SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Endovascular Graft
Device Trade Name:	Fluency® Plus Endovascular Stent Graft
Device Procode:	PFV
Applicant's Name and Address:	Bard Peripheral Vascular, Inc. 1625 West 3rd Street P.O. Box 1740 Tempe, AZ 85280-1740 USA
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P130029/S002
Date of FDA Notice of Approval:	April 26, 2016

The original PMA (P130029) was approved on June 17, 2014 and is indicated for use in the treatment of in-stent restenosis in the venous outflow of hemodialysis patients dialyzing by either an arteriovenous (AV) fistula or AV graft. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the Fluency® Plus Endovascular Stent Graft to include treatment of stenosis in the venous outflow of hemodialysis patients dialyzing by an AV graft.

II. INDICATIONS FOR USE

The Fluency® Plus Endovascular Stent Graft is indicated for use in the treatment of in-stent restenosis in the venous outflow of hemodialysis patients dialyzing by either an arteriovenous (AV) fistula or AV graft and for the treatment of stenosis in the venous outflow of hemodialysis patients dialyzing by an AV graft.

III. CONTRAINDICATIONS

There are no known contraindications.

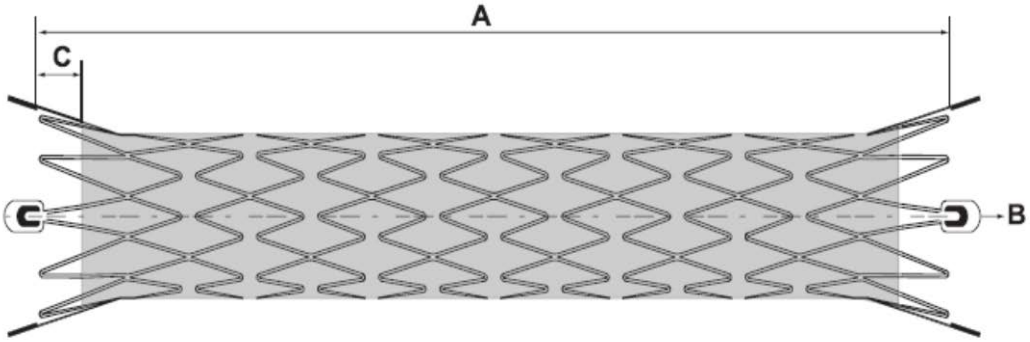
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Fluency® Plus Endovascular Stent Graft labeling (Instructions for Use).

V. DEVICE DESCRIPTION

The Fluency® Plus Endovascular Stent Graft implant is a flexible, self-expanding endoprosthesis comprised of expanded polytetrafluoroethylene (ePTFE) encapsulating a Nitinol stent framework (Figure 1). Nitinol is an alloy that can be processed to assume a pre-defined final configuration upon exposure to body temperature. There are four radiopaque tantalum markers on each end of the Nitinol stent, facilitating stent graft placement by enhancing visibility under fluoroscopy. The Nitinol stent is encapsulated with ePTFE along the entire length, except the flared stent graft ends with the radiopaque tantalum markers. The stent graft is available in a range of diameters and lengths as shown in Table 1.

