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: C. R. Bard, Inc.
1625 West 3rd Street
Tempe, AZ 85281
Registration number: 2020394

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170042/S002

Date of FDA Notice of Approval: March 1, 2019

The original PMA (P170042) was approved on July 30, 2018, and is indicated for use in the treatment of stenoses at the venous anastomosis of ePTFE or other synthetic arterio-venous (AV) access grafts. The SSED to support this indication is available on the CDRH website and is incorporated by reference here.
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P170042.

The current supplement was submitted to expand the indication for the COVERA™ Vascular Covered Stent to include the treatment of stenoses in the venous outflow of an arterio-venous fistula.

II. INDICATIONS FOR USE

The COVERA™ Vascular Covered Stent is indicated for use in hemodialysis patients for the treatment of stenoses in the venous outflow of an arterio-venous (AV) fistula and at the venous anastomosis of an ePTFE or other synthetic AV graft.

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 expanded Polytetrafluoroethylene (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.

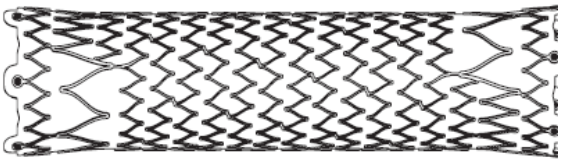

Figure 1: Straight Configuration

Figure 2: Flared Configuration

Description of Delivery System

The delivery system is illustrated in Figure 3. The covered stent is pre-mounted 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.

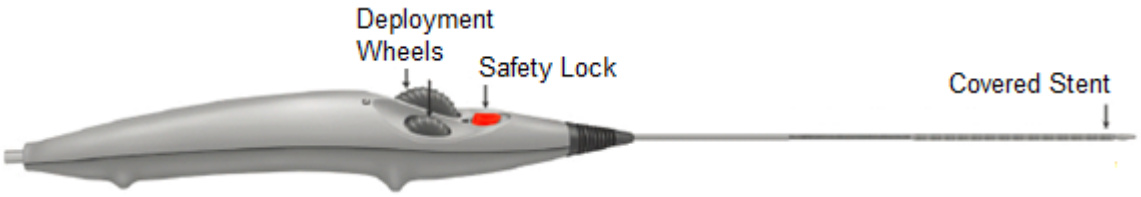

Figure 3: COVERA™ Vascular Covered Stent Delivery System

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 outflow of AV fistulae. Alternative procedures include use of percutaneous transluminal angioplasty (PTA) with plain or drug coated balloons, surgical revisions, creation of new fistulae/grafts, and non-fistula/graft methods for dialysis access (peritoneal, central vein catheter placement). 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, Oman, Indonesia, India, New Zealand, Singapore, and Brunei Darussalam.

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

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- New lesions in the access circuit requiring reinterventions
- Thrombotic occlusion
- Restenosis of target lesion 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, compression, 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 summary of previously reported preclinical studies can be found in the SSED for the original PMA. There were no modifications made to the design or manufacturing of the device; therefore, the non-clinical studies previously conducted remain applicable.

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 in the venous outflow of hemodialysis patients dialyzing with an AV fistula in the US, Europe, Australia, and New Zealand under IDE G160001. Data from this clinical study were the basis for the PMA Panel-Track Supplement approval decision. A summary of the clinical study is presented below.

A. Study Design

The AVeNEW study was a prospective, multi-center, randomized, concurrently-controlled study. One hundred and forty-two (142) subjects were randomized to COVERA™ Vascular Covered Stent (following PTA) and 138 subjects were randomized to standard PTA alone. The primary endpoint analyses occurred once 280 randomized subjects completed or discontinued before their 6 month follow up. The key secondary endpoint analyses occurred when 280 randomized subjects completed or discontinued

before their 12 month follow up. Additional secondary endpoint analyses without hypothesis testing will occur when 280 randomized subjects have completed or discontinued before their 24 month follow up. All subjects will be followed for 24 months post index-procedure.

Patients were treated between June 9, 2016 and July 20, 2017. The database for this Panel Track Supplement reflected data collected through December 7, 2018 and included 280 patients. There were 24 investigational sites including: one site in New Zealand (enrolled 2 patients), two sites in Australia (enrolled 6 patients), one site in Netherlands (enrolled 1 patient), one site in Germany (enrolled 1 patient), one site in Austria (enrolled 2 patients), one site in Belgium (enrolled 3 patients), one site in Switzerland (enrolled 3 patients) and 16 sites in the United States (enrolled 262 patients).

The following hypotheses were tested:

- Primary Safety Endpoint: The safety rate in subjects treated with the COVERA™ Vascular Covered Stent (following PTA) is non-inferior to the safety rate in subjects treated with PTA alone through 30 days in the treatment of stenotic lesions.
- Primary Effectiveness Endpoint: The (survival) rate in subjects treated with the COVERA™ Vascular Covered Stent (following PTA) with respect to Target Lesion Primary Patency (TLPP) at 6-months is greater than that in subjects treated with PTA alone in the treatment of stenoses in the upper extremity venous outflow of subjects dialyzing with an AV fistula.

For sample size determinations, safety at 30 days assumed a rate of 95% for subjects treated with the study device and 95% for subjects treated with PTA alone with attrition rate assumptions of 5%. For effectiveness, TLPP at 6 months assumed a rate of 73% for subjects treated with the study device and 50% for subjects treated with PTA alone with attrition rate assumptions of 10%. A sample size of 280 randomized subjects (allocated 1:1) would provide approximately 86% power for both primary safety and effectiveness endpoints.

An independent Clinical Events Committee (CEC) reviewed all adverse events (AEs) and performed adjudications of these events in accordance with their charter. The Medical Monitor (MM) reviewed adjudicated events for AE trends. An independent Data Safety Monitoring Board (DSMB) oversaw interim safety and effectiveness analyses as well as conducted evaluations of subject safety during the study. An independent core lab reviewed and analyzed the angiographic images.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the AVeNEW study was limited to patients who met specific inclusion criteria. Eligible patients presented with a hemodynamically significant stenosis (≥ 50% by visual estimate) in the venous outflow of the AV access circuit and presented with clinical or hemodynamic evidence of AV fistula dysfunction. 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 fistula had to be located in an upper extremity and have undergone at least one successful dialysis session prior to the index procedure.

Patients were not permitted to enroll in the AVeNEW 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, within a stent or stent graft, in the central veins (subclavian, brachiocephalic, superior vena cava (SVC)), or across the segment of fistula utilized for dialysis needle puncture (i.e. "cannulation zone").

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 12 months postoperatively. The 6 month follow up occurred via an in office visit in addition to a phone call to the dialysis center.

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 timepoints are shown in the table below.

Table 1: Schedule of Assessments

	Screening	Index Procedure	Post-Procedure / Discharge	Post Procedure Follow Ups				Un-scheduled Visit / Re-intervention
				30 Days (±7 days)	90 Days (±15 days)	6 Months (±30 days)	12 Months (±30 days)	
Informed Consent	✓							
Demographics / Medical History	✓							
Physical Examination*	✓		✓			✓		✓
Eligibility Criteria	✓	✓						
Medication Assessment	✓	✓	✓	✓	✓	✓	✓	✓
AV Access Status	✓		✓	✓	✓	✓	✓	✓
Angiographic Image Collection**		✓						✓**
Randomization		✓						
Adverse Event Assessment		✓	✓	✓	✓	✓	✓	✓
Re-intervention Data Collection#				✓	✓	✓	✓	✓

* Must be performed if there is an office visit (i.e., if there is an office visit in lieu of telephone contact).
** Angiographic images are required when a revascularization of the access circuit is performed.
# Includes all re-interventions to the access circuit post the index procedure.

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 primary endpoint was a measure based on Target Lesion Primary Patency (TLPP) 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 due to inability to treat the original treatment area. Vessel rupture caused by PTA was not a TLPP failure unless achieving hemostasis also caused thrombosis or required any treatment other than what the patient had been randomized to receive.

With regard to success/failure criteria, the primary safety and effectiveness endpoints were evaluated against standard PTA alone. A one-sided p-value for the safety endpoint (non-inferiority) was calculated based on the Farrington and Manning test. A one-sided p-value for the effectiveness endpoint (superiority) was calculated based on the log-rank test. The study device is considered to have achieved the safety and effectiveness objectives if the one-sided p-value is less than 0.025.

The study included two secondary endpoints with hypothesis testing, which are TLPP through 12 months and Access Circuit Primary Patency (ACPP) through 6 months. 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 an ACPP failure unless achieving hemostasis also caused thrombosis. Evaluation of the secondary endpoints with hypothesis testing is performed in a hierarchical fashion in the order listed.

Additional endpoints include: (1) TLPP through 30 days, 90 days, 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, 6 months, 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 deaths and device deficiencies.

B. Accountability of PMA Cohort

Of the 280 randomized subjects enrolled in the PMA study, two hundred seventy (270) completed their 30-day follow-up contact, two hundred fifty-three (253) completed their 6-month follow-up contact and two hundred thirty-five (235) completed their 12-month follow-up contact. Table 2 provides subject availability based on the Intent to Treat (ITT) population and by timepoint. The ITT population was defined as all subjects who signed the study's Informed Consent Form (ICF) and

were randomized to be in the study. Table 3 describes the number of patients discontinued through 6-month follow-up and the reasons for discontinuation based on the modified Intent to Treat (mITT) population. The mITT population was defined as subjects in the ITT population who were treated with the COVERA™ Vascular Covered Stent (following PTA) or PTA alone. There were 12 PTA subjects treated with adjunctive treatment (i.e. bare metal or stent grafts) who were excluded from the mITT population. Figure 4 depicts the number of subjects available for the primary analyses.

