CLINICAL STUDY PROTOCOL

Title:	**CONTINuous Infra-Inguinal Stenting Using the Bard® LifeStent® VascUlar Stent SysteMs ("CONTINUUM")**
Protocol Number:	**BPV-08-001**
Study Type:	**Post-Approval Study**
Date:	**April 16, 2014**
Version:	**Version 6.0**
Study Device:	**Bard® LifeStent® Vascular Stent System and LifeStent® XL Vascular Stent System**
Sponsor:	**Bard Peripheral Vascular, Inc. ("Bard")** **A division of C. R. Bard, Inc.** **1625 West 3rd Street** **Tempe, Arizona 85281**
Sponsor Contacts:	**Talar Saber** **Associate Project Manager, Clinical Affairs** **Telephone: (480) 379-2839** **Fax: (480) 449-2542** **E-mail: talar.saber@crbard.com**
Medical Monitor (MM):	**Bill Altonaga, M.D.** **1905 Bayhill Drive** **Melbourne, FL 32940** **E-mail: bill.altonaga@crbard.com**

NCT Number: 00908947 (NCT Number added post-approval per CT.gov requirement)

CONTINUUM PROTOCOL SUMMARY

Title:	**CONTINUUM** CONTINuous Infra-Inguinal Stenting Using the Bard® LifeStent® VascUlar Stent SysteMs
Objectives:	The objective of this study is to collect post-market confirmatory evidence of the safety and effectiveness of the Bard® LifeStent® Vascular Stent System, the LifeStent® XL Vascular Stent System, and the LifeStent® SOLO™ system (together the "LifeStent® Vascular Stent System").
Design:	This study is a prospective, multi-center, single-arm, non-randomized study enrolling subjects with lifestyle-limiting claudication or ischemic rest pain attributable to lesion(s) (stenosed, occluded, restenosed, or re-occluded) in the infra-inguinal segment (superficial femoral artery (SFA) and/or proximal popliteal artery) that are amenable to treatment by percutaneous transluminal angioplasty (PTA) and stenting. Investigators should select an appropriately sized device(s) to treat subjects with target lesion(s) up to 240 mm. Clinical follow-up for all subjects will be performed at hospital discharge, 30-days and 12-, 24-, and 36-months post-procedure.
Sponsor:	Bard Peripheral Vascular, Inc. ("Bard") 1625 West 3rd Street Tempe, Arizona 85281 USA
Devices:	Bard® LifeStent® Vascular Stent Systems: Stent Diameters: 6.0 and 7.0 mm Stent Lengths: LifeStent® 20, 30, 40, 60 and 80 mm LifeStent® XL 100, 120, 150 and 170 mm LifeStent® SOLO™ 20, 30, 40, 60, 80, 100, 120, 150, 170, and 200 mm
Enrollment:	A minimum of two-hundred thirty-four (234) subjects in a non-randomized fashion. At least 64 subjects with target lesion lengths < 160 mm and at least 64 subjects with target lesion lengths > 160 mm and ≤ 240 mm will be enrolled. In addition to the original 170 subjects required, at least 64 additional subjects treated with the 200 mm LifeStent® will be enrolled.

Investigational Sites:	Up to thirty-five (35) investigational sites ("sites") will be utilized for this study.
Procedures:	Subjects will undergo a clinical evaluation at baseline/screening (prior to index procedure), prior to hospital discharge, 30-days and 12-, 24- and 36-months post-procedure.
Medications:	Pre-Procedure: Subjects are to receive a minimum of 81 mg of aspirin (ASA) orally per day and a minimum of 75 mg of Clopidogrel orally per day, beginning the day of the index procedure, and no later than 2 hours following the index procedure. Post-Procedure: Subjects are to continue to receive a minimum of 81 mg of ASA orally per day for a recommended minimum of 6 months, and a minimum of 75 mg of Clopidogrel orally per day for a minimum of 12 weeks.
Study Population:	The study population will be comprised of subjects who present with lifestyle-limiting claudication or ischemic rest pain and are candidates for PTA and stenting. Prior to enrollment, each subject will have a diagnostic assessment that enables qualification of the target lesion(s). Subjects with lesion(s) in the infra-inguinal segment (SFA and/or proximal popliteal arteries) will be considered for enrollment. The reference vessel diameter must be $\geq$ 4.0 mm and $\leq$ 6.5 mm.
Primary Endpoints:	Safety (Death): – Freedom from occurrence of death at 30-days and 12-months post-index procedure. Effectiveness (Device Success): – Freedom from acute delivery failure; and, – Primary Target Lesion Patency (TLP) at 12-months post-index procedure.

