


VERNACULAR 
Clinical Study
CLINICAL STUDY PROTOCOL

Title: The BARD® VENOVO™ Venous Stent Study – A Prospective, Non-Randomized, Multi-Center, Single-Arm Study of the Treatment of Iliofemoral Occlusive Disease – an Assessment for Effectiveness and Safety (VERNACULAR)

Protocol Number: BPV-14-007

Study Type: Investigational Device Exemption (IDE)

Date: January 31, 2018

Version: Version 2.0

Study Device: VENOVO™ Venous Stent System

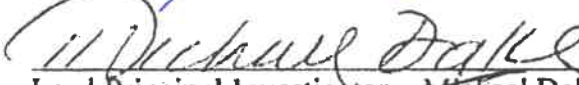
Sponsor: Bard Peripheral Vascular, Inc.
1625 West 3rd Street
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Sponsor – Josh Smale, Director, Clinical Affairs

3/13/18

Date



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03/02/18

Date



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03/03/18

Date

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Clinical Protocol Summary

Title:	The BARD [®] VENOVO [™] Venous Stent Study - A Prospective, Non-Randomized, Multi-Center, Single-Arm Study of the Treatment of Iliofemoral Occlusive Disease – an Assessment for Effectiveness and Safety (VERNACULAR)																																																																			
Sponsor:	Bard Peripheral Vascular, Inc. (“Bard”) 1625 West 3 rd Street Tempe, Arizona 85281 USA																																																																			
Objectives:	The objective of this study is to assess the safety and effectiveness of the VENOVO [™] Venous Stent for the treatment of symptomatic iliofemoral venous outflow obstruction. This would include Acute or Chronic Deep Vein Thrombosis (DVT), May-Thurner Syndrome, or any combination of the above.																																																																			
Design:	<p>This is a prospective, multi-center, non-randomized, single-arm clinical study of the VENOVO[™] Venous Stent for the treatment of symptomatic iliofemoral venous outflow obstruction. Safety and effectiveness measures of subjects receiving the VENOVO[™] Venous Stent will be compared to a Performance Goal (PG) derived from published literature.</p> <p>The study will be conducted at a maximum of 35 investigational sites (“sites”) in the United States, and Europe and Australia/New Zealand.</p> <p>Clinical follow-up for all treated subjects will be performed at hospital discharge, 30-days, and 6-, 12-, 24-, and 36-months post-index procedure.</p>																																																																			
Devices:	<p>The VENOVO[™] Venous Stent is comprised of a self-expanding nitinol (nickel-titanium) alloy. The diameter of the flared ends is approximately 3 mm larger than the diameter of the nominal stent body and contains radiopaque tantalum markers.</p> <p>Size Matrix:</p> <table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr> <th rowspan="2">Stent Diameter (mm)</th> <th rowspan="2">Delivery System Profile</th> <th colspan="7">Stent Length (mm)</th> </tr> <tr> <th>40</th> <th>60</th> <th>80</th> <th>100</th> <th>120</th> <th>140</th> <th>160</th> </tr> </thead> <tbody> <tr> <td>10</td> <td rowspan="2">8 Fr</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>12</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>14</td> <td>9 Fr</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>16</td> <td rowspan="3">10 Fr</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>18</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>20</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Stent Diameter (mm)	Delivery System Profile	Stent Length (mm)							40	60	80	100	120	140	160	10	8 Fr								12								14	9 Fr								16	10 Fr								18								20							
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Enrollment:	<p>Bard plans for enrollment to continue until a maximum of one-hundred seventy (170) subjects are treated with the VENOVO[™] Venous Stent which is an estimated three hundred forty (340) consecutive subjects in a non-randomized fashion.</p> <p>Subjects will be considered enrolled in the study at the time the informed consent document is signed (an estimated 340 subjects). After the subject has met all eligibility criteria and the VENOVO[™] Venous Stent catheter</p>																																																																			