Figure 1: Drawing of the Fluency® Plus Endovascular Stent Graft



Legend:
A Stent Graft
B Tantalum Markers
C Uncovered Portion of Stent Graft

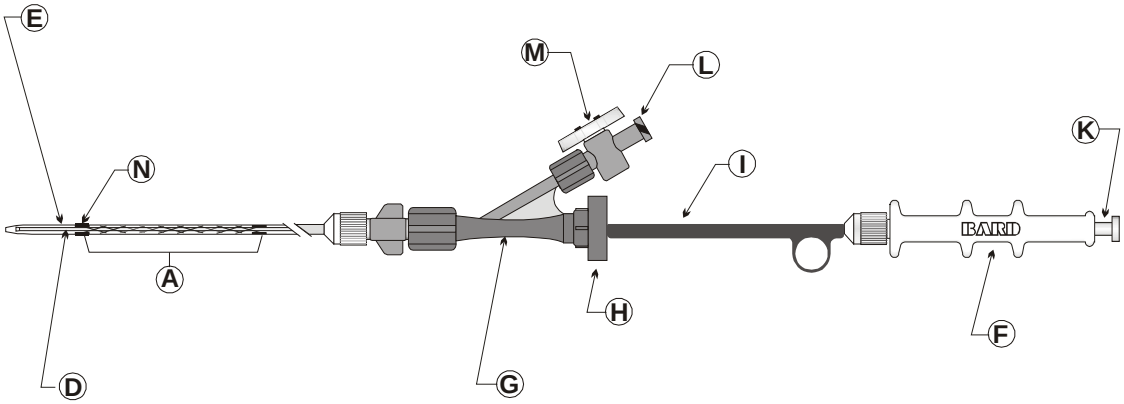
Table 1: Device Dimensions

Stent Graft Outer Diameter (mm)	Stent Graft Length (mm)					Delivery System French Size (F)	Delivery System Shaft Length (cm)
6	40	60	80	100	120	8	80 & 117
7	40	60				8	80 & 117
7			80	100	120	9	80 & 117

8	40	60	80	100	120	9	80 & 117
9	40	60	80	100	120	9	80 & 117
10	40	60	80	100	120	9	80 & 117
12	40	60	80	100	120	10	80 & 117
13.5	40	60	80	100	120	10	80 & 117

The flexible delivery system (shown in Figure 2) is a coaxial catheter system consisting of an inner catheter, which connects to the handgrip via a metal guiding tube and a coaxial outer sheath, which connects to a Y-injection-adapter with a Tuohy-Borst valve.

Figure 2: Drawing of the Fluency® Plus Endovascular Stent Graft Delivery System



Legend:

A Stent Graft (compressed)
B Reference Figure 1
C Reference Figure 1
D Inner Catheter
E Outer Sheath
F Hand Grip
G Y-Injection Adapter
H Tuohy-Borst Valve
I Safety Clip
J Intentionally Left Blank
K Female Luer Port
L Female Luer Port
M 2-Way Stopcock
N Radiopaque Markerband

The soft and flexible catheter tip is formed from the outer catheter sheath and is tapered to accommodate a 0.035 inch guide wire. The stent graft is deployed via the conventional "pin-and-pull-back" technique in which the hand grip is held in a stationary position and the Tuohy-Borst valve is pulled toward the hand grip.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are other alternatives for the treatment of stenosis in the venous outflow of hemodialysis patients dialyzing by an AV graft, such as percutaneous transluminal angioplasty (PTA), bare metal stent placement, or surgical revision. 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.

One of the current standard treatments for venous stenosis in AV access patients is percutaneous transluminal angioplasty (PTA). The average patient dialyzing with an AV fistula (AVF) or graft (AVG) will require approximately 0.5-3 PTA interventions per year [1,2, 3].

When PTA fails to treat the stenosis, bare metal stent placement may be recommended in selective circumstances [4]. Based on the reported experience at that time, the 2006 KDOQI document states "….the use of endovascular stents as the primary treatment for venous stenosis provides long-term results that are similar to those obtained with angioplasty alone. Stents should be reserved for patients with contraindications to surgical revision and for treatment of angioplasty-induced venous rupture."

VII. MARKETING HISTORY

The Fluency® Plus Vascular Stent Graft originally received U.S. marketing approval for use in the treatment of in-stent restenosis in the venous outflow of hemodialysis patients dialyzing by either an arteriovenous AV fistula or AV graft on June 17, 2014.

The Fluency® Plus Vascular Stent Graft has also been commercially available outside the United States since June 2005 with a vascular indication (iliac and femoral arteries). The device has not been withdrawn from marketing 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.

Complications and Adverse Events associated with use of the Fluency® Plus Endovascular Stent Graft may include the anticipated complications associated with endovascular stent and stent graft placement and dialysis shunt revisions.

