AVeVA
CLINICAL STUDY

CLINICAL STUDY PROTOCOL

Title:	**Prospective, Multi-Center Clinical Study of the Bard® COVERA™ Arteriovenous (AV) Stent Graft in the Treatment of Stenosis at the Graft-Vein Anastomosis of AV Graft Circuits (AVeVA)**
Protocol Number:	**BPV-15-001**
Study Type:	**Investigational Device Exemption (IDE)**
Date:	**February 3, 2016**
Version:	**1.0**
Study Device:	**COVERA™ Vascular Covered Stent**
Sponsor:	**Bard Peripheral Vascular, Inc.** 1625 West 3rd Street Tempe, AZ 85281
NCT Number:	02790606 *

*NCT Number added post-approval per CT.gov requirement

Sponsor – Joshua Smale, Associate Director, Clinical Affairs — Date: 3/31/2016

Lead Principal Investigator – Bart Dolmatch, MD — Date: 4/4/2016

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1 PROTOCOL SUMMARY

<table>
<tr><td>Title:</td><td>Prospective, Multi-Center Clinical Study of the COVERA™ Arteriovenous (AV) Stent Graft in the Treatment of Stenosis at the Graft-Vein Anastomosis of AV Graft Circuits</td></tr>
<tr><td>Sponsor:</td><td>Bard Peripheral Vascular, Inc.
1625 West 3rd Street
Tempe, AZ 85281</td></tr>
<tr><td>Objective:</td><td>The objective of this study is to assess the safety and effectiveness of the COVERA™ Vascular Covered Stent for the treatment of stenotic lesions at the graft-vein anastomosis of hemodialysis patients dialyzing with a synthetic AV graft.</td></tr>
<tr><td>Design & Overview:</td><td>This is a prospective, multi-center, non-randomized, single-arm clinical study designed to assess the safety and effectiveness of the COVERA™ Vascular Covered Stent for the treatment of stenotic lesions at the graft-vein anastomosis of hemodialysis subjects with a synthetic AV graft. Safety and effectiveness measures of subjects receiving the COVERA™ Vascular Covered Stent will be compared to Performance Goals (PG) derived from the results reported in clinical literature as well as those of other prospective pivotal and post-market studies.

Follow-up for all treated subjects will be performed at hospital discharge, 30 and 90 days, as well as 6, 12, 18, and 24 months post-index procedure.</td></tr>
<tr><td>Study Device:</td><td>The COVERA™ Vascular Covered Stent is a highly flexible self-expanding endoprosthesis comprised of expanded polytetrafluoroethylene (ePTFE) encapsulating a nitinol (nickel-titanium alloy) stent framework. The inner lumen of the stent graft (blood contacting surface) is carbon impregnated.
The COVERA™ Vascular Covered Stent is available in a straight and a flared configuration. Devices will come on either an 8F or 9F system.
Table 1: COVERA™ Vascular Covered Stent Sizes
<table>
<tr><th rowspan="2" colspan="2">Covered Stent Outer Diameter (mm)</th><th colspan="5">Covered Stent Length (mm)</th><th rowspan="2">Endovascular System Length (cm)</th></tr>
<tr><th>30*</th><th>40</th><th>60</th><th>80</th><th>100</th></tr>
<tr><td rowspan="5"></td><td>6</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td rowspan="5">80 and 120</td></tr>
<tr><td>7</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>8</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr>
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<tr><td>10</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr>
</table>
* Note: only the straight configuration of the implant is available in 30mm length.</td></tr>
<tr><td>Enrollment:</td><td>Enrollment will continue until a total of one-hundred nine (109) subjects are treated with the COVERA™ Vascular Covered Stent. All subjects will be followed for 24 months post index procedure.</td></tr>
<tr><td>Investigational Sites:</td><td>Up to 30 investigational sites in the United States (US).</td></tr>
<tr><td>Study Population:</td><td>Male or non-pregnant female ≥ 21 years of age with an expected lifespan sufficient to allow for completion of all study procedures. Eligible subjects will have a synthetic AV access graft with a hemodynamically significant stenosis at the graft-vein anastomosis.</td></tr>
</table>