	is introduced (i.e. delivery system enters the subject’s body), the subject will enter the primary analysis population (up to 170 subjects).
Investigational Sites:	Up to thirty-five (35) sites will be utilized for this study throughout the United States (U.S.), Europe, and Australia/New Zealand.
Study Population:	Subjects will be males or non-pregnant females, at least 18 years of age, with symptomatic iliofemoral venous outflow obstruction and an expected lifespan sufficient to allow for completion of all study procedures.
Eligibility Criteria:	<p><u>Inclusion Criteria</u></p> <ol style="list-style-type: none"> 1. The subject provides written informed consent using an Informed Consent Form (ICF) that is reviewed and approved by the Ethics Committee (EC) / Institutional Review Board (IRB) for the site. 2. Subject agrees to comply with the protocol-mandated follow-up procedures and visits. 3. The subject is a male or non-pregnant female ≥ 18 years old with an expected lifespan sufficient to allow for completion of all study procedures. Female subjects of childbearing potential must have a negative pregnancy test (urine or blood) within 14 days prior to the index procedure. 4. The subject has symptomatic (non-malignant) venous outflow obstruction in iliofemoral “venous segments” (unilateral obstruction of the common femoral vein, external iliac vein, common iliac vein, or any combination thereof) of $\geq 50\%$ as determined by catheter contrast venography. 5. The subject has symptomatic venous outflow obstruction (non-malignant) in iliofemoral venous segments with a Clinical-Etiology-Anatomic-Pathophysiologic Score CEAP “C” ≥ 3 or a Venous Clinical Severity Score VCSS pain score of ≥ 2. 6. The subject is able and willing to comply with any required medication regimen. 7. The reference vessel diameter(s) (RVD) is (are) between 7mm and 19mm as determined by the Investigator’s visual estimate. <p><u>Exclusion Criteria</u></p> <ol style="list-style-type: none"> 1. The subject is unable or unwilling to provide written informed consent, or is unable or unwilling to conform to the study protocol follow-up procedures and visits. 2. The subject is or plans to become pregnant during the study. 3. The subject has contralateral disease of the common femoral vein, external iliac vein, common iliac vein, or any combination thereof and does not meet the venous outflow obstruction requirement as determined by the treating Investigator or the target vessel has a malignant obstruction. 4. The subject is asymptomatic, has a CEAP “C” <3, or a VCSS pain score of <2. 5. The subject has a venous obstruction that extends into the inferior vena cava (IVC) or below the level of the lesser trochanter. 6. The subject has a known uncorrectable bleeding diathesis or active coagulopathy.

	<ol style="list-style-type: none"> 7. The subject has a known allergy or sensitivity to Nickel or Titanium or has intolerance to antiplatelet, anticoagulant or thrombolytic medications required per the protocol 8. The subject has a known allergy or sensitivity to contrast media, which cannot be adequately pre-medicated. 9. The subject has any planned surgical interventions (other than pre-stenting procedures of thrombolysis, thrombectomy, and/or vena cava filter placement in patients at high risk for pulmonary embolism) within 30 days prior to, or within 30 days after the planned study procedure. 10. The subject has a lesion(s) or occlusion(s) which cannot be traversed with a guidewire. 11. The subject has had prior stenting in the target vessel. 12. The subject has iliofemoral venous segments unsuitable for treatment with available sizes of study devices. 13. 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. 14. The subject is currently participating in an investigational drug, biologic, or another device study for which the investigational treatment has not ended. Studies requiring extended follow-up for products that are now commercially available are not considered investigational studies. 15. The subject is currently on dialysis or has a serum creatinine ≥ 2.5 mg/dl.
<p>Procedures:</p>	<p>All subjects will undergo a clinical evaluation at baseline/screening (prior to index procedure); treated subjects will undergo additional clinical evaluations prior to hospital discharge, at 30-days and 6-, 12-, 24- and 36-months post-index procedure.</p>
<p>Primary Endpoint:</p>	<p>Safety: Freedom from Major Adverse Events (MAEs) through 30 days Defined as the following:</p> <ul style="list-style-type: none"> • Device and/or procedure related death • Major amputation of target limb • Pulmonary Embolism which is clinically important (symptomatic with chest pain, hemoptysis, dyspnea, hypoxia, etc.) • Target Vessel Revascularization (TVR) • Vascular injury requiring surgical/endovascular intervention • Embolization/migration of stent • Device or procedure related acute DVT involving the treated limb <p>Efficacy: Primary Patency rate at 12 months defined as Freedom from TVR; freedom from thrombus occlusion and stenosis $> 50\%$ as measured by DUS. Note: Venography will be used only if investigator cannot successfully measure endpoint by DUS or if the investigator deems there is clinical need to perform invasive venography.</p>

<p>Secondary Endpoints:</p>	<ul style="list-style-type: none"> - Evaluation of VCSS Scores at 30 days, 6, 12, 24, and 36 months - Quality of Life Questionnaire (QOL) at 30 days, 6, 12, 24, and 36 months - Evaluation of CEAP Scores at 30 days, 6, 12, 24, and 36 months - Acute Procedure Success - Lesion Success - Acute Technical Success - Freedom From Target Lesion Revascularization (TLR) at 30 days, 6, 24, 36 months - Freedom From Target Vessel Revascularization (TVR) at 30 days, 6, 24, 36 months - Primary Patency at 24, 36 months - X-ray analysis for stent fracture at 12, 24, and 36 months
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Please refer to Site Contacts List for all Sponsor, Investigator, and Vendor contact information.