Previously reported complications include:

- Thrombotic occlusion
- Restenosis requiring re-intervention
- Pseudoaneurysm
- Aneurysm
- Vessel rupture
- Perforation
- Pain
- Infection
- Hemorrhage

- Hematoma
- Arm or hand edema
- Steal Syndrome
- Congestive heart failure
- Cerebrovascular accident
- Allergic reaction
- Rash
- Reaction to contrast
- Fever
- Cellulitis
- Sepsis
- Prolonged bleeding
- Ventricular fibrillation
- Face or neck edema
- Bleeding at access site
- Hemoptysis
- Death

For a list of adverse events (AE) that occurred during the clinical study of this device, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

No changes were made to the device design, manufacturing process, manufacturing locations or packaging. Testing for the Fluency® Plus Endovascular Stent Graft was adequately leveraged from PMA P130029 to support the expanded indication.

X. SUMMARY OF PRIMARY CLINICAL STUDY

A new clinical study was not conducted to support the expanded indication to include treatment of stenosis in the venous outflow of hemodialysis patients dialyzing by an AV graft. Based on a risk analysis, ISR represents a worst-case clinical scenario with regards to significant safety and effectiveness outcomes when compared to non-stented lesions for patients dialyzing by an AV graft. Thus, the sponsor leveraged data from the RESCUE study that supported the original PMA approval for ISR. Additionally, an analysis of studies conducted with a similar device, the Flair Endovascular Stent Graft, was also used to support the expanded indication. Please refer to Section XI for summaries of those clinical studies (FLAIR and RENOVA).

SUMMARY OF RESCUE STUDY

Please refer to the SSED for the original Fluency® Plus Endovascular Stent Graft PMA (P130029) for a detailed summary of the RESCUE study, which can be found on the CDRH website. A brief description of the study and the primary results are provided below.

The Fluency® Plus Endovascular Stent Graft was studied in a prospective, multi-center, randomized, concurrently-controlled clinical trial (RESCUE). The primary purpose of this study was to demonstrate that the Fluency® Plus Endovascular Stent Graft can effectively and safely treat in-stent restenotic lesions in the venous outflow of the AV access circuit of hemodialysis subjects with either of the two predominant vascular access types – those with an AV graft and those with an AV fistula. This study compared the use of the Fluency® Plus Endovascular Stent Graft (following PTA) to PTA alone. The RESCUE study enrolled 220 patients at 23 US sites. One-hundred and nine (109) subjects were enrolled in the treatment arm and 111 were enrolled in the control arm, and were randomized into the Intent-to-Treat (ITT) group. Primary endpoint data were obtained at six (6) months.

A. Safety Results

Non-inferiority of Fluency® Plus Endovascular Stent Graft to PTA alone for freedom from safety events through thirty (30) days was the primary safety endpoint for this study. The endpoint is defined as freedom through 30 days from any adverse event(s)

(AEs), localized or systemic, which 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. Tables 2 and 3 show the results of the analysis for Freedom from any Safety Events / Adverse Events through 30 days (ITT).

Table 2: Freedom from any Safety Event[1] through 30 days

	PTA Alone (n=137)	FLUENCY® PLUS (n=128)	Non-inferiority p-value [1]
Overall Population (Primary Safety)			
n/N (%)	122/126 (96.8)	114/118 (96.6)	0.007
95% Confidence Interval	(92.07, 99.13)	(91.55,99.07)	

[1] The p-value is based on a non-inferiority Farrington and Manning Exact Test.

Table 3: Incidence of Primary Safety Endpoint in First 30 Days

	PTA Alone (n=137)	FLUENCY® PLUS (n=128)
Number of Subjects Reporting At Least One Safety Event AE	4 (2.9)	4 (3.1)
Infection	1 (0.7)	1 (0.8)
Arm or Hand Edema	0	2 (1.6)
Vessel Rupture	1 (0.7)	0
Allergic reaction to uncertain source	0	1 (0.8)
Fever/cellulitus of both legs/sepsis	0	1 (0.8)
Ventricular fibrillation	1 (0.7)	0
Infolded covered Stent	1(0.7)	0

B. Effectiveness Results

Primary Effectiveness

Access Circuit Primary Patency (ACPP) at six months was the primary outcome used to compare the effectiveness of the Fluency® Plus Endovascular Stent Graft to the PTA Control. Per the protocol, ACPP was defined as the interval following the index procedure until the next access thrombosis or repeated intervention. ACPP ended with a reintervention anywhere within the access circuit, from the arterial inflow to the superior vena cava-right atrial junction.