Secondary Endpoints	– Freedom from Target Lesion Revascularization (TLR) and/or Target Vessel Revascularization (TVR) at 12-months post-index procedure. – Secondary Device Success (compared to RESILIENT LifeStent®). – Primary Safety of the *Target Lesion Lengths > 160 mm* subgroup compared to the *Target Lesions treated with the 200 mm LifeStent®* subgroup. – Primary Safety of the following subgroups: 1) *Target Lesion Lengths ≤ 160 mm*, 2) *Target Lesion Lengths > 160 mm and ≤ 240 mm*, and 3) *Target Lesions treated with the 200 mm LifeStent®*. – Primary Effectiveness of the *Target Lesion Lengths > 160 mm* subgroup compared to the *Target Lesions treated with the 200 mm LifeStent®* subgroup. – Primary Effectiveness of the following subgroups: 1) *Target Lesion Lengths ≤ 160 mm*, 2) *Target Lesion Lengths > 160 mm and ≤ 240 mm*, and 3) *Target Lesions treated with the 200 mm LifeStent®*. – Freedom from Fracture (FFF) at 12- and 24-months post-index procedure. – Primary TLP (Sustained and Expanded) for Target Lesion Lengths > 160 mm at 12-, 24- and 36-months post-index procedure. – Freedom from TLR and/or TVR for Target Lesion Lengths > 160 mm at 12-, 24-, and 36-months post-index procedure. – Secondary Safety defined as freedom from death (excluding 30-days and 12-months post-index procedure), stroke, myocardial infarction (MI), emergent surgical revascularization, significant distal embolization in target limb, target limb major amputation, and thrombosis of target vessel at 30-days and 12-, 24-, and 36-months post-index procedure. – Acute Technical Success defined as successful deployment of the stent to the intended location. – Acute Lesion Success defined as attainment of ≤ 30% residual stenosis of the target lesion using any percutaneous method and/or non-investigational device (i.e., post-dilatation). – Acute Procedure Success defined as lesion success and no peri-procedural complications (death, stroke, MI, emergent surgical revascularization, significant distal embolization in target limb, and thrombosis of target vessel). – Sustained Freedom from TLR and/or TVR at 24- and 36-months post-index procedure – Sustained Hemodynamic Success defined as sustained improvement of Ankle-Brachial Index (ABI) from baseline value of ≥ 0.15 at 30-days and 12-, 24-, and 36-months post-index procedure without the need for repeated TLR in surviving subjects. – Sustained Clinical Success defined as sustained cumulative improvement from baseline value of ≥ 1 category according to Rutherford et al[11] at 30-days and 12-, 24-, and 36-months post-index procedure without the need for repeated TLR in surviving subjects.

	– Sustained TLP at 24- and 36-months post-index procedure corresponding to PSR < 2.5. – Expanded TLP at 12-, 24- and 36-months post-index procedure corresponding to PSR < 3.0. – Cumulative (primary-assisted and secondary) TLP at 12-, 24-, and 36-months post-index procedure corresponding to PSR < 2.5, and PSR < 3.0. – Quality of Life as assessed by Walking Impairment Questionnaire (WIQ) at baseline, 30-days and 12-, 24- and 36-months post-index procedure.
Principal Investigators:	Mark D. Mewissen, MD Aurora St. Luke's Medical Center 2900 West Oklahoma Avenue Milwaukee, WI 53215 Jeffrey P. Carpenter, MD The Cooper Health System 1 Cooper Plaza Camden, NJ 08103
Clinical Affairs:	Talar Saber Bard Peripheral Vascular, Inc. 1625 West 3rd Street Tempe, Arizona 85281 USA
Contract Research Organization/Data Coordinator Center	Amy L. Stroud Project Manager Novella Clinical, Inc. 4309 Emperor Boulevard, Suite 400 Durham, NC 27703 Telephone: (919) 972-2442 Fax: (919) 484-7727 Email: astroud@novellaclinical.com
Angiographic/X-Ray Core Lab:	Phillippe Genereux, MD Cardiovascular Research Foundation 111 East 59th St, 12th Floor New York, NY 10022 Telephone: (646) 434-4571
Duplex Ultrasound Core Lab:	Michael R. Jaff, DO, FACP, FACC VasCore 62 Staniford Street Boston, MA 02114 Telephone: (617) 726-5552