1 STATISTICAL ANALYSIS PLAN

1.1. Analysis Populations

Several populations of patients enrolled into the trial need to be defined.

The intent-to-treat (ITT) population consists of those subjects who have signed the Informed Consent Form and had the VENOVO™ Venous Stent catheter introduced (i.e., delivery system enters the subject's body).

Subjects who do not receive the study implant (section 5.2.2), but in whom the VENOVO™ Venous Stent catheter was introduced will be included in the ITT population. Subjects who need more than two (2) VENOVO™ Venous Stents (section 5.2.3) or undergo other treatment modalities (section 5.2.4) will be included in the ITT population.

A per-protocol (PP) population may be created if there are subjects who have any major protocol deviations. Major Protocol Deviations are defined as those that occur to protect the life or physical well-being of a subject in an emergency, or those that may affect the scientific soundness of the study, or the rights, safety or welfare of human subjects. The PP population will consist of any subjects in the ITT population who receive at least one stent and do not have any major protocol deviations, including deviations of study eligibility criteria. Subjects who need more than two (2) VENOVO™ Venous Stents, require placement of a commercially-available stent (section 5.2.3), or undergo other treatment modalities (section 5.2.4) will be excluded from the PP population.

All effectiveness and safety analyses including the primary analysis will be primarily based on the ITT population. A PP analysis may also be performed for the primary endpoint. It will only serve as a sensitivity analysis for the primary analysis which is based on the ITT population.

1.2. Primary Endpoints: Primary Study Hypotheses

For this study, the primary efficacy and primary safety endpoint will be considered as co-primary endpoints. That is, both primary efficacy and safety endpoint need to be significant to claim the study as successful.

1.2.1. Primary Efficacy Endpoint

The Primary Efficacy endpoint is the *primary patency* of the VENOVO™ Venous Stent (BVS) at 12 months post index procedure, which need to be better than the Performance Goal (PG) (74%) developed from the patency of other marketed stents at 12 months (see section 6.4 sample size consideration for the derivation of the PG).

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

- H₀: The primary patency rate at 12 months post index procedure from the overall VENOVO™ Venous Stent (BVS) patients (PTS and NIVL combined) is at most as good as that of the PG;
H_a: The primary patency rate at 12 months post index procedure from the overall VENOVO™ Venous Stent (BVS) patients (PTS and NIVL combined) is better than that of the PG;

$$H_0: 0.45 \times \pi_{NIVL} + 0.55 \times \pi_{PTS} \leq PP_{PG} \text{ v.s } H_a: 0.45 \times \pi_{NIVL} + 0.55 \times \pi_{PTS} > PP_{PG}$$

Where π_{PTS} is the true primary patency rate at 12-month post index procedure for PTS patients, π_{NIVL} is the true primary patency rate at 12-month post index procedure for NIVL patients, and $PP_{PG}=74\%$. The test statistics can be formulated as:

$$Z = \frac{0.45 \times p_{NIVL} + 0.55 \times p_{PTS} - 0.74}{\sqrt{\frac{(0.45)^2 \times PG_{NIVL}(1 - PG_{NIVL})}{n_{NIVL}} + \frac{(0.55)^2 \times PG_{PTS}(1 - PG_{PTS})}{n_{PTS}}}}$$

Where p_{PTS} and p_{NIVL} are observed primary patency rate at 12-month post-index procedure for PTS and NIVL patients, respectively. PG_{PTS} ($=77\%-10\%=67\%$) and PG_{NIVL} ($=93\%-10\%=83\%$) are expected value for PTS and NIVL patients under the null; n_{PTS} and n_{NIVL} are the number of PTS and NIVL patients in the analysis. A one-sided p-value will be calculated using a normal distribution. The study device will be considered to have achieved the primary efficacy objective if the one-sided p-value is less than 0.05.

1.2.2. Primary Safety Objective

The primary safety endpoint of the study is freedom from major adverse events (MAEs) and freedom from TVR through 30 days post-index procedure, as adjudicated by a Clinical Events Committee (CEC). The performance goal of free from primary safety event is 89%.