The ACPP rate was significantly higher ($p<0.001$) in the FLUENCY® PLUS Endovascular Stent Graft group (16.7%) than in the PTA Control (3.0%), as detailed in Table 4 Additionally, the ACPP event hazard ratio demonstrated is 0.59. The reduction in the risk of failure of ACPP events due to the use of Fluency® Plus Endovascular Stent Graft compared to PTA alone is 41%.

This demonstrated superiority of the Fluency® Plus Endovascular Stent Graft to the PTA Control with respect to Access Circuit Primary Patency.

Table 4 Access Circuit Primary Patency through Six Months (ITT)

	PTA Alone (n=111)	FLUENCY® PLUS (n=109)
Percentage of ACPP at 6 months (%)	**3.0**	**16.7**
95% CI for Rate [1]	(0.00, 6.27)	(9.24, 24.16)
Time to event (days)		
Median	91.0	92.0
95% CI for Median [2]	(86.00, 91.00)	(91.00, 98.00)

	PTA Alone (n=111)	FLUENCY® PLUS (n=109)
25% and 75%-ile	70.0, 98.0	84.0, 119.0
Min, Max	1, 195	3, 211
Hazard Ratio (FLUENCY® PLUS over PTA) [3]	0.59	
95% CI	(0.44, 0.79)	
p-value: FLUENCY® PLUS vs. PTA group [4]	<0.001	

[1] The 95% confidence interval uses a normal approximation with Greenwood's estimate of variance.
[2] The 95% confidence interval about median uses the Brookmeyer and Crowley method.
[3] Proportional hazards regression model with treatment term, stratified by AV access type (graft or fistula).
[4] The p-value (one-sided) is based on a stratified log-rank test with strata of AV graft and AV fistula.

Secondary Effectiveness

Post-Intervention Lesion Patency (PLP) at six months was the only secondary effectiveness endpoint used to statistically compare the performance of the Fluency® Plus Endovascular Stent Graft to the PTA Control. Per the protocol, PLP was defined as the interval after the index procedure until the next reintervention at the original treatment site, or until the extremity (access) is abandoned for permanent access.

The PLP was significantly higher ($p<0.001$) in the FLUENCY® PLUS Endovascular Stent Graft group (65.2%) than in the PTA Control (10.4%), as detailed in Table 5 The PLP endpoint hazard ratio is 0.18, which translates to an 82% reduction in the risk of failure of PLP due to the use of FLUENCY® PLUS Endovascular Stent Graft compared to PTA alone.

This demonstrated superiority of the FLUENCY® PLUS Endovascular Stent Graft to the PTA Control with respect to Post-Intervention Lesion Patency.

Table 5 Post-Intervention Lesion Patency at 6 Months (ITT)

Overall (AV Graft and AV Fistula)		
	PTA Alone (N=111)	FLUENCY® PLUS (N=109)
Percentage of Post-Intervention Lesions Patency at 6 months (180 days)	10.4	65.2
95% CI for Rate [1]	(4.30, 16.57)	(55.59, 74.86),
Time to event (days)		
Median	91.0	189.0
95% CI for Median [2]	(91.00, 94.00)	(187.00, NE)
25% and 75%-ile	80.0, 103.0	135.0, NE
Min, Max	1, 195	12, 211

[1] The 95% confidence interval uses a normal approximation with Greenwood's estimate of variance.
[2] The 95% confidence interval about median uses the Brookmeyer and Crowley method.

C. Conclusions from the RESCUE study

For ISR, the results of RESCUE study demonstrated that the Fluency® Plus Endovascular Stent Graft was superior to the PTA Control with respect to six-month Access Circuit Primary Patency and was no different than the PTA Control with respect to safety. As mentioned above, ISR is considered worst-case compared to non-stented

lesions for patients with AV grafts. Additionally, the RESCUE study protocol mandated a minimum 10 mm stenotic segment to be located within the previously placed bare metal stent (ISR) and allowed for the lesion to extend up to 30 mm beyond the stent. As such, the stent-graft was placed across both stented and non-stented segments and the results from the RESCUE study can be considered relevant for stenosis (not in-stent) for patients with an AV graft.