Statistical Analysis Plan

1. Study Endpoints

Primary and two secondary effectiveness endpoints (i.e., freedom from TLR/TVR through 12-months post-index procedure, and secondary device success) will be compared to the RESILIENT trial results (historical control).

A. Primary Safety Endpoint

The primary safety endpoint of the study is defined as: Freedom from occurrence of death at 30-days and 12-months post-index procedure.

B. Primary Effectiveness Endpoint

The primary effectiveness endpoint of the study, device success, will collectively measure both acute and chronic effectiveness.

Acute effectiveness is defined as: Successful delivery of the stent to the intended site with the post-deployment stent length being within 10% of the pre-deployment stent length.

Chronic effectiveness is defined as: Primary Target Lesion Patency (TLP) at 12-months post-index procedure, as measured by DUS. TLP is defined as the interval following the index procedure until a DUS assessment indicates that the target lesion(s) is no longer patent; that is, the treated segment has a peak systolic velocity ratio (PSR) ≥ 2.5. PSR is determined by comparing velocities within the treated segment to the proximal normal arterial segment. In this study, a > 50% stenosis is defined as a PSR of ≥ 2.5.

C. Secondary Endpoints

1. **Freedom from TLR and/or TVR** through 12-months post-index procedure. TLR is defined as the interval following the index procedure until the first revascularization procedure (e.g. PTA, cryoplasty, etc.) of the target lesion. TVR is defined as the interval following the index procedure until the first revascularization procedure (e.g. PTA, stenting, surgical bypass, etc.) in the target vessel.

2. **Secondary Device Success** (compared to RESILIENT LifeStent®).

3. **Primary Safety** (freedom from occurrence of death at 30-days and 12-months post-index procedure) of the *Target Lesion Lengths > 160 mm* subgroup compared to the *Target Lesions treated with the 200 mm LifeStent®* subgroup.

4. **Primary Safety** (freedom from occurrence of death at 30-days and 12-months post-index procedure) of the following subgroups: 1) *Target Lesion Lengths ≤ 160 mm*, 2) *Target Lesion Lengths > 160 mm and ≤ 240 mm*, and 3) *Target Lesions treated with the 200 mm LifeStent®.*

5. **Primary Effectiveness** (Device Success) of *Target Lesion Lengths > 160 mm* subgroup compared to the *Target Lesions treated with the 200 mm LifeStent®* subgroup.

6. **Primary Effectiveness** (Device Success) of the following subgroups: 1) *Target Lesion Lengths ≤ 160 mm*, 2) *Target Lesion Lengths > 160 mm and ≤ 240 mm*, and 3) *Target Lesions treated with the 200 mm LifeStent®.*

7. **Freedom from Fracture** (FFF) at 12- and 24-months post-index procedure.

8. **Primary TLP (Sustained and Expanded) for Target Lesion Lengths > 160 mm** at 12, 24- and 36-months post-index procedure corresponding to PSR values of < 2.0, <2.5, and < 3.0.

9. **Freedom from TLR and/or TVR for Target Lesion Lengths > 160 mm** at 12-, 24-, and 36-months post-index procedure.

10. **Secondary Safety** defined as freedom from death (excluding 30-days and 12-months post-index procedure), stroke, MI, emergent surgical revascularization, significant distal embolization in target limb, target limb major amputation, and thrombosis of target vessel at 30-days and 12-, 24-, and 36-months post-index procedure.