The primary safety endpoint will be evaluated by the following hypothesis: H_0 : The primary safety endpoint absence from event rate in the VENOVO™ Venous Stent (BVS) through 30 day at most as large as that of the PG;

H_a : The primary safety endpoint absence from event rate in the VENOVO™ Venous Stent (BVS) through 30 day is better than that of the PG;

$$H_0: M_{BVS} \leq M_{PG} \quad H_a: M_{BVS} > M_{PG}$$

Where $M_{PG}=89\%$ 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.

1.2.3. Handling of Missing Data

Study endpoints may be missing due to withdrawal of consent, investigator's decision to terminate, lost to follow-up and death. As long as the missing data is unrelated to the study intervention and the observed and unobserved data, limiting the analysis to those subjects who contribute endpoints produces unbiased estimates of the event rates.

The *reason* for missing data in any subject will be reported. If there is any indication that missing data is related to the study intervention, a worst-case analysis may be performed in addition to the standard analysis. In a worst-case analysis, a failure of effectiveness or safety will be assumed to have occurred at the time the subject was censored.

In addition, regardless of whether missing data are related to the study intervention, a tipping-point analysis will 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.

Multiple imputation will also be explored as another method to handle missing data.

1.2.4. Assessment of Poolability of Sites

The sites will be tested for potential differences in the primary endpoint. Sites with fewer than 10 treated subjects will be combined for this purpose. The pooling will be restricted within country. The sites with less than 10 treated subjects will be sorted by site number within each country 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 sites effect is < 0.15 , it will be considered as evidence of statistical significance.

If there are any site effects, the sites that have similar and dissimilar results will be grouped and exploratory analyses will be performed to investigate the potential reason for the differences among sites.

An analysis will be performed to examine the potential difference in the primary endpoint between the two geographic regions (US vs. OUS). A logistic regression model will be fit that includes fixed effect for geography. If the p-value of the geography effect is < 0.15 , it will be considered evidence of a statistically significant difference between the geographic regions, and additional analyses will be performed to explore the differences between geographies to assess their potential causes and whether or not they are clinically meaningful.

1.3. Evaluation of Secondary Endpoints (with and without hypotheses)

1.3.1. Control of Study-wise Type I Error

The Secondary Endpoints will be evaluated and tested only if the Primary Safety and Effectiveness hypotheses pass (i.e., both Primary non-inferiority tests reject the null hypothesis). Two of the 4 secondary endpoints will include a hypothesis test. They will be tested along with the inequality test of the Primary Efficacy Objective. The method of adjusting the α -level of the tests described below will be used to ensure that the study-wide error rate does not exceed 0.05.

The Hochberg method for controlling multiple comparison will be used. Two p-values will be obtained for the two Secondary Endpoints with hypothesis tests. If the larger p-value is less than 0.05, then both endpoints are considered statistical significant; otherwise, if the larger p-value is greater than 0.05, the smaller p-value need to be less than 0.025 to claim statistical significance for that endpoint with smaller p-value.

1.3.2. Analysis of the VCSS Pain Assessment

The first Secondary Objective is to evaluate whether the *VCSS Pain Assessment* of the BVS improves between the baseline classification and the follow-up classifications at 6, 12, 24, and 36 months. The

emphasis will be on the change between baseline and 12 months, since that is the time of the endpoint for the Primary Efficacy Objective. The four classes of VCSS for pain have been discussed previously in this Investigational Plan. (The VCSS includes clinical signs and symptoms other than pain, but this objective focuses only on pain.)

The objective is to demonstrate that the distribution of classifications improves from baseline to each follow-up time, especially at 12 months. This requires testing the null hypothesis (H_0) that the distribution at the 12-month follow-up ($D_{BVS@12M}$) remains unchanged compared to baseline ($D_{BVS@BL}$) against the alternative hypothesis (H_a) that the distribution shifts toward lower (less pain) classes:

$$H_0: D_{BVS@12M} \geq D_{BVS@BL} \quad \text{vs} \quad H_a: D_{BVS@12M} < D_{BVS@BL}$$

The endpoint for each study subject is the VCSS pain class at baseline and at each follow-up time (6, 12, 24, and 36 months).

Paired mean difference of the 12-month follow-up and baseline pain score and 95% CI will be presented. If the mean difference < 0 and the two-sided p-value from the paired t-test is deemed significant based on the appropriate α -level as described above, this will indicate success for this endpoint.

In addition, the VCSS pain class at each time point will be summarized descriptively..

1.3.3. Analysis of the Quality of Life (CIVIQ-20 Assessment)

The second Secondary Objective is to evaluate whether the *QoL Assessment* of the BVS improves between the baseline classification and the follow-up classifications at 6, 12, 24, and 36 months. The emphasis will be on the change between baseline and 12 months, since that is the time of the endpoint for the Primary Efficacy Objective. The QoL instrument will be the CIVIQ-20 and its use in the trial has been discussed previously in this Investigational Plan.

