To verify that the force required to separate the two bonded ePTFE layers (implant encapsulation) is acceptable for the indication.	Bond peel strength of the covered stent encapsulation must be sufficient to prevent delamination associated with forces experienced by the device after simulated use in a clinically relevant anatomical model.	PASS
DELIVERY SYSTEM			
Dimensional Verification*	To verify that the delivery system meets dimensional criteria pre- and post-deployment.	80 and 120 cm delivery system working length. Delivery system profile must be able to pass through an 8F or 9F ring gage over its entire working length pre deployment. Delivery system inner diameter must be compatible with an 0.035" guidewire.	All measurements pass the applicable requirement for delivery system dimensions.

Test	Purpose	Acceptance Criteria	Results
Delivery, Deployment, and Retraction*	To ensure that the delivery system meets it pre-determined acceptance criteria with respect to its delivery, deployment, and retraction in a simulated use environment.	The endovascular system must be advanced and retracted through a clinically relevant anatomical model, and implants must be deployed into a clinically relevant landing zone. The deployment force must be rated as acceptable after simulated use in a clinically relevant anatomical model. Deployment accuracy must be equivalent to a clinically acceptable device ($\leq \pm$ 3 mm). System must also withdraw from model and pass visual inspection post deployment (i.e. must not exhibit missing components/fragments). Test conditions must simulate the physiological environment of the intended indication. Implants must be evaluated to various deployment configurations and with accessory devices representative of those clinically used for the procedure.	PASS
Catheter Bond Strength including Tip Pull Test*	To determine the bond strength of delivery system joints and verify that the strength of the bond joints are adequate for the intended use.	The delivery system must have sufficient strength to maintain its function under normal use as required per ISO 25539-1. Tension: J1 (8F) > 35.7 N J1 (9F) > 31.5 N J2, J10 > 46.5 N J3, J4, J5, J7, J8 > 6.3 N J6 > 35 N Compression: J3 (8F) > 35.7 N J3 (9F) > 31.5 N J8 > 46.5 N Torsion: J9 > 5 Ncm J11 > 14.9 Ncm	PASS
Flexibility and Kink Test*	Characterize the ability of the delivery system to withstand flexural forces typical of clinical use.	The system must not kink during delivery, deployment, or withdrawal to and from the target deployment site in a clinically relevant anatomical model. The radius of the endovascular system must be characterized at the point at which the endovascular system starts to kink.	PASS The smallest kink radius was found to be 19.5 mm.

Test	Purpose	Acceptance Criteria	Results
Torque Strength*	To determine the delivery system strength under torsional forces typical of clinical use.	The delivery system must remain functional after clockwise and counter-clockwise rotation with fixed tip while in a clinically relevant anatomical model (refer also to Catheter Bond Strength).	PASS
Force to Deploy*	To determine the deployment force at the proximal catheter of the delivery system and the thumbwheel and verify that the force required to deploy are adequate for the intended use.	The delivery system strength must be sufficient to deploy the covered stent under normal use as required per ISO 25539-1.	PASS The highest deployment force was found to be 45 N at the proximal catheter and 12 N at the thumbwheel.
Tubing Tensile Strength*	To determine the longitudinal tensile strength of the catheter tubing used in the delivery system and verify that the strength is adequate for the intended use.	The delivery system must have sufficient strength to maintain its function under normal use (refer also to Catheter Bond Strength).	PASS

* Testing conducted at accelerated aged time points.

C. Sterility, Packaging and Shelf-Life Testing

The COVERA™ Vascular Covered Stent is a single-use device. In accordance with AAMI/ANSI/ISO 11135, "Sterilization of health-care products – Ethylene oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices," the COVERA™ Vascular Covered Stent demonstrates a Sterility Assurance Level (SAL) of 10^{-6}. Stability testing of the device (summarized in Table 2) and sterile package testing was performed to ensure a 2-year shelf life.

D. Animal Studies

A chronic GLP animal study was performed to evaluate performance characteristics as well as local biological and systemic responses of the COVERA™ Vascular Covered Stent system. The *in vivo* animal studies demonstrated the safety and overall product performance of the COVERA™ Vascular Covered Stent *in vivo* in sheep models. This study was conducted in accordance with FDA 21 CFR Part 58 GLP Regulations. The results of the animal study are summarized in Table 3.

Table 3: Summary Results of the GLP Animal Study

Study	Study Numbers Test or Control	Evaluations	Outcome
Chronic Study in Sheep (30 days implantation)	8 male adult Suffolk cross sheep were implanted with 7x60mm test devices (Covera™ Vascular Covered Stent) and 7x50mm control devices (Gore™ Viabahn™) at the graft-to-vein anastomosis of mature carotid artery-to-jugular vein shunts	Histological Parameters	There was no gross evidence of thromboembolism or end organ tissue infarction. Evaluation of local biological and systemic responses to the implant revealed favorable results after 30 days, including minimal stenosis, inflammation, and a general absence of thrombus formation. No adverse events were noted for the test article. The Histopathologist concluded that the COVERA™ Vascular Covered Stent behaved similar to the control devices.

		Delivery, Deployment, and Retraction	All COVERA™ Vascular Covered Stent received passing scores for delivery, deployment, and retraction.
		Radiopacity	All COVERA™ Vascular Covered Stent received passing scores for radiopacity.
		Stent Integrity (including Kink Resistance)	Radiographic observations revealed that all implants appeared widely and evenly expanded without evidence of fractures or bends. The position of the test article was as expected and structural integrity was found to be intact at 30 days.

The following endpoints were evaluated as part of the *in vivo* study conducted to evaluate the safety and performance of the device:

- Implant: acute and subacute/subchronic systemic toxicity, implantation, and thrombogenicity
- Delivery system: thrombogenicity

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of vascular access interventions with the COVERA™ Vascular Covered Stent for the treatment of stenotic lesions at the graft-vein anastomosis of hemodialysis patients dialyzing with an AV graft in the US under IDE G160109. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between 03 August 2016 and 27 February 2017. The database for this PMA reflected data collected through 05 October 2017 and included 110 patients. There were 14 investigational sites.

The AVeVA study was a prospective, multi-center, non-randomized, single-arm study. All 110 subjects who were enrolled were treated with the Covera™ Vascular Covered Stent.