D. 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 30 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

SUMMARY OF CLINICAL STUDIES WITH THE FLAIR® ENDOVASCULAR STENT GRAFT

The FLAIR® Endovascular Stent Graft implant (approved in PMA P060002) is similar in design and materials to the Fluency® Plus Endovascular Stent Graft implant. However, unlike the FLAIR®, the Fluency® Plus has 2 mm of uncovered Nitinol on each end to accommodate radiopaque tantalum markers. The FLAIR® Endovascular Stent Graft has been approved for use in the treatment of stenoses at the venous anastomosis of ePTFE or other synthetic arteriovenous (AV) access grafts. Due to the similarities between these devices, the performance of the FLAIR® in treating stenosis for patients with unstented AV grafts was considered relevant to the Fluency® Plus in supplementing the data from the RESCUE trial.

In the two studies, the FLAIR® Endovascular Stent Graft Pivotal study and the FLAIR® Endovascular Stent Graft Post Market Study (RENOVA), eligible patients had a hemodynamically significant stenosis (≥50% reduction of normal vessel diameter) accompanied by a hemodynamic, functional or clinical abnormality (defined by KDOQI, SIR guidelines), without thrombotic occlusion at the synthetic AV access graft-vein anastomosis. To be included in the study, total stenosis length could not exceed 70 mm, and the entire lesion had to be located within 70 mm of the venous anastomosis. The AV access graft must have also been implanted at least 30 days and undergone at least one hemodialysis. Patients were excluded from the study if they had had a thrombosis of the AV access graft within 7 days before the index procedure or if their access graft was infected.

A. Flair® Endovascular Stent Graft Pivotal Study

Please refer to the SSED for the original FLAIR ® Endovascular Stent Graft PMA (P060002) for a detailed summary of this study, which can be found on the CDRH website. A brief description of the study and the primary results are provided below.

A total of 227 patients were treated at 16 U.S. investigational sites to evaluate the safety and effectiveness of the FLAIR® Endovascular Stent Graft. The study compared the FLAIR® Endovascular Stent Graft to balloon angioplasty in patients with stenoses at the venous anastomosis of a synthetic AV access graft. A total of 37 "roll-in" patients and 190 randomized patients, 97 in the treatment arm and 93 in the control arm, were enrolled in the clinical study.

1. **Study Endpoints**

Treatment Area Primary Patency (TAPP) at six months was the primary outcome used to compare the effectiveness of the study device to the PTA Control. The primary safety endpoint was evaluated based on the incidence of adverse events observed within the same time interval. Secondary endpoints included:

i. The ability to successfully deliver the FLAIR® Endovascular Stent Graft;
ii. Procedural success;
iii. Treatment area primary patency (at 2 months);
iv. Access circuit primary patency (at 2 and 6 months);
v. Assisted access circuit primary patency(at 2 and 6 months);
vi. Access circuit cumulative (i.e., secondary) patency (at 2 and 6 months); and
vii. Percent stenosis of the treatment area (at 2 and 6 months).

2. **Enrollment and Baseline Parameters**

The randomization process resulted in 97 patients treated with the study device and 93 patients treated with balloon angioplasty as a control. There was no significant difference between the treatment groups with regards to patient demographics, medical history, AV Access graft location, AV Access graft type and baseline angiographic characteristics.

3. **Safety Results**

Adverse Event rates (through 210 days) for randomized and "roll-in" patients are presented in Table 6. The statistical comparisons and p-values presented in Table 6 are from the randomized population only.

