ARABIAN TRADE HOUSE CORP.
Mr. Sherif Wady
Legal & Regulatory Affairs Dep.
Tel: +966 11 419 1820
Fax: +966 11 419 1831
Mobile: +966 542260007
Email: S.wady@ath.com.sa
Legal@ath.com.sa
Riyadh – Saudi Arabia

04/10/2018

Reference: FA2018-38

URGENT FIELD SAFETY NOTICE

NOTIFICATION OF UPDATE TO LIFESTREAM LABELLING

Dear Customer,

This letter is to inform you of a Field Safety Corrective Action initiated by Clearstream Technologies (BD) involving the LifeStream Balloon Expandable Vascular Covered Stent.

Reason for Field Safety Notice

ClearStream Technologies is issuing a Field Safety Notice to advise users of an update to the Instructions For Use (IFU) for the LifeStream Balloon Expandable Vascular Covered Stent, per the enclosed labelling attachment (Attachment 1). This information will be included in the labelling of all future units distributed by ClearStream (BD).

The labelling update provides information on the current clinical study results of the BARD® LIFESTREAM™ Balloon Expandable Vascular Covered Stent in the Treatment of Iliac Artery Occlusive Disease (BOLSTER).

Specifically, the clinical study results demonstrate the safety and effectiveness of the LifeStream Balloon Expandable Vascular Covered Stent for the treatment of atherosclerotic lesions of the common or external iliac artery.

This was a prospective, multi-center, non-randomized, single-arm clinical study where a composite safety and effectiveness measure of subjects receiving the LifeStream Balloon-Expandable Covered Stent were compared to a Performance Goal (19.5%) derived from iliac stent published literature.

The primary endpoint of the study was a composite safety and effectiveness measure defined as device and/or procedure-related death or myocardial infarction (MI) through 30 days, or any Target Lesion Revascularization (TLR), target limb(s) major amputation, or restenosis through 9-months post-index procedure.

The findings from the Bolster Study demonstrate that at nine (9) months the primary composite endpoint of 11.6% met the Performance Goal (19.5%).

This is not a product recall and ClearStream is not requesting that any units be returned from the market as a result of this notification.

Our records show that your facility has purchased one or more units of the product under the scope of this Field Safety Notice as listed in Table 1 below.

Part Number	Balloon Diameter	Balloon Length	Shaft Length
LSM0800526	5	26	80
LSM0800537	5	37	80
LSM0800616	6	16	80
LSM0800626	6	26	80
LSM0800637	6	37	80
LSM0800658	6	58	80
LSM0800716	7	16	80
LSM0800726	7	26	80
LSM0800737	7	37	80
LSM0800758	7	58	80
LSM0800816	8	16	80
LSM0800826	8	26	80
LSM0800837	8	37	80
LSM0800858	8	58	80
LSM0800938	9	38	80
LSM0800958	9	58	80
LSM0801038	10	38	80
Part Number	Balloon Diameter	Balloon Length	Shaft Length

LSM0801058	10	58	80
LSM0801238	12	38	80
LSM0801258	12	58	80
LSM1350526	5	26	135
LSM1350537	5	37	135
LSM1350616	6	16	135
LSM1350626	6	26	135
LSM1350637	6	37	135
LSM1350658	6	58	135
LSM1350716	7	16	135
LSM1350726	7	26	135
LSM1350737	7	37	135
LSM1350758	7	58	135
LSM1350816	8	16	135
LSM1350826	8	26	135
LSM1350837	8	37	135
LSM1350858	8	58	135
LSM1350938	9	38	135
LSM1350958	9	58	135
LSM1351038	10	38	135
LSM1351058	10	58	135
LSM1351238	12	38	135
LSM1351258	12	58	135

Table 1: Affected Product Codes

Please be aware that your Competent Authority is being notified of this Field Safety Corrective Action.