With regard to success/failure criteria, the safety endpoint was evaluated against a performance goal (PG) of 88%. A one-sided p-value was calculated based on an exact binomial test. The study device is considered to have achieved the safety objective if the one-sided p-value is less than 0.05. Or equivalently, the lower limit of the one-sided 95% confidence limit based on the exact method is greater than 88%.

The effectiveness endpoints are presented descriptively along with data from previous studies of devices approved for the same indication to provide clinical context.

For sample size determinations, safety at 30 days assumed a rate of 98% for subjects

treated with the study device and the PG was set at 88% with attrition rate assumptions of 5%. A sample size of 109 subjects provided 104 evaluable subjects. The sample size was adequate to provide descriptive statistics related to the effectiveness and secondary endpoints.

The analyses were conducted based on all known information for subjects who had reached pre-specified time points: 30 days for primary safety and 6 months for effectiveness and secondary endpoints. Subjects will be followed through 24 months.

An independent Clinical Events Committee (CEC) reviewed all adverse events (AEs) and performed adjudications of these events in accordance with their charter.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the AVeVA study was limited to patients who met specific inclusion criteria. Eligible patients presented with a hemodynamically significant stenosis (≥ 50% by visual estimate) accompanied by a hemodynamic functional or clinical abnormality at the AV-access, graft-vein anastomosis. To be included in the study, the target lesion was required to be ≤ 9 cm in length and have a reference vessel diameter (of the adjacent, non-stenotic vessel) between 5.0 and 9.0 mm. The AV access graft had to be located in an arm, must have been implanted for ≥ 30 days, and must have undergone at least one successful dialysis session prior to the index procedure. Thrombosed and non-thrombosed grafts were included in the study.

   Patients were not permitted to enroll in the AVeVA study if they met any of the exclusion criteria. Patients were excluded if they had additional stenotic lesions (≥ 50%) in the venous outflow (> 3 cm from the edge of the target lesion) that were not successfully treated (defined as < 30% residual stenosis) prior to treating the target lesion, if they had an aneurysm or pseudoaneurysm present within the target lesion, or if they had a target lesion located such that treatment would require the COVERA™ Vascular Covered Stent be deployed across the elbow joint or within a stent or stent graft. .

2. Follow-up Schedule

   All patients underwent a clinical evaluation at screening (prior to index procedure); treated subjects underwent a clinical evaluation prior to hospital discharge. All subjects and their respective dialysis centers were scheduled for follow-up telephone screens at 30 days, 90 days, and 6 months postoperatively.

   Preoperatively, information on subject demographics, medical history, access circuit attributes (based on the Society of Interventional Radiology (SIR) guidelines), clinical exam including overall health and assessment of the AV access in accordance with each investigational site's standard of care,

documentation of applicable medication taken within 72 hours prior to the index procedure and angiography were conducted/collected. Postoperatively, the objective parameters measured during the study included data on the AV access circuit status, AEs, reinterventions performed, and changes in applicable medications. Site investigators and dialysis centers followed their institutional procedures for hemodialysis access surveillance. Investigational sites were responsible for collecting follow-up information from subjects, dialysis centers, and any outside institutions that conducted secondary interventions on study subjects. Additionally, the majority of secondary interventions were conducted at the investigational sites.

The key time points are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

With regards to safety, the primary composite endpoint was a measure based on safety through 30 days post index procedure. Safety is defined as freedom from any AEs (CEC adjudicated), localized or systemic, that reasonably suggests the involvement of the AV access circuit (not including stenosis or thrombosis) that require or result in any of the following alone or in combination: Additional interventions (including surgery); in-patient hospitalization or prolongation of an existing hospitalization; or death. Rates of longer-term device and procedure-related adverse events were also measured to evaluate safety.

With regards to effectiveness, the study included measures based on Target Lesion Primary Patency (TLPP), Access Circuit Primary Patency (ACPP) and Post-intervention Secondary Patency (Secondary Patency) through 6 months post index procedure. TLPP was defined as the interval following the index intervention until the next clinically driven reintervention at or adjacent to (approximately 5 mm proximal or distal to, by visual estimation) the original treatment site or until the extremity was abandoned for permanent access. Primary patency ended when any of the following occurred: a) clinically driven reintervention in the treatment area; b) thrombotic occlusion within the treatment area; c) surgical intervention that excludes the original treatment area from the AV access circuit; and/or d) abandonment of the AV access graft due to inability to treat the original treatment area. ACPP was defined as the interval following the index intervention until the next access thrombosis or clinically driven repeated intervention. ACPP ended with a clinically driven reintervention anywhere within the access circuit, from the arterial inflow to the SVC-right atrial junction. Vessel rupture caused by PTA was not a TLPP or ACPP failure unless achieving hemostasis also caused thrombosis or required any treatment other than the study device. Secondary Patency was defined as the interval after the index intervention until the access is abandoned. Multiple repetitive treatments could be included in secondary patency.

Additional endpoints include: (1) TLPP through 30 days, 90 days, 12 months, 18 months, and 24 months; (2) ACPP through 30 days, 90 days, 12 months, 18 months and 24 months; (3) Rate of device and procedure related AEs involving the AV access circuit through 90 days, 6 months, 12 months, 18 months and 24 months; (4) Total Number of AV Access Circuit Reinterventions through 30 days, 90 days, 6 months, 12 months, 18 months and 24 months; (5) Total Number of Target Lesion Reinterventions through 30 days, 90 days, 6 months, 12 months, 18 months and 24 months; (6) Index of Patency Function (IPF) evaluated at 30 days, 90 days, 6 months, 12 months, 18 months and 24 months; (7) Index of Patency Function – Target Lesion (IPF-T) evaluated at 30 days, 90 days, 6 months, 12 months, 18 months and 24 months; (8) Secondary Patency evaluated through 30 days, 90 days, 12 months, 18 months and 24 months; (9) Acute Technical Success; and (10) Acute Procedure Success (Anatomic and Clinical Success).

Information was also collected regarding vessel injury, deaths, and device malfunctions.

With regard to success/failure criteria, the primary safety endpoint was evaluated against a PG of 88%. The effectiveness endpoints are presented with data from previous studies of the same indication to provide clinical context, as described in Table 4.