Table 2: Subject Availability

	COVERA™	PTA	Total
Randomized Subjects (ITT)	**142**	**138**	**280**
Completed 30-Day Follow-Up	137 (96.5)	133 (96.4)	270 (96.4)
Completed 90-Day Follow-Up	135 (95.1)	128 (92.8)	263 (93.9)
Completed 6-Month Follow-Up	130 (91.5)	123 (89.1)	253 (90.4)
Completed 12-Month Follow-Up	120 (84.5)	115 (83.3)	235 (83.9)

Note: The denominator for the percentages is the number of subjects randomized in the study.

Table 3: Subject Availability/Disposition

	COVERA™	PTA	Total
Randomized Subjects (ITT)	**142**	**138**	**280**
Treated	141* (99.3)	138 (100)	279 (99.6)
Modified ITT	141* (99.3)	126** (91.3)	267 (95.4)
Discontinued Before 6-Month Follow-Up	12 (8.5)	11 (8.0)	23 (8.2)
Primary Reason For Discontinuation:			
Withdrawal of Consent	1 (0.7)	1 (0.7)	2 (0.7)
Death	7 (4.9)	9 (6.5)	16 (5.7)
Investigator's Decision*	1 (0.7)	0	1 (0.4)
Lost to Follow-Up	2 (1.4)	1 (0.7)	3 (1.1)
Other***	1 (0.7)	0	1 (0.4)

Note: The denominator for the percentages is the number of subjects randomized in the study.
*One subject was randomized to receive COVERA™ , however, did not receive any treatment during the index procedure and was discontinued from the study via, "investigator decision". Subject was erroneously enrolled.
**Twelve PTA subjects treated with adjunctive treatment (i.e. bare metal or stent grafts) were excluded.
***One subject was randomized to COVERA™ , however, was only treated with PTA, due to the location of the target lesion that would have required the study device to be deployed at or across the segment of the fistula utilized for dialysis needle puncture, i.e., cannulation zone. Subject was followed through the 30-day follow-up to assess for safety events.

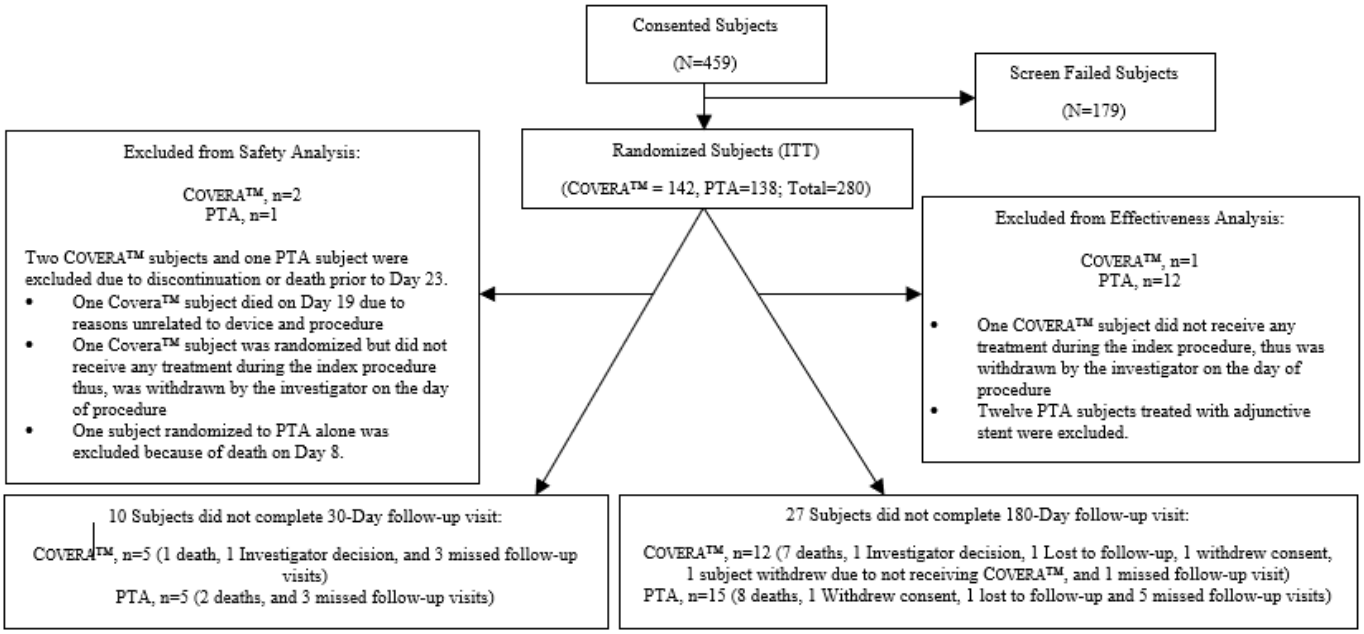

Figure 4: Subject Accountability

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical of a study performed in the US on hemodialysis patients.

Demographic and background characteristics for the ITT population are provided in Table 4 below. The majority of subjects were white (68.6%) and male (61.8%). The mean age at the time of the index procedure was 63 ± 12.4 years and there was no difference between the two treatment arms with regards to age. The Body-Mass Index (BMI) was noted to be statistically different between the two treatment arms, however, more obese patients (BMI ≥ 30) were enrolled in the COVERA™group compared to the PTA alone group, thereby favoring the outcomes of the later. A summary of relevant medical risk factors as well as selected medical history background for the ITT population is provided in Table 5. The expected co-morbidities for this population were observed, with nearly all of the subjects' hypertensive (97.1%), three quarter (75.4%) diabetic, and 67.9% having cardiovascular disease. There were no differences noted between the two treatment arms for any of the relevant medical risk factors.

Table 4: Subject Demographics (ITT Subjects)

	COVERA™ N = 142	PTA Alone N = 138	Total N = 280	P-value
Age Categories	**n (%)**	**n (%)**	**n (%)**	0.1945
< 65 years	79 (55.6)	76 (55.1)	155 (55.4)	
≥ 65 and < 75 years	36 (25.4)	45 (32.6)	81 (28.9)	

≥ 75 years	27 (19.0)	17 (12.3)	44 (15.7)	
Sex	**n (%)**	**n (%)**	**n (%)**	0.7558
Male	89 (62.7)	84 (60.9)	173 (61.8)	
Female	53 (37.3)	54 (39.1)	107 (38.2)	
Ethnicity	**n (%)**	**n (%)**	**n (%)**	0.3776
Hispanic or Latino	48 (33.8)	54 (39.1)	102 (36.4)	
Not Hispanic or Latino	93 (65.5)	84 (60.9)	177 (63.2)	
Missing	1 (0.7)	0	1 (0.4)	
Race	**n (%)**	**n (%)**	**n (%)**	0.0819
Asian	0	6 (4.3)	6 (2.1)	
Native Hawaiian or Other Pacific Island	2 (1.4)	0	2 (0.7)	
Black or African American	36 (25.4)	36 (26.1)	72 (25.7)	
White	100 (70.4)	92 (66.7)	192 (68.6)	
Other	4 (2.8)	4 (2.9)	8 (2.9)	
BMI Categories	**n (%)**	**n (%)**	**n (%)**	0.0108
< 30	68 (47.9)	87 (63.0)	155 (55.4)	
≥ 30	74 (52.1)	51 (37.0)	125 (44.6)	

Table 5: Medical History (ITT Subjects)

	COVERA™ N = 142	**PTA Alone N = 138**	**Total N = 280**	
Risk Factors	**n (%)**	**n (%)**	**n (%)**	**P-value**
Subjects With at Least One Risk Factor	*141 (99.3)*	*136 (98.6)*	*277 (98.9)*	0.5449
Diabetes – Total	108 (76.1)	103 (74.6)	211 (75.4)	0.7830
Diabetes (Type 1)	7 (4.9)	9 (6.5)	16 (5.7)	
Diabetes (Type 2)	101 (71.1)	94 (68.1)	195 (69.6)	
Dyslipidemia	95 (66.9)	85 (61.6)	180 (64.3)	0.3541
Hypertension	139 (97.9)	133 (96.4)	272 (97.1)	0.4481
Cigarette Smoking - Total	62 (43.7)	62 (44.9)	124 (44.3)	0.8312
Cigarette Smoking - Current	8 (5.6)	15 (10.9)	23 (8.2)	
Cigarette Smoking - Former	54 (38.0)	47 (34.1)	101 (36.1)	
Cardiovascular Disease	**n (%)**	**n (%)**	**n (%)**	**P-value**
Subjects With at Least One Type of Cardiovascular Disease	95 (66.9)	95 (68.8)	190 (67.9)	0.7283
Congestive Heart Failure	35 (24.6)	40 (29.0)	75 (26.8)	0.4125
New York Heart Association (NYHA) Class I	1 (0.7)	2 (1.4)	3 (1.1)	
NYHA Class II	2 (1.4)	1 (0.7)	3 (1.1)	
NYHA Class UNKNOWN	32 (22.5)	37 (26.8)	69 (24.6)	
Stroke	20 (14.1)	24 (17.4)	44 (15.7)	0.4472
Coronary Artery Disease (CAD)	46 (32.4)	52 (37.7)	98 (35.0)	0.3538
Myocardial Infarction (MI)	22 (15.5)	18 (13.0)	40 (14.3)	0.5581
Transient Ischemic Attack (TIA)	2 (1.4)	7 (5.1)	9 (3.2)	0.0822
Valvular Heart Disease	6 (4.2)	4 (2.9)	10 (3.6)	0.5498
Aortic Disease	2 (1.4)	4 (2.9)	6 (2.1)	0.3893