11. **Acute Technical Success** defined as successful deployment of the stent to the intended location.

12. **Acute Lesion Success** defined as attainment of ≤ 30% residual stenosis of the target lesion using any percutaneous method and/or non-investigational device (i.e., post-dilatation).

13. **Acute Procedure Success** defined as lesion success and no peri-procedural complications (death, stroke, MI, emergent surgical revascularization, significant distal embolization in target limb, and thrombosis of target vessel).

14. **Sustained Freedom from TLR and/or TVR** at 24- and 36-months post-index procedure.

15. **Sustained Hemodynamic Success** defined as sustained improvement of Ankle-Brachial Index (ABI) from baseline value of ≥ 0.15 at 30-days and 12-, 24-, and 36-months post-index procedure without the need for repeated TLR in surviving subjects.

16. **Sustained Clinical Success** defined as sustained cumulative improvement from baseline value of ≥ 1 category according to Rutherford et al.[1] at 30-days and 12-, 24-, and 36-months post-index procedure without the need for repeated TLR in surviving subjects.

17. **Sustained TLP** at 24- and 36-months post-index procedure corresponding to PSR < 2.5.

18. **Expanded TLP** at 12-, 24- and 36-months post-index procedure corresponding to PSR < 3.0.

19. **Cumulative (primary-assisted and secondary) TLP** at 12-, 24-, and 36-months post-index procedure corresponding to PSR < 2.5 and PSR < 3.0.

20. **Quality of Life** as assessed by Walking Impairment Questionnaire (WIQ) at baseline, 30-days and 12-, 24- and 36-months post-index procedure.

2. Study Design

A. Overview

This study is a prospective, multi-center, single-arm, non-randomized study enrolling subjects with lifestyle-limiting claudication or ischemic rest pain attributable to lesion(s) (stenosed, occluded, restenosed, or re-occluded) in the infra-inguinal segment (superficial femoral artery (SFA) and/or proximal popliteal artery) that are amenable to treatment by percutaneous transluminal angioplasty (PTA) and stenting. Investigators should select an appropriately sized device(s) to treat subjects with target lesion(s) up to 240 mm. Clinical follow-up for all subjects will be performed at hospital discharge, 30-days and 12-, 24-, and 36-months post-procedure.

B. Study Population

The study population will consist of subjects with lifestyle-limiting claudication or ischemic rest pain attributable to lesion(s) (stenosed, occluded, restenosed, or re-occluded) in the infra-inguinal segment (SFA) and/or proximal popliteal artery) that are amenable to treatment by PTA and stenting. The reference vessel diameter must be ≥ 4.0 mm and ≤ 6.5 mm.

A minimum of 234 subjects will be enrolled at up to 25 sites throughout the United States.

C. Sample Size Determination

The protocol includes sample size considerations for the primary safety endpoint, the primary effectiveness endpoint and two secondary effectiveness endpoints (freedom from TLR/TVR through 12-months post-index procedure, and secondary device success). The secondary effectiveness (device success) endpoint required the largest sample size based on the following considerations:

> *Objective: To demonstrate that device success (combined acute and chronic effectiveness) in the CONTINUUM LifeStent® group is not inferior to the observed device success of the RESILIENT12 LifeStent® group at 12-months post-index procedure.*
>
> H_0: The device success rate at 12-months post-index procedure with CONTINUUM LifeStent® ($P_{CONTINUUM}$) is inferior to the device success rate with RESILIENT12 LifeStent® ($P_{RESILIENT}$).
>
> H_1: The device success rate at 12-months post-index procedure with CONTINUUM LifeStent® ($P_{CONTINUUM}$) is not inferior to the device success rate with RESILIENT12 LifeStent® ($P_{RESILIENT}$).
>
> $$H_0: P_{CONTINUUM} < P_{RESILIENT} - \delta \text{ vs. } H_1: P_{CONTINUUM} > P_{RESILIENT} - \delta$$

The sample size estimate assumes the following:

1. The acute effectiveness failure rate was approximately 10% and the TLP failure rate was 18% in the RESILIENT LifeStent® group. Thus, the success rate at 12-months post-index procedure was 72%.