Table 6: Adverse Events through 6 Months

Adverse Events	Roll-In Patients	Randomized Patients		
	FLAIR® Device (N=37)	FLAIR® Device (N=97)	PTA Only (N=93)	P-value
Death	2.78% (1/36)	5.26% (5/95)	5.56% (5/90)	1.000
Infection	0.00% (0/36)	6.32% (6/95)	2.22% (2/90)	0.280
Stenosis	41.67% (15/36)	40.00% (38/95)	76.67% (69/90)	<0.001
Thrombotic occlusion	33.33% (12/36)	32.63% (31/95)	21.11% (19/90)	0.098
Vessel rupture	0.00% (0/36)	3.16% (3/95)	1.11% (1/90)	0.621
Pseudoaneurysm	2.78% (1/36)	5.26% (5/95)	2.22% (2/90)	0.445
Hemorrhage	0.00% (0/36)	0.00% (0/95)	0.00% (0/90)	-
Hematoma	0.00% (0/36)	2.11% (2/95)	0.00% (0/90)	0.498
Significant arm or hand edema	2.78% (1/36)	3.16% (3/95)	2.22% (2/90)	1.000
Steal syndrome	2.78% (1/36)	2.11% (2/95)	1.11% (1/90)	1.000
Congestive heart failure	2.78% (1/36)	4.21% (4/95)	2.22% (2/90)	0.683
Cerebrovascular accident	0.00% (0/36)	2.11% (2/95)	3.33% (3/90)	0.676
Device kinking	0.00% (0/36)	0.00% (0/95)	N/A	-
Device migration	0.00% (0/36)	4.21% (4/95)	N/A	-
Embolism	0.00% (0/36)	0.00% (0/95)	N/A	-
Permanent deformation of the Endoluminal Device	2.78% (1/36)	1.05% (1/95)	N/A	-

Note: p-values are unadjusted for multiple comparisons

4. **Effectiveness Results**

Treatment Area Primary Patency (TAPP) at six months was the primary outcome used to compare the effectiveness of the study device to the PTA Control. Per protocol,

TAPP was defined as patency (open to blood flow) after the study index procedure until reintervention in the treatment area (within 5 mm proximal or 5 mm distal to the study device or index balloon angioplasty treated area), or thrombotic occlusion that involved the treatment area. The Treatment Area Primary Patency at six months in the study device group was significantly higher than that observed in the PTA Control group. Primary and secondary effectiveness results are presented in Table 7.

Table 7: Primary and Secondary Effectiveness Results

	Roll-In Patients	**Randomized Patients**		
	FLAIR® Device (N=37)	**FLAIR® Device (N=97)**	**PTA Only (N=93)**	**P-value**
Treatment Area Primary Patency				
2-month	89.2% (33/37)	80.21% (77/96)	77.17% (71/92)	0.722
6-month	60.0% (21/35)	50.55% (46/91)	23.28% (20/86)	<0.001
Device delivery success by patient	100% (37/37)	98.97% (96/97)	N/A	N/A
*Procedural Success	94.59% (35/37)	93.81% (91/97)	73.12% (68/93)	<0.001
**Access Circuit Primary Patency				
2-month	86.5% (32/37)	79.17% (76/96)	77.17% (71/92)	0.860
6-month	42.9% (15/35)	38.04% (35/92)	19.77% (17/86)	0.008
***Access Circuit Assisted Primary Patency				
2-month	91.9% (34/37)	86.46% (83/96)	89.13% (82/92)	0.659
6-month	65.7% (23/35)	65.56% (59/90)	73.81% (62/84)	0.253
**** Access Circuit Cumulative Patency				
2-month	97.3% (36/37)	94.79% (91/96)	95.65% (88/92)	1.000
6-month	91.4% (32/35)	81.32% (74/91)	85.88% (73/85)	0.542
***** Binary Restenosis Rate of the Treatment Area				
2-month	0.00% (0/27)	20.00% (16/80)	70.59% (48/68)	<0.001
6-month	25.00% (7/28)	27.63% (21/76)	77.61% (52/67)	<0.001

Note: p-values are unadjusted for multiple comparisons of secondary endpoints

*Procedural Success: Anatomic success (achievement of a post procedure residual stenosis < 30% measured at the narrowest point of the lumen, as indicated by angiography) and at least one indicator of hemodynamic or clinical success.