Deep Vein Thrombosis (DVT)	5 (3.5)	4 (2.9)	9 (3.2)	0.7678
Peripheral Arterial/Vascular Disease (PAD) (PVD)	24 (16.9)	29 (21.0)	53 (18.9)	0.3797
Atrial Fibrillation (A-Fib)	15 (10.6)	16 (11.6)	31 (11.1)	0.7834
Other	38 (26.8)	37 (26.8)	75 (26.8)	0.9923
Other Disease	**n (%)**	**n (%)**	**n (%)**	**P-value**
Subjects With at Least One Other Disease	129 (90.8)	129 (93.5)	258 (92.1)	0.4130
Bleeding Disorder	3 (2.1)	3 (2.2)	6 (2.1)	0.9718
Cancer	17 (12.0)	15 (10.9)	32 (11.4)	0.7719
Steal Syndrome	2 (1.4)	1 (0.7)	3 (1.1)	0.5785
Other	128 (90.1)	126 (91.3)	254 (90.7)	0.7373

A summary of characteristics of the AV access circuit as reported by sites is shown in Table 6. The majority of subjects had upper arm access in the left arm within inflow provided by the brachial artery and outflow through the cephalic vein. The type of fistula configuration was matched between the study arms with slight majority (57.9%) having brachiocephalic access, and an additional 22.9% having a transposed brachiobasilic fistula. Overall, 28.2% of the subjects had a vein transposed to facilitate the fistula configuration.

Table 6: Description of Access Circuit (ITT Subjects)

	COVERA™ N = 142	**PTA Alone N = 138**	**Total N = 280**
Target Limb	**n (%)**	**n (%)**	**n (%)**
Left Arm	106 (74.6)	110 (79.7)	216 (77.1)
Right Arm	36 (25.4)	28 (20.3)	64 (22.9)
Access Position	**n (%)**	**n (%)**	**n (%)**
Forearm	9 (6.3)	8 (5.8)	17 (6.1)
Upper Arm	132 (93.0)	130 (94.2)	262 (93.6)
Other	1 (0.7)	0	1 (0.4)
Inflow Artery	**n (%)**	**n (%)**	**n (%)**
Axillary	2 (1.4)	2 (1.4)	4 (1.4)
Brachial	128 (90.1)	127 (92.0)	255 (91.1)
Radial	12 (8.5)	9 (6.5)	21 (7.5)
Outflow Vein	**n (%)**	**n (%)**	**n (%)**
Axillary	2 (1.4)	1 (0.7)	3 (1.1)
Basilic	35 (24.6)	42 (30.4)	77 (27.5)
Cephalic	105 (73.9)	95 (68.8)	200 (71.4)
Fistula Configuration	**n (%)**	**n (%)**	**n (%)**
Radiocephalic	12 (8.5)	9 (6.5)	21 (7.5)
Brachiocephalic	84 (59.2)	78 (56.5)	162 (57.9)
Transposed Brachiobasilic	27 (19.0)	37 (26.8)	64 (22.9)
All Other	19 (13.4)	14 (10.1)	33 (11.8)
Transposed?	**n (%)**	**n (%)**	**n (%)**

	COVERA™ N = 142	PTA Alone N = 138	Total N = 280
Yes	36 (25.4)	43 (31.2)	79 (28.2)
No	106 (74.6)	95 (68.8)	201 (71.8)

Interventions within 30 days prior to the index procedure on the index AV access circuit are shown in Table 7. A total of 10 interventions were performed in eight (8) subjects (2.9%) in the index AV access circuit within 30 days of being enrolled in this study. The majority of these interventions involved the target lesion (8 of 280, 2.9%) and comprised of PTA (8) and thrombolysis and/or thrombectomies (1).

Table 7: Previous Index AV Access Circuit Interventions (ITT Subjects)

	COVERA™ N = 142	PTA Alone N = 138	Total N = 280
	n/N (%)	n/N (%)	n/N (%)
Number of subjects who underwent any interventions of the index AV Access Circuit within 30 days prior to the index procedure	4/142 (2.8)	4/138 (2.9)	8/280 (2.9)
Number of subjects planning to undergo any interventions of the index AV Access Circuit within 30 days	0	0	0
Number of Previous Interventions	**n**	**n**	**n**
Total Number of Previous Interventions	5	5	10
Number of Subjects with Previous Interventions	4	4	8
Mean (Standard Deviation)	1.3 (0.50)	1.3 (0.50)	1.3 (0.46)

Note: Some subjects had multiple interventions.

Site-reported baseline target lesion characteristics are shown in Table 8 and Table 9. The majority of lesions (73.2%) were re-stenotic in nature and a majority of the anastomoses (72.9%) were at the cephalic vein, with the majority of stenosis located at the cephalic vein arch (52.9%).

The reference vessel diameter averaged 8.1 ± 1.14 mm, the target lesion length ranged from 2 to 80 mm, with a stenosis of 72.5 ± 12.5% on average by visual estimate.

Table 8: Target Lesion Characteristics (ITT Subjects)

	COVERA™ N = 142	PTA Alone N = 138	Total N = 280
De Novo Lesion?	**n (%)**	**n (%)**	**n (%)**
Yes	35 (24.6)	40 (29.0)	75 (26.8)
No	107 (75.4)	98 (71.0)	205 (73.2)
Vessel	**n (%)**	**n (%)**	**n (%)**
Axillary Vein	3 (2.1)	2 (1.4)	5 (1.8)
Basilic Vein	30 (21.1)	35 (25.4)	65 (23.2)
Cephalic Vein	108 (76.1)	96 (69.6)	204 (72.9)
Other	1 (0.7)	5 (3.6)	6 (2.1)
Lesion Location	**n (%)**	**n (%)**	**n (%)**

Axillary Vein	3 (2.1)	2 (1.4)	5 (1.8)
Basilic Vein Outflow	13 (9.2)	15 (10.9)	28 (10.0)
Basilic Vein Swing Point	16 (11.3)	18 (13.0)	34 (12.1)
Cephalic Vein Arch	78 (54.9)	70 (50.7)	148 (52.9)
Cephalic Vein Outflow	25 (17.6)	24 (17.4)	49 (17.5)
Forearm Venous Outflow	3 (2.1)	2 (1.4)	5 (1.8)
Juxta-Anastomotic	2 (1.4)	0	2 (0.7)
Axillary Basilic Junction	2 (1.4)	7 (5.1)	9 (3.2)

Table 9: Angiographic Target Lesion Characteristics (ITT Subjects)

	COVERA™ N = 142	PTA Alone N = 138	Total N = 280
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Reference Vessel Diameter (mm)	8.1 (1.35)	8.0 (0.87)	8.1 (1.14)
Target Lesion Length (mm)	28.8 (17.40)	29.7 (16.98)	29.3 (17.17)
Target Lesions Stenosis (mm)	72.5 (12.40)	72.5 (12.65)	72.5 (12.50)

Table 10: Summary of Study Device Details (As Treated Population)

	COVERA™ N = 141
Stent Graft Configuration	**n (%)**
Flared	65 (46.1)
Straight	76 (53.9)
Stent Graft Diameter	**n (%)**
6 mm	1 (0.7)
7 mm	4 (2.8)
8 mm	26 (18.4)
9 mm	42 (29.8)
10 mm	68 (48.2)
Stent Graft Length	**n (%)**
30 mm	3 (2.1)
40 mm	59 (41.8)
60 mm	52 (36.9)
80 mm	23 (16.3)
100 mm	4 (2.8)
Placement Configuration	**n (%)**
Single Stent Graft Only	140 (99.3)
Other*	1 (0.7)
Was Placement Successful at intended site?	
Yes	141 (100)

**Although only one COVERA™ Vascular Covered Stent could be implanted in each patient per the study protocol, in one subject, a second COVERA™ Vascular Covered Stent was placed in an overlap configuration during the index procedure.*

The protocol and IFU required pre-dilation of the target lesion and successful effacement of the angioplasty balloon to meet the final eligibility criterion. Residual stenosis ranged from 0.0 to 90% where 54 subjects (19.3%) were reported to have an unsuccessful pre-dilation (defined as a residual stenosis of >30%). Of which, 33 subjects (23.2%) were randomized to COVERA™ Vascular Stent post PTA and 21 subjects (15.2%) were randomized to PTA. A summary of the pre-dilation details is provided in Table 11.