Table 4: Summary of Previous Studies of the Same Indication

Study	Study Design	N (Study Device)	N (PTA)	Number of U.S. Sites	Study Duration	Primary Endpoints
FLAIR® Pivotal Study	The Flair Pivotal study was a prospective, multi-center, randomized clinical trial. This study compared the FLAIR® Endovascular Stent Graft to balloon angioplasty in patients with stenoses at the venous anastomosis of a synthetic AV access graft.	97	93	16	6-months	• Treatment Area Primary Patency (TAPP) at six months was the primary outcome used to compare the effectiveness of the study device to the PTA Control. • The primary safety endpoint was evaluated based on the incidence of adverse events observed within the same time interval.

Study	Study Design	N (Study Device)	N (PTA)	Number of U.S. Sites	Study Duration	Primary Endpoints
RENOVA Postmarket Study (FLAIR®)	The RENOVA study was a prospective, multi-center, randomized, concurrently-controlled post-approval study evaluating the safety and effectiveness of the FLAIR® Endovascular Stent Graft when compared to percutaneous transluminal balloon angioplasty (PTA) alone. One arm received only PTA (the PTA group); the second arm received PTA and a FLAIR® Endovascular Stent Graft(s) in the stenotic area (the Study Device group).	138	132	28	24-months	• Demonstrate that the post intervention ACPP in the Study Device group is superior to that of the PTA group through 12 months and to estimate the patency at 24 months. • Demonstrate that the IPF [the average number of days between interventions] of the Study Device group is not inferior to that of the PTA group at 12 months and to estimate the IPF at 24 months. • Demonstrate that the safety (defined as the number of device and/or procedure related adverse events) of the Study Device group is not inferior to that of the PTA group at 12 months, and to estimate the safety at 24 months. • Post-hoc analysis of Treatment Area Primary Patency (TAPP) at 12 and 24 months

B. Accountability of PMA Cohort

At the time of database lock, of the 110 treated subjects enrolled in the PMA study, one-hundred and eight (108) completed their 30-day follow-up contact. Of the two (2) subjects that did not complete their 30-day follow-up contact, one (1) subject was withdrawn due to the investigator's decision and one (1) subject died. One hundred and two (102) subjects (92.7%) were available for analysis at the completion of the study, the 6-month follow-up contact. Of the six (6) additional subjects that did not complete their 6-month follow-up contact, one (1) subject was lost to follow-up and five (5) additional subjects died.

Figure 4 depicts the number of subjects included in the safety and effectiveness analyses. One hundred and ten (110) subjects were included in the safety analysis. Two (2) subjects missed the 30-day follow-up contact yet were included in the analysis because they were both in the study for at least 23 days. One (1) subject died on Day 29 and the other discontinued on Day 33.

One hundred (100) subjects were included in the effectiveness analysis. Nine (9) subjects were excluded from the All Treated population due to discontinuation or abandonment of their index AV access circuit for non-effectiveness reasons prior to Day 150 of their follow-up. Five (5) of these were discontinuation due to death

before Day 150 and four (4) subjects were excluded from the analysis due to abandonment of their AV access before reaching Day 150. It should be noted that one additional subject with a major protocol deviation was also excluded but was included in the ACPP analysis because the subject was a failure for ACPP only. Two (2) of the subjects noted above had 6-month follow-up contact completed but were not included in the analysis because of the major protocol deviation (n=1) and access abandonment for reasons other than effectiveness (n=1).

Deaths were not considered to be related to the study device or the index procedure. The denominators used in safety and effectiveness analyses are different, and are described in respective sections.

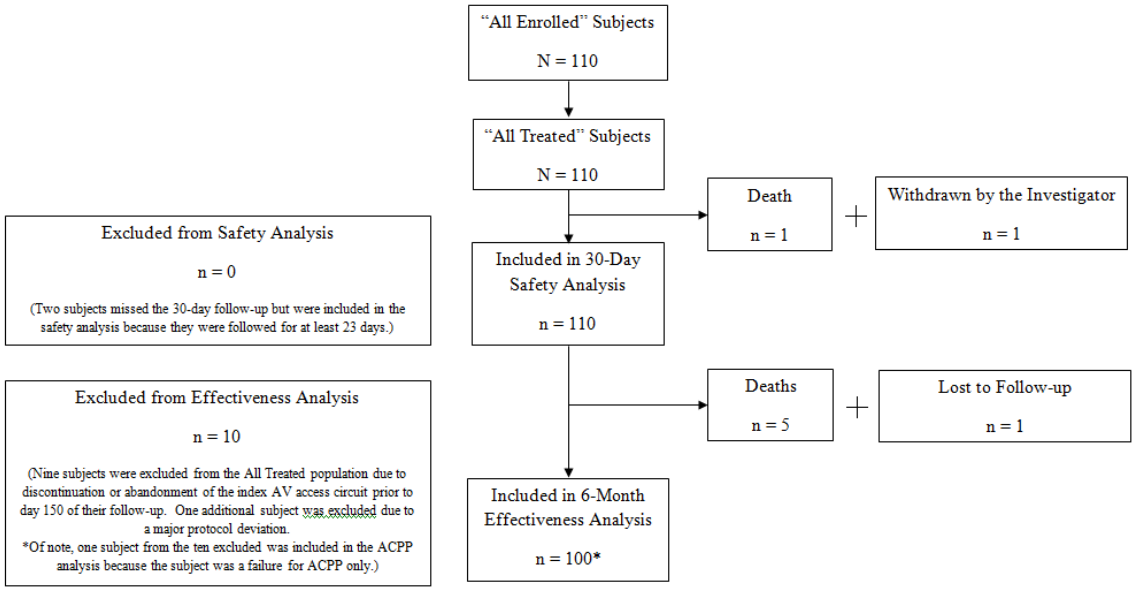

Figure 4: Subject Accountability

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a vascular access intervention study performed in the US.

Subject demographics and baseline characteristics are consistent with those in the pivotal and post market (RENOVA) studies of the FLAIR® device. When comparing to the previous studies, specific areas of similarity include age, sex, graft location in the left, upper arm, as well as comparable mean target lesion length and target lesion percent stenosis. The most common stent graft diameter across all studies was an 8 mm, and the most common stent graft length utilized was in the range of 40 – 60 mm. A notable difference between the studies is that only the AVeVA study included thrombosed patients. Specific demographics and baseline characteristics for the subjects enrolled in the AVeVA study are provided in Table 5 through Table 10.