Inclusion Criteria:	**Clinical Inclusion Criteria** 1. Subject must voluntarily sign and date the Informed Consent Form (ICF) prior to collection of study data or performance of study procedures. 2. Subject must be either a male or non-pregnant female ≥ 21 years of age with an expected lifespan sufficient to allow for completion of all study procedures. 3. Subject must be willing to comply with the protocol requirements, including clinical and telephone follow-up. 4. Subject must have a synthetic AV access graft located in an arm that has been implanted for ≥ 30 days and must have undergone at least one successful dialysis session prior to the index procedure. **Angiographic Inclusion Criteria** 5. Subject must have angiographic evidence of a stenosis ≥ 50% (by visual estimation) located at the graft-vein anastomosis of the subject's synthetic AV access graft and present with clinical evidence of graft dysfunction at the synthetic AV graft-vein anastomosis. 6. The target lesion must be ≤ 9cm in length. Note: multiple stenoses may exist within the target lesion. 7. The reference vessel diameter of the adjacent non-stenotic vessel must be between 5.0 and 9.0mm.
Exclusion Criteria:	**Clinical Exclusion Criteria** 1. The subject is dialyzing with an AV fistula. 2. The hemodialysis access is located in the lower extremity. 3. The subject has an infected AV access graft or uncontrolled systemic infection. 4. The subject has a known uncontrolled blood coagulation/bleeding disorder. 5. The subject has a known allergy or hypersensitivity to contrast media which cannot be adequately pre-medicated. 6. The subject has a known hypersensitivity to nickel-titanium (Nitinol) or tantalum. 7. The subject has another medical condition, which, in the opinion of the Investigator, may cause him/her to be non-compliant with the protocol, confound the data interpretation, or is associated with a life expectancy insufficient to allow for the completion of study procedures and follow-up. 8. The subject is currently participating in an investigational drug or another device study that has not completed the study treatment or that clinically interferes with the study endpoints. *Note: Studies requiring extended follow-up visits for products that were investigational, but have since become commercially available, are not considered investigational studies.* **Angiographic Exclusion Criteria** 9. Additional stenotic lesions (≥ 50%) in the venous outflow that are > 3cm from the edge of the target lesion and are **not** successfully treated (defined as < 30% residual stenosis) prior to treating the target lesion. 10. An aneurysm or pseudoaneurysm is present within the target lesion. 11. The location of the target lesion would require the COVERA™ Vascular Covered Stent be deployed across the elbow joint. 12. The target lesion is located within a stent or stent graft. 13. The location of the target lesion would require that the COVERA™ Vascular Covered Stent be placed in the central veins (subclavian, brachiocephalic, Superior Vena Cava (SVC)) or under the clavicle at the thoracic outlet. 14. There is incomplete expansion of an appropriately-sized angioplasty balloon to its

	expected profile, in the operator's judgment, during primary angioplasty at the target lesion prior to implantation of the study device.
Procedures:	All subjects will undergo a clinical evaluation at screening (prior to index procedure); treated subjects will undergo a clinical evaluation prior to hospital discharge. A telephone screen to the subject and the dialysis center will be performed at all follow-up visits.
Primary Endpoints:	The primary effectiveness endpoint of the study is an effectiveness measure based on Target Lesion Primary Patency (TLPP) through 6-months post index procedure. The primary effectiveness endpoint will be evaluated against a performance goal (PG) of 40%. The primary safety endpoint is a safety measure based on safety through 30 days post index procedure. The primary safety endpoint will be evaluated against a PG of 88%.
Secondary Endpoints:	**Secondary Endpoints without Hypothesis Testing** • TLPP through 30 days, 90 days, 12 months, 18 months, and 24 months. • Access Circuit Primary Patency (ACPP) through 30 days, 90 days, 6 months 12 months, 18 months, and 24 months. • Rate of device and procedure related AEs involving the AV access circuit through 90 days, 6 months, 12 months, 18 months, and 24 months. • Total Number of AV Access Circuit Reinterventions through 30 days, 90 days, 6 months, 12 months, 18 months, and 24 months. • Total Number of Target Lesion Reinterventions through 30 days, 90 days, 6 months, 12 months, 18 months, and 24 months. • Index of Patency Function (IPF) evaluated at 30 days, 90 days, 6 months, 12 months, 18 months, and 24 months. • Index of Patency Function – Target Lesion (IPF-T) evaluated at 30 days, 90 days, 6 months, 12 months, 18 months, and 24 months. • Secondary Patency evaluated through 30 days, 90 days, 6 months, 12 months, 18 months, and 24 months. • Acute Technical Success. • Acute Procedure Success (Anatomic and Clinical Success).
Lead Principal Investigator:	Bart Dolmatch, M.D. Interventional Radiology The Palo Alto Medical Foundation 701 E. El Camino Real, 3rd Floor Mountain View, CA 94040 Telephone: (650) 404-8446