Table 11: Target Lesion Pre-Dilatation

	COVERA™ N = 142	PTA Alone N = 138	Total N = 280
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Balloon Diameter (mm)	8.5 (1.03)	8.4 (1.11)	8.5 (1.07)
Balloon Length (mm)	46.8 (14.85)	49.0 (16.75)	47.9 (15.83)
Number of Balloon Inflations	1.3 (0.56)	1.3 (0.59)	1.3 (0.58)
Maximum Pressure of Balloon Inflation (atm)	20.6 (5.38)	21.2 (5.78)	20.9 (5.58)
Total Duration of Inflation (sec)	43.4 (52.83)	41.2 (40.96)	42.3 (47.28)
Residual Stenosis (%)	21.7 (20.52)	15.4 (16.58)	18.6 (18.91)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the ITT cohort of subjects available for the 30-day evaluation. The proportion of subjects free from primary safety events was 95.0% in subjects treated with the COVERA™ Vascular Covered Stent compared with a safety rate of 96.4% in subjects treated with PTA alone (p-value = 0.0022). Thus, the non-inferiority of COVERA™ Vascular Covered Stent to PTA alone with regard to this primary safety endpoint is met. The key safety outcome for this study is presented in Table 12.

Table 12: Freedom from any Safety Event through 30 days (ITT Subjects)

Primary Safety Endpoint	COVERA™ n/N (%)	PTA n/N (%)	Difference 90% CI [2]	P-value [1]
Proportion Free from Primary Safety Events	133/140* (95.0)	132/137** (96.4)	-1.4 (-7.3, 4.6)	0.0022
Had Failure:	7/140 (5.0)	5/137 (3.6)		
Death	0	0		
Required Additional Intervention	7/140 (5.0)	5/137 (3.6)		
In-Patient Hospitalization or Prolongation	0	1/137 (0.7)		

**Two subjects were excluded from the analysis due to discontinuation or death prior to day 23 of their follow-up.*
***One subject was excluded from the analysis due to death prior to day 23 of their follow-up.*
[1] The p-value is calculated using Farrington and Manning non-inferiority test with non-inferiority margin=10%.
[2] 95% confidence interval is estimated using the Farrington and Manning method.
Note: The safety events are based on CEC adjudicated outcomes.

Adverse effects that occurred in the PMA clinical study:

A list of CEC adjudicated device and procedure related Safety Events observed in the Clinical Study at 30 days, 6 and 12 months can be found in Table 13 and Table 14, respectively. Adverse Events (AEs) are defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to study device.

Overall at 12 months there were 17 subjects with at least one device related AE in the COVERA™ Vascular Covered Stent arm and 4 subjects with at least one device related AE in the PTA-only arm. There is no single reason identified for this difference in number of AE's.

There have been a total of 7 arteriovenous fistula site complications that were adjudicated to be device related. Of these, 5 were adjudicated to also be procedure related at 12 months (Tables 13 and 14 below). These AEs include site-reported event terms such as: pain in the access arm, erythematous skin over stent, swelling, thrill / bruit, and pulsatility.

Table 13: CEC Adjudicated Device Related AEs through 12 months (ITT Subjects)

Adverse Event	COVERA™ (N=142)			PTA (N=138)		
	30 days n(%)	6 months n(%)	12 months n(%)	30 days n(%)	6 months n(%)	12 months n(%)
Subjects with at Least One Device Related AE	**12 (8.5%)**	**15 (10.6%)**	**17 (12.0%)**	**1 (0.7%)**	**1 (0.7%)**	**4 (2.9%)**
Arteriovenous fistula site complication	5 (3.5%)	5 (3.5%)	7 (4.9%)	0	0	0
Arteriovenous fistula site haematoma	1 (0.7%)	1 (0.7%)	1 (0.7%)	0	0	0
Bradycardia	0	0	0	0	0	1 (0.7%)
Hyperkalaemia	0	0	0	0	0	1 (0.7%)
Musculoskeletal pain	0	1 (0.7%)	1 (0.7%)	0	0	0
Pain in extremity	1 (0.7%)	2 (1.4%)	2 (1.4%)	0	0	0
Procedural pain	2 (1.4%)	2 (1.4%)	2 (1.4%)	0	0	0
Staphylococcal bacteraemia	0	0	1 (0.7%)	0	0	1 (0.7%)
Stent malfunction	0	2 (1.4%)	2 (1.4%)	0	0	0
Steal syndrome	0	1 (0.7%)	1 (0.7%)	0	0	0
Subclavian artery occlusion	0	0	0	1 (0.7%)	1 (0.7%)	1 (0.7%)
Vascular pseudoaneurysm	0	0	0	0	0	1 (0.7%)
Vasospasm	2 (1.4%)	2 (1.4%)	2 (1.4%)	0	0	0
Vessel puncture site haemorrhage	1 (0.7%)	1 (0.7%)	1 (0.7%)	0	0	0

Note that n=subjects with at least one event.
Note that events were coded using MedDRA version 16.1.

Table 14: CEC Adjudicated Procedure Related AEs through 12 months (ITT Subjects)

Adverse Event	COVERA™ (N=142)			PTA (N=138)		
	30 days n(%)	6 months n(%)	12 months n(%)	30 days n(%)	6 months n(%)	12 months n(%)
Subjects With At Least One Procedure Related AE	**13 (9.2%)**	**13 (9.2%)**	**13 (9.2%)**	**8 (5.8%)**	**9 (6.5%)**	**10 (7.2%)**
Abdominal pain lower	0	0	0	1 (0.7%)	1 (0.7%)	1 (0.7%)
Arteriovenous fistula site complication	5 (3.5%)	5 (3.5%)	5 (3.5%)	0	0	0
Arteriovenous fistula site haematoma	1 (0.7%)	1 (0.7%)	1 (0.7%)	0	0	0
Contrast media reaction	0	0	0	1 (0.7%)	1 (0.7%)	1 (0.7%)
Flushing	0	0	0	1 (0.7%)	1 (0.7%)	1 (0.7%)
Musculoskeletal pain	0	1 (0.7%)	1 (0.7%)	0	0	0
Pain in extremity	1 (0.7%)	1 (0.7%)	1 (0.7%)	0	0	0
Procedural pain	2 (1.4%)	2 (1.4%)	2 (1.4%)	0	0	0
Steal syndrome	0	0	0	0	1 (0.7%)	1 (0.7%)
Stent malfunction	0	1 (0.7%)	1 (0.7%)	0	0	0
Subclavian artery occlusion	0	0	0	1 (0.7%)	1 (0.7%)	1 (0.7%)
Vascular fragility	0	0	0	1 (0.7%)	1 (0.7%)	1 (0.7%)
Vascular procedure complication	1 (0.7%)	1 (0.7%)	1 (0.7%)	0	0	0
Vascular pseudoaneurysm	0	0	0	0	0	1 (0.7%)
Vascular rupture	0	0	0	3 (2.2%)	3 (2.2%)	3 (2.2%)
Vasospasm	2 (1.4%)	2 (1.4%)	2 (1.4%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Vessel puncture site haemorrhage	1 (0.7%)	1 (0.7%)	1 (0.7%)	0	0	0

Note that n=subjects with at least one event.
Note that events were coded using MedDRA version 16.1.

2. Effectiveness Results

The analysis of effectiveness was based on the mITT cohort of subjects at the 6-month time point. The Kaplan-Meier (K-M) estimates at day 180 for subjects receiving the COVERA™ Vascular Covered Stent was 78.7% and for subjects receiving PTA alone was 47.9% (p-value <0.001). The primary effectiveness endpoint for superiority of COVERA™ Vascular Covered Stent to PTA alone was met with a p-value of <0.001. Key effectiveness outcomes for this study are presented in Figure 5 and Table 15.

Figure 5: Kaplan-Meier Analysis of the Primary Effectiveness Endpoint (mITT Subjects)

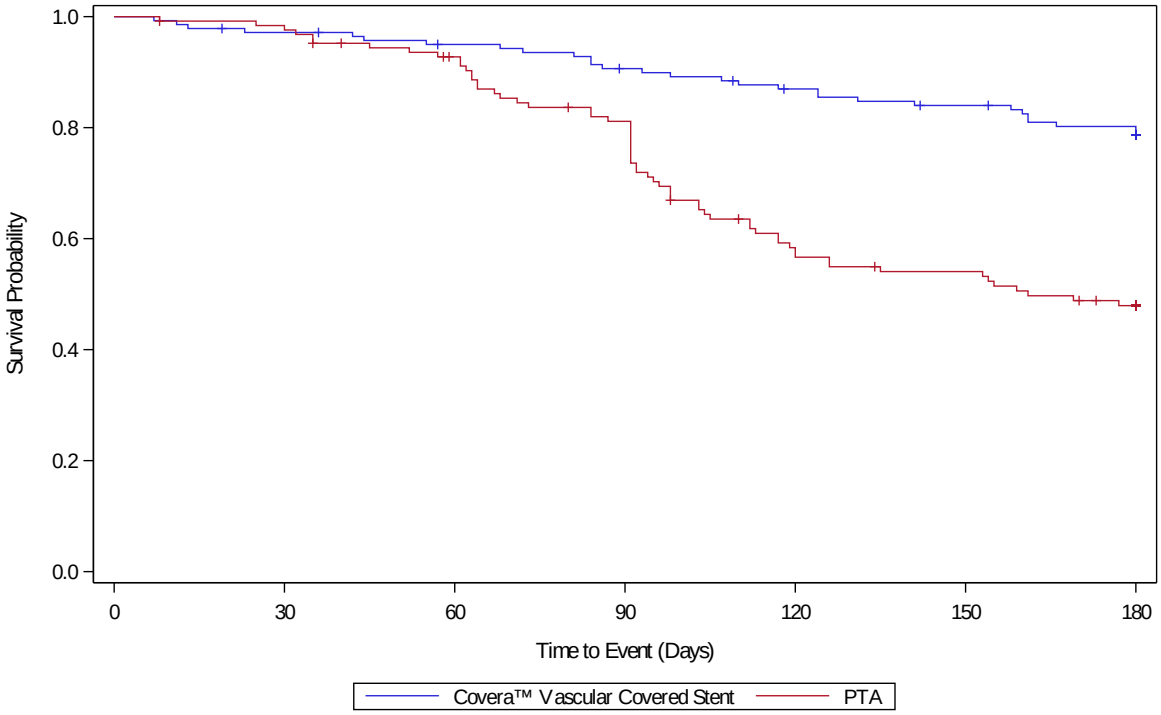

Table 15: Analysis of the Primary Effectiveness Endpoint (mITT Subjects)