Table 5: Subject Demographics

Age Categories	**n (%)**
< 65 years	52 (47.3)
≥ 65 and < 75 years	31 (28.2)
≥ 75 years	27 (24.5)
Sex	**n (%)**
Male	50 (45.5)
Female	60 (54.5)
Ethnicity	**n (%)**
Hispanic or Latino	24 (21.8)
Not Hispanic or Latino	86 (78.2)
Race	**n (%)**
American Indians/Alaska Native	1 (0.9)
Asian	4 (3.6)
Black or African American	44 (40.0)
White	60 (54.5)
Other	1 (0.9)
BMI Categories	**n (%)**
< 30	68 (61.8)
≥ 30	42 (38.2)

Note that N=110 subjects.

Table 6: Medical History

Risk Factors	**n (%)**
Subjects With at Least One Risk Factor	*110 (100.0)*
Diabetes - Total	72 (65.5)
Diabetes (Type 1)	4 (3.6)
Diabetes (Type 2)	68 (61.8)
Dyslipidemia	62 (56.4)
Hypertension	108 (98.2)
Cigarette Smoking - Total	43 (39.1)
Cigarette Smoking - Current	9 (8.2)
Cigarette Smoking - Former	34 (30.9)
Cardiovascular Disease	**n (%)**
Subjects With at Least One Type of Cardiovascular Disease	*80 (72.7)*
Congestive Heart Failure	32 (29.1)
Stroke	21 (19.1)
Coronary Artery Disease (CAD)	40 (36.4)
Myocardial Infarction (MI)	9 (8.2)
Transient Ischemic Attack (TIA)	11 (10.0)
Valvular Heart Disease	5 (4.5)
Aortic Disease	1 (0.9)
Deep Vein Thrombosis (DVT)	7 (6.4)

Peripheral Arterial/Vascular Disease (PAD) (PVD)	14 (12.7)
Atrial Fibrillation (A-Fib)	14 (12.7)
Other	33 (30.0)
Other Disease	**n (%)**
Subjects With at Least One Other Disease	*105 (95.5)*
Bleeding Disorder	4 (3.6)
Cancer	20 (18.2)
Steal Syndrome	1 (0.9)
Other	103 (93.6)

Note that N=110 subjects

Table 7: Description of Access Circuit

Target Limb	**n (%)**
Left Arm	88 (80.0)
Right Arm	22 (20.0)
Graft Location	**n (%)**
Forearm	2 (1.8)
Upper Arm	108 (98.2)
Arterial Anastomosis	**n (%)**
Axillary	14 (12.7)
Brachial	94 (85.5)
Radial	1 (0.9)
Ulnar	1 (0.9)
Venous Anastomosis	**n (%)**
Axillary	54 (49.1)
Basilic	44 (40.0)
Brachial	9 (8.2)
Cephalic	2 (1.8)
Median Cubital	1 (0.9)
Graft Configuration	**n (%)**
Loop	33 (30.0)
Straight	77 (70.0)
Graft Material	**n (%)**
Bovine	10 (9.1)
ePTFE	85 (77.3)
Other	4 (3.6)
Unknown [1]	11 (10.0)
Graft Tapered?	**n (%)**
Yes	32 (29.1)
No	78 (70.9)
Graft Diameter (mm)	**N=107 [2]**
Mean (SD)	6.6 (0.77)
Min - Max	4.0 - 9.0

Thrombus Present at Index Procedure?	n (%)
Yes	28 (25.5)
No	82 (74.5)
Non-Target Lesions Present at Index Procedure?	**n (%)**
Yes	44 (40.0)
No	66 (60.0)

Note that N=110 subjects unless otherwise noted.
[1] For subjects whose graft material was indicated to be unknown it was verified to be nonautologous.
[2] For three (3) subjects the diameter of the graft at the time of implantation was unknown.

Table 8: Previous Index AV Access Circuit Interventions

	n/N (%)
Number of subjects who underwent any interventions of the index AV Access Circuit within 30 days	16/110 (14.5)
Number of Previous Interventions within 30 days prior	**n**
Total Number of Previous Interventions	22
Number of Subjects with Previous Interventions	16
Intervention	**n/n (%)**
Standard PTA	10/22 (45.5)
Thrombolysis/Thrombectomy	12/22 (54.5)
Involved Target Lesion	**n/n (%)**
Yes	16/22 (72.7)
No	6/22 (27.3)
Location	**n/n (%)**
Anastomotic	11/22 (50.0)
Basilic Vein Outflow	3/22 (13.6)
Intra-Graft	4/22 (18.2)
Subclavian Vein	1/22 (4.5)
Other	3/22 (13.6)

Note that some subjects had multiple interventions.

Table 9: Target Lesion Characteristics

Lesion Characteristics	n (%)
de Novo	31 (28.2)
Re-stenotic	79 (71.8)

Note that N=110 target lesions.

	N	Mean (SD)	Min-Max
Number of Lesions within Target Lesion Area	110	1.0 (0.16)	1 - 2
Target Lesion Length (mm)	110	24.1 (15.27)	2 - 70
Target Lesion Stenosis (%)	110	71.5 (14.82)	50 - 100

Table 10: Summary of Study Device* Details

Stent Graft Configuration	n (%)
Flared	92 (83.6)
Straight	18 (16.4)
Stent Graft Diameter	**n (%)**
7 mm	10 (9.1)
8 mm	62 (56.4)
9 mm	33 (30.0)
10 mm	5 (4.5)
Stent Graft Length	**n (%)**
40 mm	54 (49.1)
60 mm	47 (42.7)
80 mm	9 (8.2)

* Only one Covera™ Vascular Covered Stent could be implanted in each patient per the study protocol.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on 30-day data for the All Treated Subjects cohort of 110 subjects. The proportion of subjects free from primary safety events was 96.4% which met the PG of 88% (p-value=0.0021). The key safety outcome for this study is presented in Table 11. Adverse effects are reported in Table 12 and Table 13.

Table 11: Freedom from any Safety Event through 30 days (All Treated Subjects)

Primary Safety Endpoint	Proportion n/N (%) [3]	90% CI (%) [2]	P-value [1]
Proportion Free from Primary Safety Events	106/110 (96.4)	(91.9, 98.7)	0.0021
Had Failure:			
Death	0		
Required Additional Intervention	4/110 (3.6)		
In-Patient Hospitalization or Prolongation	1/110 (0.9)		

[1] The p-value is compared to the PG (88%) and computed using the exact binomial test.
[2] 90% confidence interval is calculated using the exact binomial method.
[3] Two subjects missed the 30-day follow-up but were included in the denominator because they were followed for at least 23 days.
Note: The safety events are based on CEC adjudicated outcomes.