As part of this action, we require that you follow the instructions below and notify Saudi Arabia International Business Centre (IBC) of your compliance with this Field Safety Corrective Action.

Required actions for you and your Healthcare Facility relating to this FSN

1. Pass this Field Safety Notice to all personnel involved with the use of the LifeStream Balloon Expandable Vascular Covered Stent System.
2. Ensure that the contents of this Field Safety Notice is understood by the associated personnel.
3. The enclosed labelling update (Attachment 1) is to be used in conjunction with the LifeStream Balloon Expandable Vascular Covered Stent Instructions for Use (IFU) for all LifeStream devices currently distributed.
4. If you have further distributed this product then please identify the organisation and notify them at once of this notification. You may include a copy of this letter in your notification.
5. Please complete the attached Reply Effectiveness Check Form and return to Saudi Arabia either by fax to: +966 11 4555072. Alternatively this can be emailed to: Ahmed.Shebah@crbard.com

Note: Although the return of product is not required by this FSN, it is extremely important that we receive your completed Reply Effectiveness Check Form as soon as possible.

We appreciate your cooperation and assistance in dealing with this matter and sincerely apologise for any inconvenience that may result from this action.

Should you have any questions or require assistance in this matter, please contact your local sales specialist or local BD Customer Service Representative.

Your Sincerely,

Ahmed Shebah
QA & Regulatory Manager
QA Regulatory

Ahmed.Shebah@crbard.com
C.R. BARD GmbH l Rabwa Plaza (Building# 4366) Umar Ibn Abdul Aziz Branch Rd l Al Rabwah Dist
2nd Floor l Office# 23A l P.O. Box 4366 Riyadh 12816
Kingdom of Saudi Arabia
t: +966 11 4555071
c: **+966 50 570 1439**
f: +966 11 4555072

1. Attachment 1: Text to be added to LifeStream IFU

REFERENCE: FA2018-38

REPLY EFFECTIVENESS CHECK FORM

LifeStream Balloon Expandable Vascular Covered Stent System

By completing the below information you confirm that the Field Safety Corrective Action Reference Number 2018-38 has been received by your Healthcare Facility or Organisation, that it has been read and understood and the requested actions have been completed.

Please PRINT Your Contact Information and fill form out completely	
Name	
Title	
Name of Account / Hospital	ARABIAN TRADE HOUSE CORP.
Contact Phone Number	
Signed	
Date	

Please return completed form to:

Ahmed Shebah
QA & Regulatory Manager
QA Regulatory
Ahmed.Shebah@crbard.com
t: +966 11 4555071
c: **+966 50 570 1439**
f: +966 11 4555072

Summary of Clinical Study

A total of 155 patients were treated at 17 investigational sites in the United States, Europe, and New Zealand in the prospective, multi-center, non-randomized, single- arm study of the Bard® LifeStream™ Balloon Expandable Vascular Covered Stent in the treatment of iliac artery occlusive disease (BOLSTER). Overall, 228 subjects were enrolled, of which 155 were treated with the study device and included in the As Treated Population. The objective of this study was to assess the safety and effectiveness of the Bard® LifeStream™ Balloon Expandable Vascular Covered Stent for the treatment of atherosclerotic lesions in common and external iliac arteries. A composite safety and effectiveness measure of subjects receiving the Bard® LifeStream™ Balloon Expandable Vascular Covered Stent was compared to a Performance Goal (PG) derived from iliac stent published literature.

At the time of this analysis, 155 subjects passed their 9-month visit and were evaluated for the primary and secondary endpoints. Patients will be followed through 36 months.

Study Endpoints

The primary endpoint of the study is a composite safety and effectiveness measure defined as device and/or procedure-related death or myocardial infarction (MI) through 30 days, or any Target Lesion Revascularization (TLR), target limb(s) major amputation, or restenosis through 9-months post-index procedure.