	COVERA™				PTA Alone				
Time Point	**#of Subjects at Risk**	**#of Subjects Censored**	**#of Subjects with TLPP Fail**	**K-M Rate (95% CI) [1]**	**#of Subjects at Risk**	**#of Subjects Censored**	**#of Subjects with TLPP Fail**	**K-M Rate (95% CI) [1]**	
30 Days	136	1	4	97.2% (92.6%,98.9%)	122	1	3	97.6% (92.8%,99.2%)	
90 Days	124	4	13	90.6% (84.4%,94.5%)	97	6	23	81.1% (73.0%,87.1%)	
180 Days	0	112	29	78.7% (70.8%,84.7%)	0	64	62	47.9% (38.7%,56.6%)	
Hazard Ratio [3] (95% CI)									0.322% (0.207%, 0.503%)
P-value [2]									<0.001

[1] The rates are estimated using Kaplan-Meier method and the 95% confidence interval are estimated using Greenwood's formula.
[2] One sided P-value is calculated using Log-rank test.
[3] Hazard ratio calculated using COX regression with treatment in the model.
Note: The involvement of the target lesion is based on the core lab evaluation. If images were not evaluable by the core lab, site reported evaluation was used.

3. Secondary Endpoints with Hypothesis Testing

3.1 TLPP at 12 months

Testing of secondary endpoints was performed in a hierarchical fashion in the order listed. Thus, in order to perform hypothesis testing of ACPP at 6 months, TLPP at 12 months must be successful.

Figure 6: Kaplan-Meier Analysis of TLPP at 12-Months (mITT)

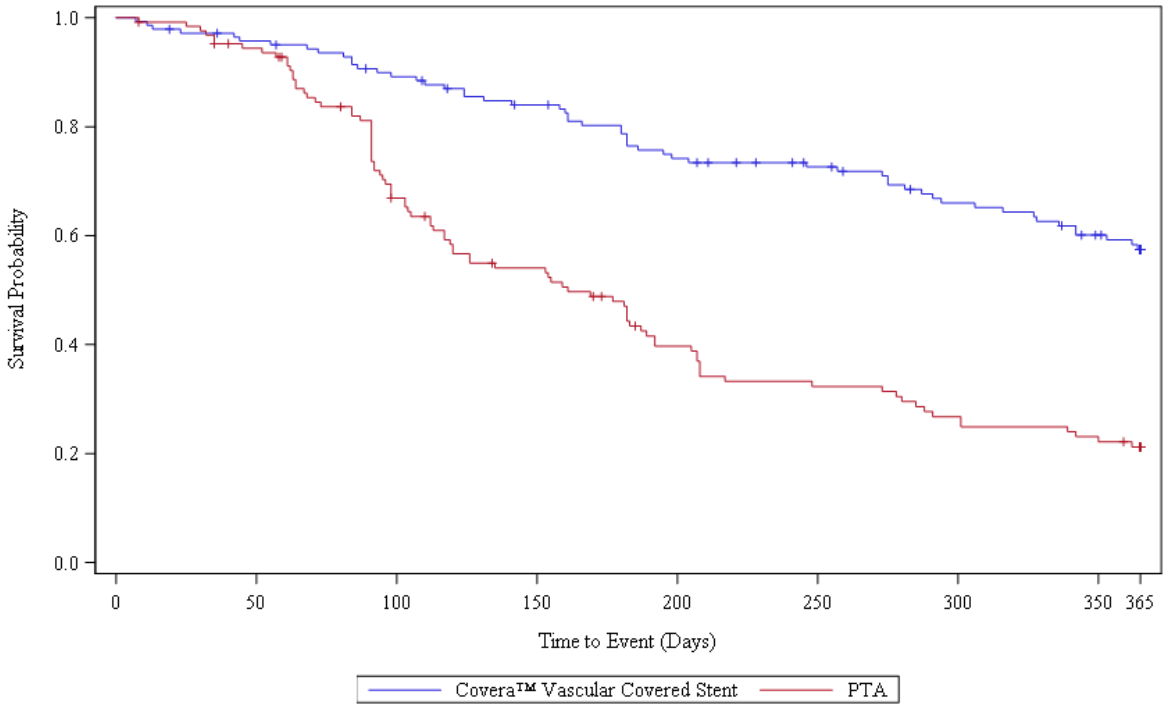

Table 16: Analysis of Subjects with TLPP through 12-Months (mITT)

	COVERA™				PTA Alone				
Time Point	**#of Subjects at Risk**	**#of Subjects Censored**	**#of Subjects with TLPP Fail**	**K-M Rate (95% CI) [1]**	**#of Subjects at Risk**	**#of Subjects Censored**	**#of Subjects with TLPP Fail**	**K-M Rate (95% CI) [1]**	
30 Days	136	1	4	97.2 (92.6,98.9)	122	1	3	97.6 (92.8,99.2)	
90 Days	124	4	13	90.6 (84.4,94.5)	97	6	23	81.1 (73.0,87.1)	
180 Days	0	112	29	78.7 (70.8,84.7)	53	11	62	47.9 (38.7,56.6)	
365 Days	0	86	55	57.5 (48.4,65.5)	0	35	91	21.2 (14.2,29.2)	
Hazard Ratio [3] (95% CI)									0.337 (0.240,0.474)
P-value [2]									<0.001

[1] The rates are estimated using Kaplan-Meier method and the 95% confidence interval are estimated using Greenwood's formula.
[2] One sided P-value is calculated using Log-rank test.
[3] Hazard ratio calculated using COX regression with treatment in the model.
Note: The involvement of the target lesion is based on the core lab evaluation. If images were not evaluable by the core lab, site reported evaluation was used.

As shown in Figure 6 and Table 16 , the results of TLPP achieved statistical significance, indicating that it provides evidence that the COVERA™ Vascular Covered Stent is superior to PTA alone on this key secondary endpoint at 12 months.

3.2 ACPP at 6-months

ACPP is defined as the interval following the index intervention until the next access thrombosis or clinically driven repeated intervention. A survival analysis

of ACPP was performed by Kaplan-Meier estimates for 180 days. The survival curve is shown in Figure 7 and supporting data in Table 17.

Figure 7: Kaplan-Meier Analysis of ACPP (mITT Subjects)

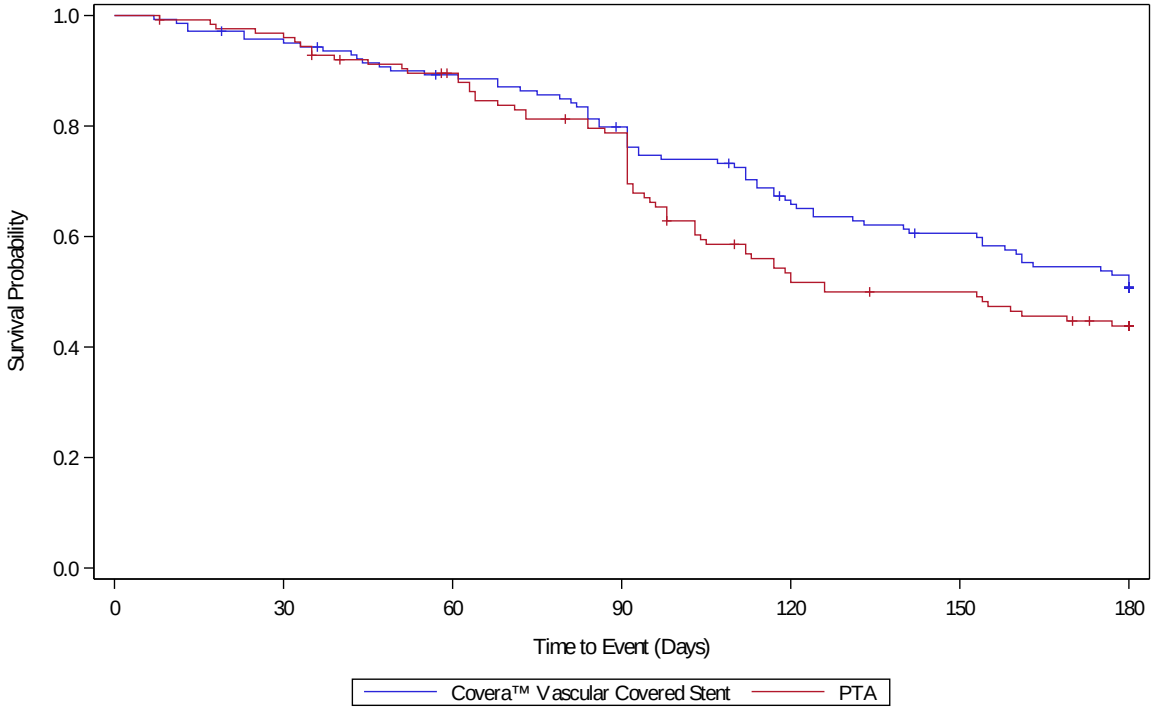

Table 17: Kaplan-Meier Analysis of ACPP (mITT Subjects)