Four (4) subjects experienced safety events which counted as failures of the primary safety endpoint. One (1) subject experienced two (2) vessel ruptures in their AV access circuit during two (2) separate reinterventions performed after the index procedure. Another subject was reported to have an open wound infection proximal to the AV graft and as a precautionary measure their graft (and as such the previously implanted study device at the anastomosis) was explanted and discarded. A venous spasm in the axillary vein was noted in another subject, which ultimately resulted in the placement of a bare metal stent for adequate resolution. The remaining subject reported pain in their access arm during the

index procedure and the subject preferred that the arm not be used for cannulation, which led to the placement of an alternate access.

Adverse effects that occurred in the PMA clinical study:

A list of Safety Events observed in the Clinical Study through 6 months can be found in Table 12, and a list of CEC adjudicated device and/or procedure related AEs can be found in Table 13. AEs are defined as those that reasonably suggest the involvement of the AV access circuit (not including stenosis or thrombosis).

Table 12: Safety Events through 6 months (All Treated Subjects)

AEs by Type	Follow-Up Time Point		
	30 Days n (%)	90 Days n (%)	6 Months n (%)
Subjects With At Least One AE	**11 (10.0)**	**19 (17.3)**	**26 (23.6)**
Arteriovenous Fistula*	0	1 (0.9)	1 (0.9)
Arteriovenous Graft Site Hemorrhage	0	1 (0.9)	2 (1.8)
Arteriovenous Graft Site Infection	1 (0.9)	1 (0.9)	3 (2.7)
Local Swelling	0	1 (0.9)	1 (0.9)
Paraesthesia	0	1 (0.9)	1 (0.9)
Steal Syndrome	1 (0.9)	3 (2.7)	3 (2.7)
Vascular Graft Complication**	4 (3.6)	8 (7.3)	17 (15.5)
Vascular Rupture	1 (0.9)	1 (0.9)	1 (0.9)
Vasospasm	5 (4.5)	5 (4.5)	5 (4.5)

Note that n=subjects with at least one event.
Note that events were coded using MedDRA version 16.1.
Note that AEs that occurred through 180 days for each subject are included.
Note that N=110 subjects.
*Arteriovenous Fistula refers to a site reported event of an abnormal connection from the arteriovenous graft near the arterial anastomosis to the brachial vein.
**Vascular Graft Complication includes events such as: access pain, AV access dysfunction, AVG dysfunction, AVG circuit issues, decreased blood flow, decreased access flow rate in AVG circuit, difficult puncture of AVG circuit, high venous pressures, increased pulsatility, infiltration of vascular access, intra-graft dissection and vessel dissection of synthetic graft, poor thrill progression and wound over upper cannulation site.

Table 13: CEC Adjudicated Device and/or Procedure Related Adverse Events through 6 months (inclusive of reported Safety Events in Table 12) (All Treated Subjects)

AEs by Type	Device Related			Procedure Related		
	Definitely n (%)	Possibly n (%)	Not Related n (%)	Definitely n (%)	Possibly n (%)	Not Related n (%)
Subject with at Least One AE	**1 (0.9)**	**8 (7.3)**	**23 (20.9)**	**7 (6.4)**	**4 (3.6)**	**21 (19.1)**
Arteriovenous Graft Site Infection	0	1 (0.9)	2 (1.8)	0	1 (0.9)	2 (1.8)
Paraesthesia	0	1 (0.9)	0	0	1 (0.9)	0
Steal Syndrome	0	2 (1.8)	1 (0.9)	0	2 (1.8)	1 (0.9)
Vascular Graft Complication*	0	3 (2.7)	17 (15.5)	2 (1.8)	1 (0.9)	17 (15.5)
Vasospasm	1 (0.9)	1 (0.9)	3 (2.7)	5 (4.5)	0	0

Note that n=subjects with at least one event.
Note that events were coded using MedDRA version 16.1.
Note that AEs that occurred through 180 days for each subject are included.
Note that N=110 Subjects.
*The three events associated with Vascular Graft Complication were reported as access pain. One of the events was adjudicated as possibly related to device and procedure, and the other two were adjudicated as possibly related to device and definitely related to procedure.

2. Effectiveness Results

The analysis of effectiveness was based on the All Treated Subjects cohort of 110 evaluable subjects at the 6-month time point; up to 10 patients were excluded from the effectiveness analysis as described in the footnotes of Table 14 and Tables 16-17. Effectiveness was evaluated using multiple endpoints, with TLPP being an important endpoint as it was used as the primary endpoint for previous studies of the same indication. To provide clinical context, the 6-month TLPP rates from the pivotal and post market (RENOVA) studies of the FLAIR® device are provided in Table 14 below. The results of the AVeVA study demonstrate that the TLPP rates for the COVERA™ Vascular Covered Stent are similar to results from the study device arm of the previous studies and greater than the patency rates for PTA from these studies.

Table 14: TLPP Rates in AV Grafts at 6 Months

Study	N	Study Device	90% Confidence Intervals	Randomized PTA	90% Confidence Intervals
FLAIR® Pivotal Study	91	51%*	(42%, 60%)	23% (N=86)	(16%, 32%)
RENOVA Study (FLAIR®)	138	66%	(59%, 73%)	40% (N=132)	(33%, 48%)
AVeVA Study (COVERA™)	**100****	**71%**	**(61%, 80%)**	-	-

* Physicians unfamiliar with the study device enrolled "roll-in" patients before starting the randomized phase of the trial. This resulted in 37 "roll-in" FLAIR® patients, resulting in a 60% TLPP rate for those patients at 6 months.
**Nine subjects were excluded from the denominator due to discontinuation or abandonment of the index AV access circuit prior to day 150 of their follow-up. One additional subject was excluded due to a major protocol deviation; refer to Table 20, Footnote [1] for additional detail.

Figure 5 presents the Kaplan-Meier curve for TLPP through 6 months for all treated subjects.