Device and/or procedure-related death, MI, and target limb(s) major amputation is adjudicated by a Clinical Events Committee (CEC). TLR is defined as the first revascularization procedure (e.g., PTA, atherectomy, etc.) of the target lesion(s) following the index procedure as determined by an Independent Angiographic Core Lab (or CEC, as necessary). Restenosis is assessed by duplex ultrasonography (DUS), where the target lesion(s) is determined to have a peak systolic velocity ratio (PSVR) > 2.4 with post-stenotic turbulence, as determined by an Independent DUS Core Lab. In this study, a PSVR of > 2.4 suggests > 50% restenosis.

Secondary endpoints included the following which are evaluated at various timepoints throughout the study: (1) Rate of Major Adverse Events (MAEs), (2) Acute Lesion Success, (3) Acute Procedure Success, (4) Acute Technical Success, (5) Target Lesion Revascularization (TLR), (6) Target Vessel Revascularization (TVR), (7) Sustained Clinical Success, (8) Primary Patency, (9) Primary Assisted Patency, (10) Secondary Patency, and (11) Quality of Life.

Patients Studied

Eligible patients had intermittent claudication or ischemic rest pain and angiographic confirmation of either de novo or restenotic (non-stented) lesion(s) ≥ 50% (including total occlusions) in the common and/or external iliac arteries. To be included in the study, the reference vessel diameter(s) was between 4.5mm and 12.0mm in diameter and the target lesion(s) was ≤ 100 mm in combined length (per side.) The patients must have had angiographic evidence of a patent profunda and/or superficial femoral artery.

Patients were excluded from the study if they had a vascular graft previously placed in the native iliac vessel, or if the subject suffered a hemorrhagic stroke or transient ischemic attack (TIA) within 3 months prior to the index procedure.

Methods

Eligible subjects were considered enrolled once he / she has agreed to study participation and provided consent. Once treated with the LifeStream™ balloon expandable vascular covered stent, clinical follow-up occurred at discharge, 30-days, and 9-, 12-, 24-, and 36-months post index procedure. Follow-up visits included
a comprehensive physical exam, duplex ultrasound, Rutherford classification assessment, ABI measurement, and quality of life assessment among other measures. A telephone screen for all treated subjects occurred at 6-months post- procedure.

An independent Clinical Events Committee (CEC) reviewed all adverse events and adjudicated all serious, unanticipated, and device-related adverse events.
Additionally, an independent Data Safety Monitoring Board (DSMB) reviewed safety information including site reported events and summaries of CEC adjudication activities. The DSMB determined and made recommendations on whether the study should continue as described, or if changes should be made.

Results

Patient Demographics

Tables 1-4 summarize the patient demographics, medical history, baseline characteristics, and target lesions treated.

Table 1: Patient Demographics

	Bolster (N=155)
Age(Years)	
N	155
Mean (SD)	64.3 (9.75)
Min - Max	42.0 – 86.0
Gender	
Male	107 (69.0%)
Female	48 (31.0%)
Weight(kg)	
N	151
Mean (SD)	79.6 (16.60)
Height(cm)	
N	154
Mean (SD)	170.7 (8.80)
BMI(kg/m2)	
N	151
Mean (SD)	27.2 (4.81)

Table 2: Patient Medical History

Category	Term	Bolster (N=155)
Cardiovascular Disease	Total	142 (91.6%)
	AAA	7 (4.5%)
	Angina	11 (7.1%)
	Aortic Disease	7 (4.5%)
	Atrial Fibrillation (A-FIB)	12 (7.7%)
	Congestive Heart Failure(CHF)	9 (5.8%)
	Coronary Artery Disease (CAD)	49 (31.6%)
	Dyslipidemia	101 (65.2%)
	Hypertension	117 (75.5%)
	Myocardial Infarction (MI)	21 (13.5%)
	Stroke	8 (5.2%)
	Other	54 (34.8%)
Renal Disease	Total	27 (17.4%)
	Hemodialysis	1 (0.6%)
	Renal Failure	3 (1.9%)
	Other	27 (17.4%)
Other Disease	Total	152 (98.1%)
	Cancer	13 (8.4%)
	Cigarette Smoking	132 (85.2%)
	Diabetes	50 (32.3%)
	Gastrointestinal Disorder	17 (11.0%)
	Respiratory Disorder	23 (14.8%)
	Other	78 (50.3%)