	COVERA™				PTA Alone				
Time Point	**#of Subjects at Risk**	**#of Subjects Censored**	**#of Subjects with ACPP Failure**	**K-M Rate (95% CI) [1]**	**#of Subjects at Risk**	**#of Subjects Censored**	**#of Subjects with ACPP Failure**	**K-M Rate (95% CI) [1]**	
30 Days	133	1	7	95.0% (89.8%,97.6%)	120	1	5	96.0% (90.7%,98.3%)	
90 Days	109	4	28	79.8% (72.1%,85.6%)	94	6	26	78.8% (70.4%,85.0%)	
180 Days	0	74	67	50.7% (42.0%,58.8%)	0	59	67	43.8% (34.7%,52.5%)	
Hazard Ratio [3] (95% CI)									0.787% (0.560%, 1.108%)
P-value[2]									0.0846

[1] The rates are estimated using Kaplan-Meier method and the 95% confidence interval are estimated using Greenwood's formula.
[2] p-value is calculated using Log-rank test.
[3] Hazard ratio calculated using COX regression with treatment in the model.

The results of ACPP did not meet statistical significance, indicating that it does not provide evidence that COVERA™ Vascular Covered Stent is superior to PTA alone on this key secondary endpoint at 6 months.

4. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: sex, race, age, target lesion characteristics, target lesion location, presence of secondary lesion(s), and fistula configuration. Primary endpoint and key secondary endpoints were explored in subgroups on evaluable subjects (Table 18 through Table 20).

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

Subgroup	Covera™ n/N (%)	PTA Alone n/N (%)
Geography		
USA	96/124 (77.4)	52/110 (47.3)
Outside United States (OUS)	9/10 (90.0)	3/7 (42.9)
Gender		
Male	62/82 (75.6)	38/71 (53.5)
Female	43/52 (82.7)	17/46 (37.0)
Race		
White	74/96 (77.1)	36/76 (47.4)
African-American	26/33 (78.8)	15/32 (46.9)
Other	5/5 (100.0)	4/9 (44.4)
Age		
<65 years	60/77 (77.9)	32/65 (49.2)
≥65 and <75 years	26/34 (76.5)	19/39 (48.7)
≥75 years	19/23 (82.6)	4/13 (30.8)
Target Lesion Characteristics		
de Novo	25/31 (80.6)	21/32 (65.6)
Re-stenotic	80/103 (77.7)	34/85 (40.0)
Target Lesion Location		
Cephalic Vein Arch	58/77 (75.3)	23/60 (38.3)
Cephalic Vein Outflow	18/22 (81.8)	12/18 (66.7)
Basilic Vein Outflow	9/11 (81.8)	6/14 (42.9)
Basilic Vein Swing-Point	13/15 (86.7)	9/15 (60.0)
Others	7/9 (77.8)	5/10 (50.0)
Presence of Secondary Lesion(s)?		
Yes	36/47 (76.6)	17/45 (37.8)
No	69/87 (79.3)	38/72 (52.8)

Table 19: Analysis of TLPP at 12 months by Subgroup (mITT Subjects)

Subgroup	COVERA™ N/N (%)	PTA Alone n/N (%)
Geography		
USA	62/114 (54.4)	23/107 (21.5)
OUS	7/10 (70.0)	0/7 (0.0)
Gender		
Male	42/74 (56.8)	13/68 (19.1)
Female	27/50 (54.0)	10/46 (21.7)
Race		
White	51/89 (57.3)	13/73 (17.8)
African-American	14/30 (46.7)	9/32 (28.1)
Other	4/5 (80.0)	1/9 (11.1)
Age		
<65 years	40/71 (56.3)	13/63 (20.6)
≥65 and <75 years	16/32 (50.0)	9/38 (23.7)
≥75 years	13/21 (61.9)	1/13 (7.7)
Target Lesion Characteristics		
de Novo	18/29 (62.1)	12/32 (37.5)
Re-stenotic	51/95 (53.7)	11/82 (13.4)
Target Lesion Location		
Cephalic Vein Arch	38/75 (50.7)	7/58 (12.1)
Cephalic Vein Outflow	13/20 (65.0)	9/18 (50.0)
Basilic Vein Outflow	4/9 (44.4)	2/14 (14.3)
Basilic Vein Swing-Point	8/12 (66.7)	3/15 (20.0)
Others	6/8 (75.0)	2/9 (22.2)
Presence of Secondary Lesion(s)?		
Yes	25/46 (54.3)	7/44 (15.9)
No	44/78 (56.4)	16/70 (22.9)
Fistula Configuration		
Radiocephalic	8/11 (72.7)	0/5 (0.0)
Tranposed Brachiobasilic	12/21 (57.1)	5/33 (15.2)
Brachiocephalic	43/77 (55.8)	13/63 (20.6)
All Other	6/15 (40.0)	5/13 (38.5)

Table 20: Analysis of ACPP by Subgroup at 6 months (mITT Subjects)

Subgroup	Covera™ n/N (%)	PTA Alone n/N (%)
Geography		
USA	64/124 (51.6)	49/110 (44.5)
OUS	7/10 (70.0)	2/7 (28.6)
Gender		

Male	41/82 (50.0)	37/71 (52.1)
Female	30/52 (57.7)	14/46 (30.4)
Race		
White	50/96 (52.1)	34/76 (44.7)
African-American	17/33 (51.5)	13/32 (40.6)
Other	4/5 (80.0)	4/9 (44.4)
Age		
<65 years	38/77 (49.4)	30/65 (6.2)
≥65 and <75 years	17/34 (50.0)	18/39 (446.2)
≥75 years	16/23 (69.6)	3/13 (23.1)
Target Lesion Characteristics		
de Novo	17/27 (63.0)	18/30 (60.0)
Re-stenotic	54/107 (50.0)	33/87 (37.9)
Target Lesion Location		
Cephalic Vein Arch	40/77 (51.9)	23/60 (38.3)
Cephalic Vein Outflow	16/22 (72.7)	11/18 (61.1)
Basilic Vein Outflow	3/11 (27.3)	5/14 (35.7)
Basilic Vein Swing-Point	8/15 (53.3)	9/15 (60.0)
Others	4/9 (44.4)	3/10 (30.0)
Presence of Secondary Lesion(s)?		
Yes	19/47 (40.4)	15/45 (33.3)
No	52/87 (59.8)	36/72 (50.0)

5. Additional Endpoints

Table 21 through Table 25 presents information on additional endpoints with proportional values through 12-months.

Acute Technical Success is 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. Acute 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. 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.

Secondary Patency is defined as the interval after the index intervention until the access is abandoned. Multiple repetitive treatments can be included in post-intervention secondary patency.

Table 21: TLPP, Proportional Values (mITT Subjects)

Subgroup	COVERA™ n/N (%)	PTA Alone n/N (%)
30 days	136/140 (97.1%)	122/125 (97.6%)
90 days	125/138 (90.6%)	98/121 (81.0%)

Note N= number of subjects in the mITT population

Table 22: ACPP, Proportional Values (mITT Subjects)

Subgroup	COVERA™ n/N (%)	PTA Alone n/N (%)
30 days	133/140 (95.0%)	120/125 (96.0%)
90 days	110/138 (79.7%)	95/121 (78.5%)
12 months	34/128 (26.6%)	19/114 (16.7%)

Note N= number of subjects in the mITT population

Table 23: Additional Endpoints at Index Procedure, Proportional Values (mITT Subjects)

Subgroup	COVERA™ n/N[1] (%)	PTA Alone n/N (%)
Acute technical success	140/140 (100)	--
Acute procedure success	138/140 (98.6)	124/126 (98.4%)

Note N= number of subjects in the mITT population
[1] One subject randomized to COVERA™ was treated with PTA only, therefore the post device residual stenosis was missing thus not evaluable for this endpoint

Table 24: Secondary Patency, Proportional Values (mITT Subjects)

Subgroup	COVERA™ n/N (%)	PTA Alone n/N (%)
30 days	139/140 (99.3)	125/125 (100.0)
90 days	136/138 (98.6)	119/120 (99.2)
6 months	131/134 (97.8)	113/115 (98.3)
12 months	116/123 (94.3)	102/105 (97.1)

Note N= number of subjects in the mITT population

Table 25: Proportion Free from Device and Procedure-Related AEs (ITT Subjects)

Subgroup	COVERA™ n/N (%)	PTA Alone n/N (%)
30 days	127/140 (90.7)	132/137 (96.4)
90 days	124/138 (89.9)	127/133 (95.5)
6 months	118/134 (88.1)	123/129 (95.3)
12 months	108/126 (85.7)	114/ 123 (92.7)

Note that the relationships with device/procedure of the events are based on CEC adjudications.
Note N = number of subjects in the ITT population

The following tables present information on additional timepoints with total number and mean values through 12-months.