2. The acute effectiveness failure rate in the CONTINUUM LifeStent® group is expected to be 1%. The TLP failure rate in the CONTINUUM LifeStent® group is expected to be equal to the RESILIENT LifeStent® group when the rates are adjusted for disease severity using the Cox's regression covariates (Rutherford Category, target lesion(s) lengths, total treated segment length and perhaps age, gender, etc.). Thus, the success rate at 12-months post-index procedure is expected to be 81%.

3. The number of subjects in the RESILIENT LifeStent® group was 134, and 112 subjects were evaluable for TLP at 12-months post-index procedure.

4. A Cox's time-to-event (survival) analysis with regression covariates will be used to estimate the survival proportions and their standard errors.

5. The Type 1 error, $\alpha = 0.05$ (one-sided because the hypothesis is non-inferiority).

6. The Type 2 error, $\beta \leq 0.20$ (Power = $1 - \beta = 80\%$).

7. Non-inferiority margin, $\delta = 7.5\%$.

8. The censoring rate through 12-months post-index procedure will be 15%.

According to PASS 2008 (using the Cox's survival analysis module), the sample size required for 80% power is 252 subjects with just over 50% in one of the groups. The RESILIENT LifeStent® group has 112, so implanting 140 (56%) or more CONTINUUM LifeStent® subjects will provide at least 80% power. When this is inflated to accommodate 15% censoring through 12-months post-index procedure, the CONTINUUM sample size is 165 subjects. This sample size estimate demonstrates that secondary effectiveness (device success) is the sample-size driver for this study.

However, a minimum of 170 subjects are required to be enrolled as originally agreed upon and referenced in the FDA Post-Market Approval (PMA) Approval Order of the Bard® LifeStent® Vascular Stent (P070014). The secondary endpoint, "Device Success" demonstrated that 165 subjects are necessary to power this endpoint, including adjusting for censoring; this is very close to the 170 subjects initially stipulated by FDA. In addition to this requirement, at least 64 additional subjects treated with the 200 mm LifeStent® will be enrolled (including adjustment for censoring), which results in a minimum enrollment of 234 subjects in the study.

D. Assessment Schedule

Subjects will undergo a clinical evaluation at baseline/screening (prior to index procedure), prior to hospital discharge, 30-days, and 12-, 24-, and 36-months post-procedure.

Time and Events Schedule

Observation	Baseline/ Screening	Intra-Procedure	Hospital Discharge	30 d (± 7d)	12 mo (± 30d)	24 & 36 mo (± 30d)
Eligibility Criteria	✓	✓				
Informed Consent	✓					
Demographics	✓					
Medical History	✓					
BUN/Creatinine and CBC	✓					
Pregnancy test HCG	✓[1]					
*Concomitant Medications	✓	✓	✓	✓	✓	✓
Comprehensive Physical Exam	✓		✓	✓	✓	✓
Angiogram	✓[2]	✓[3]				
Resting ABI	✓		✓	✓[4]	✓	✓
Rutherford (Category & Grade)	✓			✓	✓	✓
Adverse Event Assessment		✓	✓	✓	✓	✓
X-Ray (AP & lateral)					✓[3]	✓[3,5]
Color Flow Duplex Ultrasound				✓[6]	✓[6]	✓[6]
Quality of Life Questionnaire	✓			✓	✓	✓

[1]Perform urine pregnancy test for women who are of childbearing potential < 7 days prior to enrollment.
[2]Baseline angiogram may be performed, 30 days prior to study enrollment or day of study enrollment just prior to intervention
[3]Send images to Angiographic/X-Ray Core Laboratory
[4]Only required if subject's symptoms/vascular function has worsened.
[5]X-Ray Not Required at 36-Month Follow-Up.
[6]Send images to Ultrasound Core Laboratory
*Concomitant Medications; only record (anti-platelets, anti-coagulants, and direct thrombin inhibitors)