Note: One subject may take multiple medications

Table 3: Summary of Baseline Characteristics by Subject

	Bolster (N=155)
Treated Limb	
Bilateral	34 (21.9%)
Left Leg	72 (46.5%)
Right Leg	49 (31.6%)
Number of Target Lesions	
1	117 (75.5%)
2	34 (21.9%)
3	4 (2.6%)
Target Lesion Location	
Common Iliac Artery	103 (66.5%)
External Iliac Artery	36 (23.2%)
Both Common and External Iliac Artery	16 (10.3%)
Number of Treated Lesion Location	
1	111 (71.6%)
2	40 (25.8%)
3	4 (2.6%)
Treated Lesion Location	
Left Common Iliac Artery	83 (53.5%)
Right Common Iliac Artery	65 (41.9%)
Left External Iliac Artery	30 (19.4%)
Right External Iliac Artery	25 (16.1%)
Baseline/Pre-Procedure Stenosis[1]	
Occlusion	21 (13.5%)
Stenosis	134 (86.5%)
Baseline TASC Score[2]	
A	96 (61.9%)
B	42 (27.1%)
C	15 (9.7%)
D	2 (1.3%)

[1,2] If a subject has more than one lesion, the worst type will be used as the category for the Baseline / Pre-procedure Stenosis and Baseline TASC Score.

At the time of this analysis, the 197 lesions were treated with the LifeStream™ balloon expandable vascular covered stent. Table 4 shows the lesion characteristics that were treated.

Table 4: Summary of Target Lesions

	Bolster (N=155)
Degree of Calcification	
None	19 / 197 (9.6%)
Mild	51 / 197 (25.9%)
Moderate	89 / 197 (45.2%)
Severe	38 / 197 (19.3%)
Target Lesion Length (mm)	
N	197
Mean (SD)	30.7 (17.35)
Min – Max	3.0 - 100.0
Reference Vessel Diameter (mm)	
N	197
Mean (SD)	8.0 (1.27)
Min – Max	5.0 - 12.0
Target Lesion Stenosis (pre-intervention) %	
N	197
Mean (SD)	80.3 (13.60)
Min – Max	30.0 - 100.0

As reported by the Investigational Site.

Patient Accountability

Investigators treated 155 patients at 17 sites. In a Pre-Specified analysis, 130 subjects were evaluable at the 9-month timepoint. A Post-Hoc analysis was performed based on 138 subjects.

Primary Effectiveness Results

The primary endpoint of the study is a composite safety and effectiveness measure defined as device and/or procedure-related death or myocardial infarction (MI) through 30 days, or any Target Lesion Revascularization (TLR), target limb(s) major amputation, or restenosis through 9-months post-index procedure. The primary composite endpoint was analyzed by subject. The proportion of subjects with these efficacy events was compared to the performance goal of 19.5%.

Restenosis was determined by the DUS Core Lab based on objective measures of DUS imaging and did not rely on other imaging modalities, the need for re- intervention, or other clinical factors in order to determine the patency of lesions treated with the LifeStream™ device.

In a Pre-Specified analysis of the 155 subjects who were treated in the study, a total of 25 subjects were excluded from the 9-month analysis. 17 of these subjects were excluded for reasons such as unevaluable imaging, lost to follow-up before the 9-month assessment, or early termination. 8 subjects missed or did not have evaluable imaging at their 9-month visit and completed their 12-month visit at the time of this analysis.