Total Number of AV Access Circuit Reinterventions is defined as the number of reinterventions to the AV access circuit until access abandonment or through study completion. Total Number of Target Lesion Reinterventions is defined as the number of reinterventions to maintain target lesion patency.

Table 26: Total Number of AV Access Circuit Reinterventions (mITT Subjects)

Subgroup	COVERA™		PTA Alone	
	n	mean (SD)	n	mean (SD)
30 Days	7	0.05 (0.219)	6	0.05 (0.215)
90 Days	35	0.25 (0.528)	34	0.28 (0.609)
6 Months	103	0.77 (0.933)	107	0.91 (0.970)
12 Months	224	1.74 (1.487)	241	2.10 (1.606)

Table 27: Total Number of Target Lesion Reinterventions (mITT Subjects)

Subgroup	COVERA™		PTA Alone	
	n	mean (SD)	n	mean (SD)
30 Days	5	0.04 (0.186)	3	0.02 (0.154)
90 Days	16	0.12 (0.385)	24	0.20 (0.442)
6 Months	40	0.30 (0.615)	92	0.79 (0.850)
12 Months	93	0.76 (0.996)	195	1.71 (1.335)

Table 28: Number of Reinterventions at 12-months Based on Site Reported Data (mITT Subjects)

	COVERA™		PTA Alone	
	N[1]	n[2]	N[1]	n[2]
Total Number of AV Access Reinterventions	100	*226	102	*242
Total Number of Target Lesion Reinterventions	47	73	98	186
Non-Target Lesion at Time of Index Procedure	28	59	24	45
New Lesion within the Access Circuit	75	142	49	98
Access Thrombosis	16	19	13	17

[1] N = number of subjects with at least one AV access circuit / target lesion intervention
[2] n = total number of AV access circuit / target lesion interventions
*Note: in the site reported data there are 3 reinterventions (2 for the COVERA arm and 1 PTA) that were captured after abandonment of the AV Access, whereas the core lab adjudicated data (Table 29 below) summarizes reinterventions prior to abandonment only.

Table 29: Number of Reinterventions at 12-months Based on Core Lab Adjudicated Data (mITT Subjects)

	COVERA™		PTA Alone	
	N[1]	n[2]	N[1]	n[2]
Total Number of AV Access Reinterventions	100	*224	102	*241
Total Number of Target Lesion Reinterventions	57	93	100	195
Non-Target Lesion at Time of Index Procedure	25	54	23	44

	COVERA™		PTA Alone	
	N[1]	n[2]	N[1]	n[2]
New Lesion within the Access Circuit	60	103	40	72
Access Thrombosis	12	12	10	12

[1] N = number of subjects with at least one AV access circuit / target lesion intervention.
[2] n = total number of AV access circuit / target lesion interventions.
*Note: 3 reinterventions (2 for the COVERA arm and 1 PTA) occurred after the AV access was abandoned, and hence were not included in this table.

Table 30: All Access Circuit Reinterventions at 12 months (mITT Subjects)

	COVERA™ n/N (%)	PTA n/N (%)
AV Access Circuit Reinterventions Performed	226	242
Vessel		
Cephalic Vein	122 (54.2%)	124 (51.2%)
Basilic Vein	42 (18.7%)	77 (31.8%)
Subclavian Vein	13 (5.8%)	4 (1.7%)
Axillary Vein	3 (1.3%)	3 (1.2%)
Brachial Vein	0	1 (0.4%)
Other	45 (20.0%)	33 (13.6%)
Location		
Cephalic Vein Arch	37 (16.4%)	68 (28.1%)
Cephalic Vein Outflow	36 (16.0%)	11 (4.5%)
Juxta-Anastomotic	21 (9.3%)	3 (1.2%)
Basilic Vein Outflow	17 (7.6%)	27 (11.2%)
Basilic Vein Swing Point	2 (0.9%)	24 (9.9%)
Subclavian Vein	13 (5.8%)	3 (1.2%)
Anastomotic	7 (3.1%)	2 (0.8%)
Brachio Cephalic Vein	6 (2.7%)	0
Cannulation Zone	4 (1.8%)	3 (1.2%)
Forearm Venous Outflow	0	2 (0.8%)
Axillary Vein	2 (0.9%)	2 (0.8%)
Arterial Inflow	1 (0.4%)	1 (0.4%)
Superior Vena Cava (SVC)	1 (0.4%)	0
Other	78 (34.7%)	96 (39.7%)

Reinterventions were performed within the access circuit to treat target lesions, non-target lesions, new lesions, access thrombosis or for a combination of these factors. Considering all of these clinical factors for reintervention in the access circuit, subjects within the COVERA™ Vascular Covered Stent arm had 142 reinterventions that included at least one new lesion and subjects in the PTA-only arm had 98 reinterventions that included at least one new lesion. Table 31 identifies the treatment that was performed during these reinterventions and treatment outcome for each study arm.

Table 31: Access Circuit Reinterventions Involving New Lesion (mITT Subjects)

	COVERA™ n / N[1] (%)	PTA Alone n / N[1] (%)
Total Number of AV Access Circuit Reinterventions Involving New Lesion	142	98
Total Number of Subjects with at least one Reintervention involving New Lesion	75	49

	COVERA™ n / N[1] (%)	PTA Alone n / N[1] (%)
Treatment		
Standard PTA	140 (81.9%)	97 (78.9%)
Bare Metal Stent	11 (6.4%)	16 (13.0%)
Thrombectomy/Thrombolysis	11 (6.4%)	5 (4.1%)
Stent Graft	5 (2.9%)	4 (3.3%)
*Treatment, Other	3 (1.75%)	1 (0.6%)
Reintervention Successful		
Yes	138 (97.2%)	97 (99.0%)
**No	4 (2.8%)	1 (1.0%)

[1] N = total number of treatments involving new lesions
*Other treatment include: one surgical revision in each cohort, one thrombin injection for one subject in the Covera™ cohort and one procedure abandonment due to guidewire prolapse in the Covera™ cohort.
**Site reported reasons for unsuccessful reintervention include; inability to gain retrograde AV access, thus procedure abandoned, persistent spasm and poor flow, insufficient fistula, high clot burden, and largely compliant lesion. The Covera™ device did not play a role in the reintervention outcome being negative.

Index of Patency Function (IPF) is defined as the time from the index study procedure to study completion or access abandonment divided by the number of visits for a reintervention performed on the AV access circuit in order to maintain vascular access for hemodialysis. A visit is defined as one (1) procedural event, regardless of the number or type of interventions performed during the visit. The index procedure is counted as the first visit to ensure all subjects have a denominator of at least one. Index of Patency Function – Target Lesion (IPF-T) is 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 32:Analysis of Index of Patency Function, Mean Values (mITT Subjects)

	COVERA™ Mean (SD)	PTA Alone Mean (SD)
Index of Patency Function (days)		
30 Days	29.22 (3.420)	29.28 (3.219)
90 Days	79.41 (20.511)	78.98 (20.770)
6 Months	126.06 (54.449)	116.11 (53.175)
12 Months	174.25 (109.601)	146.09 (89.723)
Index of Patency Function – Target Lesion (days)		
30 Days	29.44 (2.958)	29.64 (2.305)
90 Days	85.15 (15.349)	81.35 (18.243)
6 Months	156.32 (43.724)	121.75 (51.940)
12 Months	259.77 (115.373)	160.64 (87.338)

6. Summary of Deaths

There were thirty five (35) deaths reported in the 12-month follow-up period, of which fifteen (15) subjects (10.6%) were randomized to COVERA™ Vascular Covered Stent (following PTA) and twenty (20) subjects (14.5%) were

randomized to PTA. Deaths were not considered to be related to the study device or index procedure.

Table 33: Number of Deaths by Primary Reason of Death through 12 Months (ITT Subjects)

Primary Reason of Death	COVERA™ (N=142)	PTA (N=138)
Total Number of Deaths	15 (10.6%)	20 (14.5%)
Brain Aneurysm/Subdermal Hematoma	0 (0.0%)	1 (0.7%)
Cardiac Arrest	3 (2.1%)	6 (4.3%)
Cardiac Arrest - Cause Unknown	0 (0.0%)	1 (0.7%)
Cardiac Arrest Due To Ischemic Heart Disease	1 (0.7%)	0 (0.0%)
Cardio-Pulmonary Arrest	1 (0.7%)	0 (0.0%)
Cardiopulmonary Arrest	1 (0.7%)	0 (0.0%)
ESRD hospice- Stopped Dialysis	1 (0.7%)	0 (0.0%)
ESRD	0 (0.0%)	1 (0.7%)
ESRD Hospice- Stopped Dialysis	1 (0.7%)	0 (0.0%)
ESRD, Elective Withdrawal From Dialysis	1 (0.7%)	0 (0.0%)
Heart Failure And Traumatic Bleeding	0 (0.0%)	1 (0.7%)
Hospital Acquired Pneumonia	0 (0.0%)	1 (0.7%)
Hyperkalemia	0 (0.0%)	2 (1.4%)
Hypoglyceamia	1 (0.7%)	0 (0.0%)
Hypotension, Respiratory Failure	1 (0.7%)	0 (0.0%)
Metastatic Gastric Adenocarcinoma	0 (0.0%)	1 (0.7%)
Possible Infection Vs Encephalitis With Hyperkalemia	0 (0.0%)	1 (0.7%)
Profound Shock, Bradycardia, Altered Mental Status	0 (0.0%)	1 (0.7%)
Pulmonary Embolism	0 (0.0%)	1 (0.7%)
Respiratory Failure	1 (0.7%)	0 (0.0%)
Respiratory Failure; Persistent Refractory Septic Shock Due To Recurrent Infections With Waxing/Waning Lactic Acidosis	1 (0.7%)	0 (0.0%)
Sepsis.	1 (0.7%)	0 (0.0%)
Staph. Aureus Sepsis	1 (0.7%)	0 (0.0%)
Subject Terminated Dialysis	0 (0.0%)	1 (0.7%)
Terminal Colon carcinoma With Liver And Lung Metastasis	0 (0.0%)	1 (0.7%)
Suspected MI	0 (0.0%)	1 (0.7%)