The objective is to demonstrate that the mean improves from baseline to each follow-up time, especially at 12 months. This requires testing the null hypothesis (H_0) that the mean score at the 12-month follow-up ($QoL_{BVS@12M}$) remains unchanged compared to baseline ($QoL_{BVS@BL}$) against the alternative hypothesis (H_a) that the mean is lower (better):

$$H_0: QoL_{BVS@12M} \geq QoL_{BVS@BL} \quad \text{vs} \quad H_a: QoL_{BVS@12M} < QoL_{BVS@BL}$$

The endpoint for each study subject is the CIVIQ-20 score at baseline and at each follow-up time (6, 12, 24, and 36 months).

The QoL hypothesis test:

$$H_0: QoL_{BVS@12M} \geq D_{BVS@BL} \quad \text{vs} \quad H_a: QoL_{BVS@12M} < D_{BVS@BL}$$

will be tested using a paired t-test with the appropriate α -level as described above.

In addition, descriptive statistics of total CIVIQ-20 score as well as score of each dimension at each time point will be presented by visit.

1.3.4. Analysis of the CEAP Scores

The third Secondary Objective is to assess the CEAP scores at baseline, 6, 12, 24, and 36 months. Each classification factors at each time points will be summarized descriptively. No hypotheses will be tested.

1.3.5. Analysis of other Secondary Objective

The following secondary endpoints are intended to be reported in the device's labeling and will be summarized using descriptive statistics (sample size of reported values, means or proportions, standard deviations, and 95% confidence intervals). The details of the definition of the secondary endpoints are described in Section 3.2.

- Acute Procedure Success
- Lesion Success
- Acute Technical Success
- Target Lesion Revascularization (TLR)
- Target Vessel Revascularization (TVR)
- Patency at 24 and 36 months
- X-ray analysis for fracture at 12, 24, and 36 months

1.4. Sample Size Consideration

Primary Efficacy Endpoints:

Table 6.3-1 shows the possible combinations of proportions of patients that could be enrolled in the study along with the weighted mean primary patency (PP) and the sample size required for 85% power against the PG (PP_{PG}).

Bard has chosen the sample size for the trial required for 85% power when the proportion of NIVL patients with endpoints is 20% and the proportion of PTS patients is 80%. This is the company's best guess for the actual enrollment. The estimate from the literature of the PP is 80% (used as the alternative proportion in the sample size estimate) and the PP_{PG} is 70% (used as the null proportion). The sample size is 138 patients. (This row is highlighted in yellow in Table 1.3-1.). With 45:55 split of the sample size, the PP_{PG} becomes 74%. As indicated in Table 6.3-1, the sample size required for 85% power will be between 121 and 125, which is less than planned sample size 138. In other words, with the same sample size as planned, >85% power can be achieved.

All sample size estimates in Table 1.3-1 were made with PASS 12 (Hintze, J. (2013). PASS 12. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com) using the Fisher's Exact Binomial test for one proportion.

Note that the sample size of 138 patients is the number of evaluable patients. Up to 170 patients may be enrolled, depending on the losses-to-follow-up, deaths, and study withdrawals. Bard further estimates that approximately 50% of consented subjects will not meet the eligibility criteria (i.e., will

be Screen Failures), and therefore will not be enrolled in the study. The estimated consented population will therefore be 340 ($170/.5 = 340$).

Table 1.3 -1. Estimates of the Sample Size Based on the Proportions of NIVL and PTS Subjects in the Clinical Trial

NIVL %	PTS %	Weighted Mean PP	α	Performance Goal (PP _{PG})	Sample Size of BVS for 85% Power
5%	95%	77.9%	5%	68%	146
10%	90%	78.7%	5%	69%	140
20%	80%	80.4%	5%	70%	138
30%	70%	82.0%	5%	72%	132
40%	60%	83.6%	5%	74%	125
50%	50%	85.2%	5%	75%	121
60%	40%	86.9%	5%	77%	112

Primary Safety Endpoint:

The freedom-from-MAE rate estimated from the literature was 99%, which was used as the alternative proportion. The null proportion was the M_{PG} of 89%. With 42 BVS subjects, the study will have 85% power to detect a difference, and with 138 BVS subjects, the study power will be over 99%.

Overall study power: with taking into consideration of both co-primary efficacy and safety endpoints, with 138 BVS subjects, the overall study power is at least $85\% * 99\% = 84\%$.