**Access Circuit Primary Patency: Patency (open to blood flow) following the index study procedure until access thrombosis or an intervention of a lesion anywhere within the access circuit (arterial anastomosis to the superior vena cava-right atrial junction). Access primary patency ends when: 1) there was an intervention for a stenosis anywhere within the access circuit, 2) there was an occlusion anywhere within the access circuit, or 3) there was a surgical intervention that excluded the index stenotic area from the access circuit.

***Access Circuit Assisted Primary Patency: Patency (open to blood flow) following the index study procedure until access thrombosis or a surgical intervention that excludes the treated lesion from the access circuit. Percutaneous treatment(s) of either restenosis of the previous treated lesion or a new arterial or venous outflow stenosis/occlusion, excluding access thrombosis, are compatible with assisted primary patency. Assisted primary patency ends when: 1) there is an occlusion anywhere within the access circuit, or 2) there is a surgical intervention that excludes the index stenotic area from the access circuit.

****Access Circuit Cumulative Patency (i.e., secondary patency): Patency (open to blood flow) following the index study procedure until the access is surgically revised or abandoned because of inability to treat the original lesion. Multiple/ repetitive treatments for occlusions that restore patency are compatible with cumulative patency. Cumulative patency ends when: 1) there is a surgical intervention that excludes the index stenotic area from the access circuit, or 2) the AV access venous anastomosis is surgically revised, or 3) the AV graft is abandoned due to an inability to treat the primary lesion.

*****Binary Restenosis Rate of the Treatment Area: Binary restenosis rates, as demonstrated by procedural, 2 and 6-month follow-up angiograms, were calculated by the core lab. Quantitative vessel analysis was performed to identify the restenosis rate at 2 and 6-months. Lesions within, just proximal to or just distal to the study device or index balloon angioplasty treatment area with a ≥50% diameter stenosis were categorized as restenotic.

5. Conclusions of FLAIR® Endovascular Stent Graft Clinical Study

Data from the clinical trial provided a reasonable assurance that the FLAIR® Endovascular Stent Graft was safe and effective for the treatment of stenoses at the

venous anastomosis of ePTFE or other synthetic AV access grafts. Due to the similarities between the FLAIR® Endovascular Stent Graft and the Fluency® Plus Endovascular Stent Graft stated above, these data are also informative for the expanded indication of the Fluency® Plus in the treatment of stenosis (not ISR) in the venous outflow of patients dialyzing with AV grafts.

B. A Post-Approval Study of the FLAIR® Endovascular Stent Graft (RENOVA)

A total of 270 patients were treated at 28 U.S. investigational sites. All subjects enrolled in the study were to be followed through 24 months (±30 days) post-index procedure.

1. Study Endpoints

a. The primary objectives of this Post Approval study were to:
   i. Demonstrate that the post intervention ACPP in the FLAIR® Endovascular Stent Graft group is superior to that of the PTA group through 12 months and to estimate the patency at 24 months;
   ii. Demonstrate that the Index of Patency Function (IPF) [the average number of days between interventions] of the FLAIR® Endovascular Stent Graft group is not inferior to that of the PTA group at 12 months and to estimate the IPF at 24 months; and,
   iii. Demonstrate that the safety (defined as the number of device and/or procedure related adverse events) of the FLAIR® Endovascular Stent Graft group is not inferior to that of the PTA group at 12 months, and to estimate the safety at 24 months.

b. Secondary Endpoints included:
   i. The number of re-interventions to the access circuit until graft abandonment or through 12 months post-index procedure;
   ii. Post-Intervention Assisted Primary Patency (PAPP) at 6, 12 and 24 months;
   iii. Post-intervention Secondary Patency at 6, 12 and 24 months;
   iv. Procedural success;
   v. Demonstrate the effectiveness of the clinician training program assessed by the incidence of major device-related and procedure-related adverse events from the index procedure through 30-day post-procedure; and
   vi. Evaluate FLAIR® Endovascular Stent Graft safety in terms of Serious Adverse Events.

Treatment Area Primary Patency (TAPP) at 12 and 24 months was evaluated in a post-hoc analysis.