2 STATISTICAL ANALYSIS PLAN

2.1 Overview of Study Design

The clinical study will be a prospective, multi-center, non-randomized, single-arm study with the primary objective to demonstrate the effectiveness and safety of the COVERA™ Vascular Covered Stent for treatment of lesions at the graft-vein anastomosis of patient's dialyzing with synthetic AV grafts.

2.2 Analysis populations

The analysis populations will be defined as follows for this study:

- The ITT population will consist of all subjects that have met all eligibility criteria, undergone successful PTA of the target lesion, and into which the COVERA™ Vascular Covered Stent System is introduced (i.e. the delivery system enters the subject's body).

  Subjects who do not receive the study device, but into which the COVERA™ Vascular Covered Stent System was introduced, will be included in the ITT population. Subjects who require additional treatment modalities will be included in the ITT population.

- The Modified ITT (MITT) population will consist of any subjects in the ITT population who are treated with the COVERA™ Vascular Covered Stent (following PTA).

- A Per-Protocol (PP) population may be created if there are subjects who have any major protocol deviations. The PP population will consist of any subjects in the MITT population who do not have any major protocol deviation. The protocol deviations that are considered to have a "major" grade will be defined a priori in the analysis plan.

All analyses including the primary analyses will be primarily based on the MITT population. Key safety analysis will be performed based on ITT population as well. PP analyses may also be performed for the primary endpoints. They will only serve as sensitivity analyses for the primary analyses which are based on the MITT population.

2.3 Assessment of the Poolability of Investigational Sites

The sites will be tested for potential differences in the primary endpoints. Sites with fewer than 10 treated subjects may be combined for this purpose. The sites with less than 10 subjects will be sorted by site number and pooled by order to form one or more combined site(s) with at least 10 treated subjects. A logistic regression analysis will be performed with sites as a fixed effect. If the p-value associated with the site effect is <0.15, it will be considered as evidence of statistical significance. Additional analyses

will be performed to explore the differences between sites to assess their potential causes and whether or not they are clinically meaningful.

2.4 Handling of Missing Data

Study endpoints may be missing due to withdrawal of consent, Investigator's decision, LTF and subject death. It is important to minimize missing data by all means and always record the reason for missing. Missing data will be handled as described subsequently.

As a sensitivity analysis, the primary effectiveness and safety endpoints will also be analyzed using survival analysis techniques. In survival analyses, unobserved endpoints are a standard part of the analysis; they are known as "censored observations". As long as the censoring is unrelated to the treatment, this method of handling missing endpoints produces unbiased estimates of the freedom-from-event rates. For both primary endpoints, the reason for the censoring of all subjects with missing endpoints will be reported. If there is any indication that the censoring is related to the study intervention, a worst-case analysis may be performed for each primary endpoint, in addition to the standard analysis. In a worst-case analysis, an event will be assumed to have occurred at the time the subject was censored for all such subjects.

In addition, regardless of whether missing data are related to the study intervention, a tipping-point analysis will also be performed, in which assumptions about missing data are varied from worst-case to best-case to examine at what point the missing data would alter the results of the analysis.

2.5 Sample Size Estimation

The sample size calculation assumes the following:

1) Primary Effectiveness Endpoint – TLPP at 6 months performance goal.
   - Assumptions:
     - The COVERA™ Vascular Covered Stent composite freedom from event rate is estimated at 55%;
     - The PG is set at 40%;
     - Attrition (drop-out) rate (by 6 months) = 15%;
     - The Type 1 error, $\alpha = 0.05$ (one-sided); and
     - The Type 2 error, $\beta = 0.10$ (Power = 1 - β = 90%).
   - Sample Size:
     - 109 treated subjects [93 evaluable] will give 90% power with one-sided type I error =0.05.

2) Primary Safety Endpoint – Safety at 30 days:
   - Assumptions:
     - The primary safety rate through 30 days in the study device treated subjects is 98%;
     - The PG is set at 88%;

- Attrition rate (by day 30) = 5%; and
- The Type 1 error, $\alpha = 0.05$ (one-sided).