Table 5: Primary Composite Endpoint Results (Pre-Specified Analysis)

	Bolster (N=155)	93.3% Confidence Interval
Subjects with the Composite Events	21/130 (16.2%)	(10.6%, 23.2%)
Subjects fail due to		
Device and/or procedure-related death (<=30 day)	0 / 130 (0.0%)	
Device and/or procedure-related MI (<=30 day)	0 / 130 (0.0%)	
Target limb(s) major amputation through 9 months*	1/ 130 (0.8%)	
TLR through 9 months	6 / 130 (4.6%)	
Restenosis through 9 months	15 / 130 (11.5%)	

* Not device and / or procedure related

As analyzed on a Pre-Specified basis, the primary composite endpoint result was 16.2% (p-value 0.1987) and did not meet the pre-defined statistical performance goal.

A Post-Hoc analysis was done. This analysis includes the 8 subjects who missed or did not have evaluable imaging at their 9-month visit but were evaluable at the 12-month visit. All 8 were subsequently judged patent by DUS Core Lab. Additionally, 5 subjects were deemed patent at the 9-month analysis by the CEC chair based on a review of DUS imaging and including evaluation of additional imaging where available, re-intervention status, improvements in Rutherford Category, and other clinical factors. Table 6 includes the results of this Post-Hoc analysis in which all of these 13 subjects were determined to be patent.

Table 6: Primary Composite Endpoint Results (Post-Hoc Analysis)

	Bolster (N=155)	93.3% Confidence Interval[1]
Subjects with the Composite Events	16 / 138 (11.6%)	(7.0%, 17.8%)
Subjects fail due to		
Device and/or procedure-related death (<=30 day)	0 / 138 (0.0%)	
Device and/or procedure-related MI (<=30 day)	0 / 138 (0.0%)	
Target limb(s) major amputation through 9 months[2]	1/ 138 (0.7%)	
TLR through 9 months	6 / 138 (4.3%)	
Restenosis through 9 months	10 / 138 (7.2%)	

[1] Confidence intervals have not been adjusted for multiplicity and are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

[2] Not device and / or procedure related

The primary composite endpoint based on the Post-Hoc analysis utilizing 12-month assessments and additional clinical factors was 11.6%.

Per-Limb Analysis

On a Pre-Specified basis, the per-limb primary composite endpoint is evaluated to be 21/157 = 13.4%. As analyzed on a Post-Hoc per-limb basis, the primary composite endpoint is evaluated to be 16/168 = 9.5%.

Secondary Effectiveness Results

Table 7 and 8 below provide a summary of the secondary effectiveness endpoints at the time of this analysis.

Table 7: Secondary Effectiveness Results (Pre-Specified Analysis)

	Result	N	95% Confidence Interval[1]
Rate of Major Adverse Events (MAEs)	4.7%	150[2]	(1.9%, 9.4%)
Acute Lesion Success	98.4%	191[3]	(95.5%, 99.7%)
Acute Procedure Success	97.4%	152[3]	(93.4%, 99.3%)
Acute Technical Success	98.3%	230[3]	(95.6%, 99.5%)
Target Lesion Revascularization (TLR)	4.0%	150[2]	(1.5%, 8.5%)
Target Vessel Revascularization (TVR)	4.0%	150[2]	(1.5%, 8.5%)
Sustained Clinical Success	90.5%	137[4]	(84.3%, 94.9%)
Primary Patency	84.5%	129[5]	(77.1%, 90.3%)
Primary Assisted Patency	85.3%	129[5]	(78.0%, 90.9%)
Secondary Patency	87.5%	128[5]	(80.5%, 92.7%)

Table 8: Secondary Effectiveness Endpoints (Post-Hoc Analysis)

	Result	N	95% Confidence Interval[1]
Primary Patency	89.1%	137[6]	(82.6%, 93.7%)
Primary Assisted Patency	89.8%	137[6]	(83.4%, 94.3%)
Secondary Patency	91.9%	136[6]	(86.0%, 95.9%)

[1] Confidence intervals have not been adjusted for multiplicity and are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