7. Device Deficiencies

There have been two (2) device deficiencies reported as shown in Table 34. One patient had an uneventful index procedure and was successfully treated with a COVERA™ Vascular Covered Stent. During the 6 month follow-up physical exam the patient was found to have palpable high venous pressure, pulsatility of the access, and a pointed thrill in the central veins. The subsequent fistulagram showed an 80% stenosis and stent graft compression in the center portion of the device which was successfully resolved with balloon angioplasty.

Another patient had an uneventful index procedure and was successfully treated with a COVERA™ Vascular Covered Stent. Two months later, the patient presented with elevated venous pressure. A fistulagram was performed and the study device presented with stent graft compression at the proximal end. The narrowing was successfully treated with balloon angioplasty. During the 6-month follow up the patient did not experience any further AV access dysfunction or re-intervention.

These events were confirmed, however, a definite root cause could not be determined.

Table 34: Summary of Device Deficiencies through 12-months (As Treated Population)

	COVERA™ (N=140) n (%)	PTA (N=139) n (%)	Total (N=279) n (%)
Device Malfunction			
Yes	2 (1.4)	0	2 (0.7)
Failure Code			
Insufficient Stent Graft	1 (0.7)	0	1 (0.4)
Other	1 (0.7)	0	1 (0.4)
Was Device Used to Treat Subject?			
Yes	2 (1.4)	0	2 (0.7)

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 122 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 Circulatory Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM CLINICAL STUDY

A. Effectiveness Conclusions

To demonstrate clinically acceptable effectiveness, the primary effectiveness endpoint was evaluated against the rate of Target Lesion Primary Patency (TLPP) at 6 months for standard PTA alone. TLPP at 6 months post-index procedure was evaluated using the Kaplan-Meier analysis and results were 78.7% in the COVERA™ group and 47.9% in the PTA group. The results demonstrated that, with respect to TLPP, the COVERA™ Vascular Covered Stent was superior to the PTA control ($p < 0.001$) for treatment of stenoses in the venous outflow of patients dialyzing with an arteriovenous fistula. The key secondary effectiveness endpoint of TLPP at 12 months was also met. At 12 months, TLPP was 57.5% for COVERA™ treated subjects versus 21.2% in the PTA group.

The significant benefit in TLPP did not carry over to Access Circuit Primary Patency (ACPP). At 6 months, ACPP was 50.7% for COVERA™ treated subjects versus 43.8% in the PTA group. The key secondary effectiveness endpoint for ACCP at 6 months was not met (p-value = 0.0846).

Reintervention data for the two study cohorts at 12 months are tabulated below:

Table 35: Reintervention Data for the two study cohorts

	COVERA™ Group	PTA Group
Total number of access circuit reinterventions	226	242
Total number of target lesion reinterventions	93	195
Total number of reinterventions for new lesions in the access circuit	142	98
Number of subjects requiring access circuit reinterventions	100	102
Number of subjects requiring target lesion reinterventions	57	100
Number of subjects with reinterventions for new lesions in the access circuit	75	49

While the total number of reinterventions for access circuit were similar, there was a considerable reduction in the number of reinterventions for the target lesions after treatment with COVERA™ Vascular Covered Stent compared to PTA alone. However, more reinterventions for new lesions in the access circuit were required in the COVERA™ treated group compared to the PTA alone group. Secondary patency for the COVERA™ treated subjects was 94.3% and for the PTA group was 97.1%.

With regards to enhancing primary patency of the target lesion, the clinical study results are adequate to provide a reasonable assurance of the effectiveness of the COVERA™ Vascular Covered Stent.

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.

The primary safety endpoint was a measure of safety through 30 days post-index procedure. The primary safety endpoint was evaluated against standard PTA alone. Freedom from protocol-defined primary safety events through 30 days post-index procedure was 95.0% in the COVERA™ group and 96.4% in the PTA group. This confirms non-inferiority of the COVERA™ device with respect to primary safety with a p-value of 0.0022.

The rate of arteriovenous fistula site complications was higher in the COVERA™ group compared to the PTA group, which reported no AV site complications. For the COVERA™ group, at 12 months, a total of 7 of these events were adjudicated by the CEC as device related, of which 5 of them were adjudicated as procedure related as well. The events included pain in the access arm, erythematous skin over stent, swelling, thrill/ bruit and pulsatility. These minor events do not impact the safety profile of the COVERA™ Vascular Covered Stent.

A total of 35 deaths were reported in the study (15 in the COVERA™ group and 20 in the PTA group) and none of the deaths were considered to be related to the study device or index procedure.

Overall, 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 outflow of AV fistulae.

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 outflow of AV fistulae is improved target lesion primary patency. The likelihood of a patient experiencing a benefit is high, based on the TLPP rate of 78.7% at 6 months compared to 47.9% in the PTA arm. The significant improvement in TLPP after treatment with COVERA™ did not equate to a similar degree of improvement in ACPP. ACPP at 6 months was 50.7% in subjects treated with COVERA™ compared to 43.8% in the PTA arm.

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 95.0% (133/140) in subjects treated with the COVERA™ Vascular Covered Stent as compared to 96.4% (132/137) in subjects treated with PTA alone. 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 outflow of AV fistula, the probable benefits in improved TLPP after COVERA™ treatment outweigh the probable risks of safety events.

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 indication for use. The results of the AVeNEW study demonstrate safety and effectiveness for treatment of stenoses in the venous outflow of AV fistulas. The benefits of the use of the COVERA™ Vascular Covered Stent include superior TLPP at 6 months, as well as reduction in the need for target lesion reintervention at 12 months, as compared to standard PTA alone. ACPP at 6 months was numerically better for subjects treated with the COVERA™ Vascular Covered Stent than those treated with PTA alone, however, the difference was not statistically significant. The difference in ACPP rates between the two treatment arms increased slightly at 12 months, favoring the COVERA™ Vascular Covered Stent. The number of access circuit reinterventions was similar between the two treatment arms. The benefits in enhanced TLPP are clinically meaningful and were achieved with minimal added risk of safety events through 30 days when considered in the context of known risks of PTA alone.

XIII. CDRH DECISION

CDRH issued an approval order on March 1, 2019. The final conditions of approval cited in the approval order are described below.

Bard has agreed to provide a Clinical Update to physician users of the ongoing experience with the COVERA™ Vascular Covered Stent to physician users at least annually through completion of the AVeNEW study and the COVERA™ Post Approval Study. At a minimum, this update will include a summary of the number of patients for whom data are available, with the rates of acute technical success, acute procedural success, target lesion primary patency, access circuit primary patency, and secondary patency, index of patency function, index of patency function-target lesion, total number of reinterventions for the access circuit, total number of reinterventions for the target lesion, and device/procedure related adverse events. Reasons for reinterventions, along with their description and outcome, and reasons for loss of secondary patency are to be provided. Additional relevant information from commercial experience within and outside the United States is also to be included as well as a summary of pertinent published literature. The clinical update for physician users must be provided to the FDA in the Annual Report.

In addition to the Annual Report requirements, Bard has agreed to provide the following data in post-approval study (PAS) reports for each PAS listed below.

1. Completion of AVeNEW Study: This study includes continued follow up of the previously enrolled IDE subjects (142 in the COVERA™ group and 138 in the PTA alone group) at 24 sites. The purpose of the study is to evaluate the long-term safety and effectiveness of the COVERA™ Vascular Covered Stent. All study subjects are to be followed through 36 months. A telephone screen to the subject and the dialysis center is to be performed at all follow-up visits. Clinical outcomes at 18, 24, and 36 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.

2. COVERA™ Post Approval Study: The COVERA™ Post Approval Study includes new enrollment of 100 subjects at up to 35 sites who will be treated using the COVERA™ Vascular Covered Stent only. The purpose of the study is to evaluate clinical outcomes under real world conditions and to evaluate the long-term safety and effectiveness of the COVERA™ Vascular Covered Stent. All study subjects are to be followed through 36 months. A telephone screen to the subject and the dialysis center is to be performed at all follow-up visits. The 6-month follow-up is to occur via an office visit to the investigational site in addition to the phone call to the dialysis center. Clinical outcomes at 30 days, 90 days, 6, 12, 18, 24, and 36 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. Acute technical success and acute procedural success will also be evaluated. These endpoints will be analyzed descriptively and presented both separately and combined with the AVeNEW study cohort.

   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.