- Sample Size:
  - 109 treated subjects [104 evaluable] will give 99% power with one-sided type I error =0.05.

Hence, the sample size of 109 subjects will provide approximately (99%)*(90%)=89% power for the both primary effectiveness and primary safety endpoint.

2.6 Primary Endpoints

2.6.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint of the study is an effectiveness measure based on Target Lesion Primary Patency (TLPP) through 6-months post index procedure.

2.6.2 Primary Effectiveness Endpoint Hypothesis Test

The primary effectiveness endpoint is TLPP through 6-months. Objective: To assess if the 6 month TLPP for the COVERA™ Vascular Covered Stent is greater than the effectiveness PG.

The primary effectiveness endpoint will be evaluated by the following hypothesis:

H_0: The proportion of subjects in the study device treatment group (P_{CE}) with TLPP through 6 month post index procedure is less than or equal to that of the effectiveness PG of 40%.

H_1: The proportion of subjects in the study device treatment group (P_{CE}) with TLPP through 6 month post index procedure is greater than that of the effectiveness PG of 40%.

That is:

H_0: $P_{CE} \leq 40\%$,

H_1: $P_{CE} > 40\%$,

Rejection of the null hypothesis will signify that the 6 month TLPP of the COVERA™ Vascular Covered Stent is greater than the effectiveness PG of 40%.

A one sided p-value will be derived based on an exact binomial test. The study device will be considered to have achieved the primary effectiveness 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 exact method is greater than 40%.

2.6.3 Primary Safety Endpoint

The primary safety endpoint is a safety measure based on safety through 30 days post index procedure.

2.6.4 Primary Safety Endpoint Hypothesis Test

The primary safety endpoint is safety through 30 days. Objective: To assess if the 30-day primary safety rate for the study device is greater than the safety PG:

H_0: The proportion of subjects in the study device treatment group (P_{CS}) free from safety events in the primary safety endpoint is less than or equal to the safety PG of 88%.

H_1: The proportion of subjects in the study device treatment group (P_{CS}) free from safety events in the primary safety endpoint is greater that of the safety PG of 88%.

That is:

H_0: $P_{CS} \leq 88\%$,

H_1: $P_{CS} > 88\%$,

Rejection of the null hypothesis will signify that the 30 day safety of the COVERA™ Vascular Covered Stent is greater than the safety PG of 88%.

A one sided p-value will be derived based on an exact binomial test. The study device will be considered to have achieved the primary 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 exact method is greater than 88%.

2.7 Evaluation of Secondary Endpoints

The following secondary endpoints will be summarized with descriptive statistics (without formal statistical hypothesis testing) using the MITT population. For categorical variables, summary statistics will include frequency counts and percentages. For continuous variables, summary statistics will include mean, standard deviation, minimum, median, and maximum.

- TLPP through 30 days, 90 days, 12 months, 18 months, and 24 months.
- ACPP through 30 days, 90 days, 6 months, 12 months, 18 months, and 24 months.
- Rate of device and procedure related AEs involving the AV access circuit through 90 days, 6 months, 12 months, 18 months, and 24 months.

- Total Number of AV Access Circuit Reinterventions through 30 days, 90 days, 6 months, 12 months, 18 months, and 24 months.
- Total Number of Target Lesion Reinterventions through 30 days, 90 days, 6 months, 12 months, 18 months, and 24 months.
- IPF evaluated at 30 days, 90 days, 6 months, 12 months, 18 months, and 24 months follow-up.
- IPF-T evaluated at 30 days, 90 days, 6 months, 12 months, 18 months, and 24 months.
- Secondary Patency evaluated through 30 days, 90 days, 6 months, 12 months, 18 months, and 24 months.
- Acute Technical Success.
- Acute Procedure Success (Anatomic and Clinical Success).

2.8 Exploratory Analyses and Subgroup Analyses

The primary endpoints will be explored in subgroups:

- Gender;
- Geography;
- Lesion characteristics; and
- Presence of secondary lesion(s).

The information is intended to be reported in the device's labeling and will be summarized using descriptive statistics.

2.9 Interim Analysis

An interim analysis will be performed when all subjects have completed the 6-month follow-up visit.