[2] All subjects followed through day 240

[3] All treated lesions / subjects / stents with evaluable angiographic imaging at implant

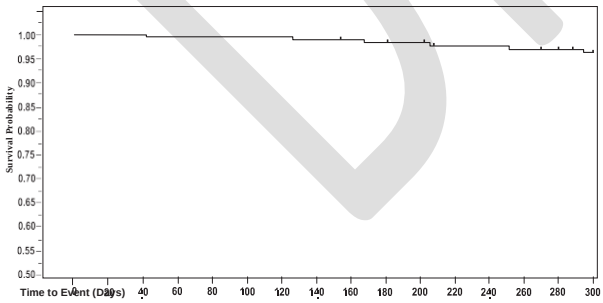
[4] All subjects completing the 9-month visit where Rutherford Category was assessed by the Investigator

[5] All subjects that completed the 9-month visit with evaluable duplex ultrasound imaging

[6] All subjects that completed the 9-month visit and/or 12-month visit with evaluable duplex imaging

The Kaplan-Meier analysis of TLR per subject was performed and results are provided in Figure 3. The Kaplan-Meier estimate of the incidence of TLR at 9 months (day 300) was 3.9% (95% CI 1.8%, 8.6%).

Figure 3: Kaplan-Meier Analysis of TLR per Subject (As Treated Population)



Quality of Life was assessed by the Walking Impairment Questionnaire (WIQ). The mean baseline total score was 32.0. At 9 months, the mean total score was 64.7, which represents an increase over baseline in total score of 32.7. Overall, improvements were seen in each domain of the WIQ.

Summary of Safety

Of the 155 subjects, 110 subjects (71.0%) reported 299 adverse events (AEs.) Sixty (60) subjects reported serious adverse events (60/110 = 54.5%). The majority of the subjects had AEs that were not related to device (86/110; 78.2%) and/or related to the procedures (81/110; 73.6%). There were no unanticipated adverse device effects (UADEs) reported.

Table 9: Summary of Safety

	Bolster (N=155)
	Site Reported
Total# of Events	299
Total# of Subjects with at Least One AE	110 (71.0%)
Device Relatedness [1, 2]	
Definitely Related	8 (7.3%)
Possibly Related	16 (14.5%)
Not Related	86 (78.2%)
Procedure Relatedness [1, 2]	
Definitely Related	20 (18.2%)
Possibly Related	9 (8.2%)
Not Related	81 (73.6%)
Serious AE (SAE) [1]	60 (54.5%)
Definitely or Possibly Device Related SAE	9 (15.0%)
Not Device Related SAE	51 (85.0%)

[1] Subjects are only counted once with the highest level of relatedness.

[2] Percentages are based on denominator of 110, the total number of subjects with at least 1 AE

The types of safety events experienced in the study are expected for this patient population. All of the device and procedure related adverse events reported were consistent with those identified in section F Potential Adverse Events. Overall, the adverse event profiles appear comparable to standard of care for PTA and stenting of the iliac arteries.

Patient Death Summary

Five subjects died as of the date of this report. None of the deaths were considered to be related to the study device or procedure, as adjudicated by the CEC.

Conclusions Drawn from the Study

The prospective, multi-center, non-randomized, single-arm study of the Bard® LifeStream™ Balloon Expandable Vascular Covered Stent in the treatment of iliac artery occlusive disease (BOLSTER) compared a composite safety and effectiveness measure to a Performance Goal (PG) derived from iliac stent published literature. At the time of this analysis, 155 subjects passed their 9-month visit and were evaluated for the primary and secondary endpoints.

The types of safety events experienced in the study are expected for this patient population. Overall, the adverse event profiles appear comparable to standard of care PTA and stenting of the iliac arteries.

The clinical study results demonstrate the safety and effectiveness of the LifeStream Balloon Expandable Vascular Covered Stent for the treatment of atherosclerotic lesions of the common or external iliac artery.