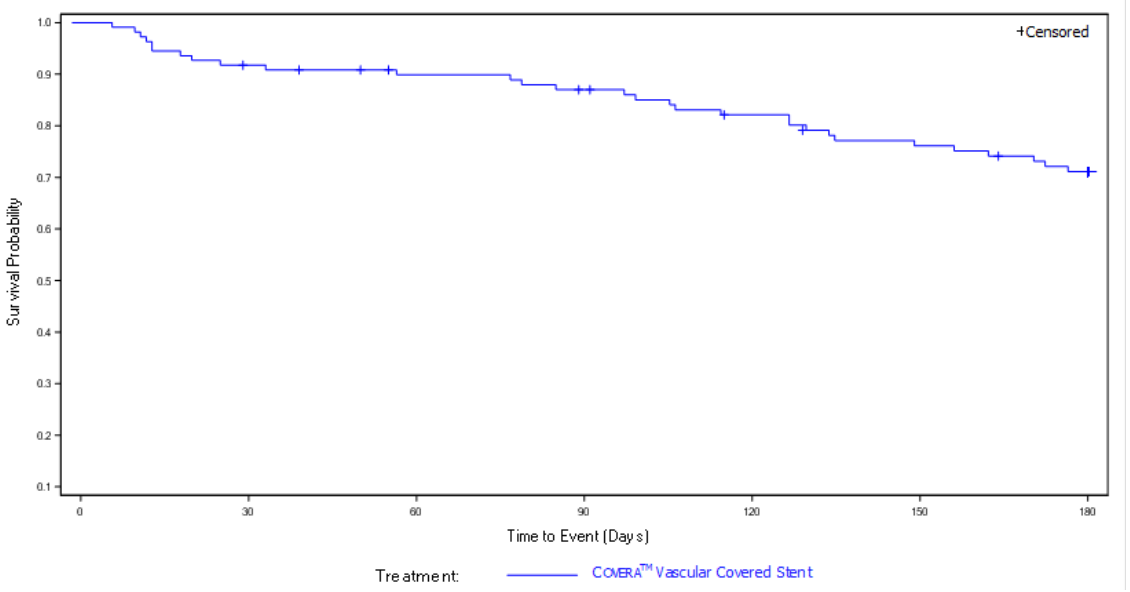

Figure 5: Kaplan-Meier Analysis of TLPP (All Treated Subjects)

Table 15: Kaplan-Meier Analysis of TLPP (All Treated Subjects)

Time Point	#of Subjects Left	#of Subjects Censored	#of Subjects with TLPP Failure	TLPP Rate (95% CI) [1]
30 Days	99	1	8	92.6% (85.7%, 96.2%)
90 Days	90	5	13	87.8% (79.9%, 92.7%)
180 Days	70	9	29	71.7% (61.9%, 79.4%)

[1] The rates are estimated using the Kaplan-Meier method and the 95% confidence intervals are estimated using Greenwood's formula.

ACPP and secondary patency are also important effectiveness endpoints evaluated in this study. ACPP and secondary patency are inclusive of all patency events including those that occurred at the target lesion (i.e. inclusive of TLPP). The 6-month ACPP and secondary patency rates from the pivotal and post market (RENOVA) studies of the FLAIR® device are provided in Table 16 and Table 17 below. The results of the AVeVA study demonstrate that the ACPP rates for the COVERA™ Vascular Covered Stent are similar to results from the study device arm of the previous studies and greater than the ACPP rates for PTA from these studies. Furthermore, the secondary patency rates are proportionate for the study device across these studies.

Table 16: ACPP Rates in AV Grafts at 6 Months

Study	N	Study Device	95% Confidence Intervals	Randomized PTA	95% Confidence Intervals
FLAIR® Pivotal Study	91	38%*	(28%, 49%)	20% (N=86)	(12%, 30%)
RENOVA Study (FLAIR®)	138	41%	(33%, 50%)	25% (N=132)	(18%, 33%)
AVeVA Study (COVERA™)	**101****	**40%**	**(30%, 50%)**	-	-

* Physicians unfamiliar with the study device enrolled "roll-in" patients before starting the randomized phase of the trial. This resulted in 37 "roll-in" FLAIR® patients, resulting in a 43% ACPP rate for those patients at 6 months.
**One subject from the ten excluded from TLPP was included in the ACPP analysis because the subject was a failure for ACPP only.

Table 17: Secondary Patency Rates in AV Grafts at 6 Months

Study	N	Study Device	95% Confidence Intervals	Randomized PTA	95% Confidence Intervals
FLAIR® Pivotal Study	91	81%*	(72%, 89%)	86% (N=85)	(77%, 92%)
RENOVA Study (FLAIR®)	138	75%	(67%, 82%)	79% (N=132)	(71%, 85%)
AVeVA Study (COVERA™)	**100****	**92%**	**(85%, 97%)**	-	-

* Physicians unfamiliar with the study device enrolled "roll-in" patients before starting the randomized phase of the trial. This resulted in 37 "roll-in" FLAIR® patients, resulting in a 91% secondary patency rate for those patients at 6 months.
**Nine subjects were excluded from the denominator due to discontinuation or abandonment. One additional subject was excluded due to a major protocol deviation; refer to Table 20, Footnote [1] for additional detail.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: sex, race, age, target lesion characteristics, outflow vessel, presence of secondary lesion(s), and presence of thrombus. Subgroup analyses were performed on evaluable subjects (Table 18). Per these analyses, it

is likely that there are no differences in effectiveness outcomes for sex, race, age, target lesion characteristics, outflow vessel, and presence of secondary lesion(s). A difference that is likely significant was observed between subjects that presented with thrombosis at the time of the index procedure compared to subjects without thrombosis (p-value 0.0169, note this is not adjusted for multiplicity) where subjects presenting with thrombosis were observed to have 50.0% TLPP versus 76.9% TLPP for the non-thrombotic group. A similar trend between the two subgroups of subjects was also observed when subjects that had been treated for thrombosis within 30 days of the index procedure were included (multiplicity unadjusted p-value 0.0418).

Table 18: Analysis of TLPP at 6 months by Subgroup (All Treated Subjects)

Subgroup	Proportion n/N (%)	95% CI (%) [2]	P-Value [1]
Target Lesion Characteristics			
de novo	17/26 (65.4)	(44.3, 82.8)	0.4644
Re-stenotic	54/74 (73.0)	(61.4, 82.6)	
Outflow Vessel			
Axillary Vein	33/49 (67.3)	(52.5, 80.1)	0.2914
Basilic Vein	31/40 (77.5)	(61.5, 89.2)	
Presence of Secondary Lesion(s)			
Yes	26/40 (65.0)	(48.3, 79.4)	0.2821
No	45/60 (75.0)	(62.1, 85.3)	
Presence of Thrombus Prior to Treatment at Index Procedure			
Yes	11/22 (50.0)	(28.2, 71.8)	0.0169
No	60/78 (76.9)	(66.0, 85.7)	
Presence of Thrombus at and /or within 30 days of Index Procedure			
Yes	15/27 (55.6)	(35.3, 74.5)	0.0418
No	56/73 (76.7)	(65.4, 85.8)	

[1] P-values are calculated using the chi squared test and are not adjusted for multiplicity.
[2] The 95% confidence interval is calculated using the exact binomial method. Confidence intervals are unadjusted for multiple comparisons.

The subgroup analysis for ACPP for subjects that presented with thrombosis at the time of the index procedure and within 30 days prior to the index procedure is shown in Table 19.

Table 19: ACPP by Subgroup at 6 months of Follow-Up (All Treated Subjects)

Subgroup	Proportion n/N (%)	95% CI (%) [2]	P-Value [1]
Presence of Thrombus Prior to Treatment at Index Procedure			
Yes	7/23 (30.4)	(13.2, 52.9)	0.3092
No	33/78 (42.3)	(31.2, 54.0)	
Presence of Thrombus at and /or within 30 days of Index Procedure			
Yes	9/28 (32.1)	(15.9, 52.4)	0.3442

Subgroup	Proportion n/N (%)	95% CI (%) [2]	P-Value [1]
No	31/73 (42.5)	(31.0, 54.6)	

[1] P-values are calculated using the chi squared test and are not adjusted for multiplicity.
[2] The 95% confidence interval is calculated using the exact binomial method. Confidence intervals are unadjusted for multiple comparisons.

4. Additional Endpoints

Table 20 presents information on additional endpoints with proportional values for all available follow-up time points. The 12-month data are site reported and have not been verified and therefore are subject to minor changes at completion of the study (24-month follow-up). Acute Technical Success was defined as successful deployment, based on the operator's opinion, of the implant to the intended location assessed at the time of the index procedure. Procedure Success was defined as anatomic success and resolution of the pre-procedural clinical indicator(s) (clinical success) of a hemodynamically significant stenosis as further defined by Anatomic and Clinical Success. Anatomic Success was determined during the primary procedure and was defined as the achievement of a post-procedure residual stenosis of less than or equal to 30%, measured at the narrowest point of the lumen when compared to the adjacent non-stenosed venous segment. Whereas Clinical Success was defined as resolution of pre-procedural clinical indicators of access malfunction in the opinion of the investigator prior to hospital discharge which could include an abnormal physical exam, abnormal pressure monitoring parameters, decreased access flow, difficulty with dialysis needle puncture, pulling thrombus, prolonged bleeding, increased recirculation, and/or inadequate dialysis clearance.

Table 20: Additional Endpoints, Proportional Values (All Treated Subjects)

	Procedure n/N (%)	30 days n/N (%)	90 days n/N (%)	6 months n/N (%)	12 months n/N (%)
Acute Technical Success [1]	110/110 (100)	N/A	N/A	N/A	N/A
Acute Procedure Success [1]	110/110 (100)	N/A	N/A	N/A	N/A
TLPP	N/A	100/108 (92.6)	91/104 (87.5)	71/100 (71.0)	46/90 (51.1)
ACPP	N/A	96/108 (88.9)	72/105 (68.6)	40/101 (39.6)	15/96 (15.6)
Secondary Patency	N/A	106/108 (98.1)	100/104 (96.2)	92/100 (92.0)	76/87 (87.4)
Proportion Free From Device and Procedure Related AEs [2]	N/A	101/110 (91.8)	96/108 (88.9)	93/105 (88.6)	86/95 (90.5)

[1]One (1) subject presented with a clotted graft at the time of the index procedure and a 100% stenosis at the target lesion. During the initial inflation of the target lesion, rupture of the vessel occurred. After the urgency of resolving the rupture had passed, the investigator determined that there was an additional lesion about 1 cm peripheral to the stent graft. Because the first target lesion segment was stenosed to 100%, it is unlikely the additional lesion would have been seen until after pre-dilatation. A major protocol deviation was required as the remaining segment had to be treated with an adjunctive therapy as placement of a secondary study device in an overlapped configuration was not allowed per the protocol. This deviation does not implicate the technical and procedural success of the device as the study device was placed as initially intended as assessed by the investigator, however the subject was excluded from the follow-up patency analysis due to the major protocol deviation.

[2]Refer to Table 13 for a complete list of device and procedure related AEs at 6 months.

Table 21 presents information on additional endpoints with mean values for all available follow-up time points. Total Number of AV Access Circuit Reinterventions was defined as the number of reinterventions to the AV access circuit until access abandonment or through study completion. Total Number of

Target Lesion Reinterventions was defined as the number of reinterventions to maintain target lesion patency. Index of Patency Function (IPF) was defined as the time from the index study procedure to study completion or access abandonment divided by the number of visits for reinterventions performed on the AV access circuit in order to maintain vascular access for hemodialysis. A visit was defined as one (1) procedural event, regardless of the number or type of interventions performed during the visit. The index procedure was counted as the first visit to ensure all subjects have a denominator of at least one. Index of Patency Function – Target Lesion (IPF-T) was defined as the time from the index study procedure to study completion or complete access abandonment divided by the number of visits for a reintervention performed at the target lesion in order to maintain vascular access for hemodialysis.

Table 21: Additional Endpoints, Mean Values (All Treated Subjects)

Total Number of AV Access Circuit Reinterventions	**n**	**mean (SD)***
30 Days	15	0.1 (0.44)
90 Days	48	0.5 (0.74)
6 Months	108	1.1 (1.23)
12 Months	215	2.3 (2.24)
Total Number of Target Lesion Reinterventions	**n**	**mean (SD)***
30 Days	9	0.1 (0.34)
90 Days	15	0.1 (0.43)
6 Months	41	0.4 (0.74)
12 Months	78	0.9 (1.40)
Index of Patency Function (days)	**mean (SD)**	
30 Days	28.23 (5.32)	
90 Days	72.58 (25.81)	
6 Months	110.58 (57.84)	
12 Months	147.59 (105.24)	
Index of Patency Function – Target Lesion (days)	**mean (SD)**	
30 Days	28.88 (4.29)	
90 Days	83.72 (17.86)	
6 Months	146.98 (52.07)	
12 Months	254.50 (127.39)	

* Mean (SD) is the average number of reinterventions per subject.

5. Vessel Ruptures

During the index procedure, two (2) subjects experienced vessel rupture at the target lesion during pre-dilation prior to study device implantation. The protocol allowed for vessel rupture at the target lesion to be treated using the study device and as such, the ruptures were resolved after implantation of the COVERA™ Vascular Covered Stent. The investigators deemed the procedures a success and no further AEs were reported for these subjects through the 6-month follow-up period.

6. Summary of Deaths

There were six (6) deaths reported in the 6-month follow-up period. Two (2) deaths were cardiac-related and two (2) subjects expired due to voluntary termination of dialysis. The remaining two (2) primary causes of death were reported as volume overload (1), and worsening terminal cerebrovascular disease (1). Deaths were not considered to be related to the study device or index procedure.

7. Observed Device Malfunctions

There were zero (0) device malfunctions reported.

8. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient 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 72 investigators of which none were full-time or part-time employees of the sponsor and 9 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: 9
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 1

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. 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 Cardiovascular 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 CLINICAL STUDY

A. Effectiveness Conclusions

Acute technical success and acute procedure success was achieved in all 110 study subjects. The 6-month TLPP rate for the Covera™ Vascular Covered Stent (71%) is similar to prior stent graft devices (i.e., 51-66%) and greater than the patency rates for PTA in the prior studies (i.e., 23-40%). The 6-month ACPP rate for the Covera™ Vascular Covered Stent (40%) is also similar to prior stent graft devices (i.e., 38-41%) and greater than the patency rates for PTA in the prior studies (i.e, 20-25%). In addition, the 6-month secondary patency rate for the Covera™ Vascular Covered Stent (92%) is similar to prior stent graft devices (i.e., 75-81%) and PTA in the prior studies (i.e, 79-86%). Subgroup analyses suggested presentation with thrombosis at the time of the index procedure and treatment for thrombosis within 30 days of the index procedure are risk factors associated with loss of TLPP.

The number of AV access circuit and target lesion reinterventions, as well as the indexes of patency function, were consistent with clinical expectations through 12 months.

Unadjudicated 12-month patency rates for TLPP, ACPP and secondary patency (i.e., 51%, 16%, and 87%, respectively) also support the effectiveness of the Covera™ Vascular Covered Stent.

Despite the limitations with the design of this clinical study (i.e., single arm, telephone contact follow-up), the clinical study results are adequate to provide a reasonable assurance of the effectiveness of the Covera™ Vascular Covered Stent to treat stenoses at the venous anastomosis of ePTFE and other synthetic AV access grafts.

B. Safety Conclusions

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

All 110 enrolled subjects were included in the 30-day primary safety analysis. The proportion of subjects free from primary safety events was 96.4% which met the PG of 88%.

The CEC adjudicated 1 vasospasm as definitely device related, with 8 additional events being possibly device-related adverse events through 6 months. These 8 events included 1 report of vasospasm, 3 reports of access pain, 2 reports of steal syndrome, 1 report of paraesthesia, and 1 report of AV graft site infection. The CEC adjudicated 2 of 3 reports of access pain as definitely procedure related, with the other being possibly procedure related. All 5 of the vasospasms reported in the study

through 6 months were adjudicated as definitely procedure related. The other 4 possibly procedure-related events included the 2 reports of steal syndrome, 1 report of paraesthesis, and 1 report of AV graft site infection.

During the index procedure, 2 subjects experienced vessel rupture at the target lesion during pre-dilation prior to study device implantation. The ruptures were resolved after implantation of the Covera™ Vascular Covered Stent.

The 6 deaths reported within 6 months were not considered to be related to the study device or index procedure.

The clinical study results are adequate to provide a reasonable assurance of the safety of the Covera™ Vascular Covered Stent to treat stenoses at the venous anastomosis of ePTFE and other synthetic AV access grafts.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefit of using the COVERA™ Vascular Covered Stent to treat stenoses in the venous anastomosis of ePTFE and other synthetic AV access grafts is prolonging the ability to use the treated access site to perform hemodialysis access. The magnitude of this benefit appears consistent with similar marketed devices and likely more than associated with PTA treatment alone. The likelihood of a patient experiencing a benefit is high, based on the secondary patency rate of 92% at 6 months. Although long-term data are not yet available, the unadjudicated data suggest continued benefit through 12 months.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The proportion of subjects free from primary safety events was 96.4% (106/110) which met the performance goal of 88%. The use of the COVERA™ Vascular Covered Stent was associated with little added risk over PTA alone.

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

In conclusion, given the available information above, the data support that for treatment of stenoses at the venous anastomosis of an ePTFE or other synthetic AV access graft the probable benefits outweigh the probable risks.

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.

The benefits of the use of the COVERA™ Vascular Covered Stent include satisfactory TLPP at 6 months, as well as an early reduction in the need for target lesion reintervention, consistent with similar marketed covered stents. These benefits are clinically meaningful and were achieved with minimal added risk when considered in the context of known risks to use of PTA alone.

XIII. CDRH DECISION

CDRH issued an approval order on July 30, 2018. The final conditions of approval cited in the approval order are described below.

ODE Lead PMA Post-Approval Study – AVeVA Continued Follow-up Study: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. This study should be conducted per the pivotal study protocol approved under G160109. The AVeVA study is a prospective, multi-center, non-randomized, single-arm study that enrolled 110 subjects at 14 investigational sites.

The purpose of the AVeVA study is to evaluate the long-term safety and effectiveness of the Covera Vascular Covered Stent. All study subjects remaining in the study will continue to be followed every 6 months through 24 months. Clinical outcomes at 12, 18, and 24 months will include target lesion primary patency, access circuit primary patency, secondary patency, total number of target lesion reinterventions and access circuit reinterventions, index of patency function, index of patency function – target lesion, and rate of device and procedure related adverse events. These endpoints will be analyzed descriptively.

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.