2. Safety Results

The randomization process resulted in 138 patients treated with the study device and 132 patients treated with balloon angioplasty as a control. There was no difference between the treatment groups with regards to baseline patient demographics, medical history, AV Access graft location, AV Access graft type and baseline angiographic characteristics. A summary of all adverse events through 24 months is presented in Table 8

There was no significant difference between the groups for the percentage of subjects with at least one AE: 97.0% (128/132) for PTA and 94.2% (130/138) for FLAIR® Endovascular Stent Graft (p = 0.378). The incidence of all categories of AEs was similar between treatment groups, with the exception of stenosis requiring intervention, which occurred significantly more frequently in the PTA group (82.6%, 109/132) than in the FLAIR® Endovascular Stent Graft group (63.0% (87/138) (p <0.001)).

Table 8: Summary of All Adverse Events*

	FLAIR® Device (N=138)	**PTA (N=132)**
Subjects with at least one event	130 (94.2%)	128 (97.0%)
Adverse Event Description		
Cerebrovascular accident	2 (1.4%)	6 (4.5%)
Congestive heart failure	9 (6.5%)	6 (4.5%)
Device kinking	0 (0.0%)	0 (0.0%)
Device migration	1 (0.7%)	1 (0.8%)**
Embolism	1 (0.7%)	0 (0.0%)
Hematoma	5 (3.6%)	1 (0.8%)
Hemorrhage	10 (7.2%)	10 (7.6%)
Infection	40 (29.0%)	42 (31.8%)
Pain	14 (10.1%)	6 (4.5%)
Perforation	1 (0.7%)	0 (0.0%)
Permanent deformation of device	0 (0.0%)	0 (0.0%)
Pseudoaneurysm	9 (6.5%)	16 (12.1%)
Significant arm or hand edema	3 (2.2%)	3 (2.3%)
Steal syndrome	6 (4.3%)	3 (2.3%)
Stenosis requiring intervention	87 (63.0%)	109 (82.6%)
Thrombotic occlusion	60 (43.5%)	48 (36.4%)
Vessel rupture	2 (1.4%)	2 (1.5%)
Other	82 (59.4%)	83 (62.9%)

*Subjects reporting a particular event more than once are only counted once for that event.
** After the index procedure (PTA), the patient experienced stenosis at the venous anastomosis, and with the physician's selected standard of care intervention, there was a stent migration.

3. Effectiveness Results

Primary and secondary effectiveness endpoint results are presented in Table 9.

Table 9: Summary of Effectiveness Endpoint Results

	Randomized Patients		
	FLAIR® Device (N=138)	**PTA Only (N=132)**	**P-value**
Access Circuit Primary Patency			
12-Month rate (95% CI)	24% (0.165, 0.315)	11% (0.054, 0.167)	0.007*
24-Month rate (95% CI)	9.5% (0.029, 0.162)	5.5% (0.013, 0.097)	0.011*
Index of Patency Function (months/intervention) ± SD			
12-Month	5.2 ± 4.08	4.4 ± 3.51	0.009**
24-Month	7.1 ± 7.04	5.3 ± 5.22	
Procedural Success Rate	112 (81.2%)	99 (75.0%)	
Anatomic Success Rate	112 (81.2%)	99 (75.0%)	
Hemodynamic Success Rate	138 (100%)	130 (98.5%)	
Clinical Success Rate	135 (97.8%)	130 (98.5%)	
Estimated Number of Re-Interventions ***			
12-Month Mean ± SD (min, max)	1.9±2.18 (0, 10)	2.4±2.31 (0, 19)	
24-Month Mean ± SD (min, max)	3.4±3.52 (0, 20)	4.3±3.86 (0, 30)	
Post-Intervention Assisted Primary Patency (PAPP)			
12-Month (95% CI)	49.7% (0.410, 0.584)	56.3% (0.474, 0.653)	
24-Month (95% CI)	38.4% (0.282, 0.486)	40.6% (0.312, 0.500)	
Post-Intervention Secondary Patency (PSP)			
12-Month (95% CI)	65.3% (0.569, 0.736)	71.0% (0.629, 0.792)	
24-Month (95% CI)	51.8% (0.410, 0.626)	57.4% (0.481, 0.668)	
Treatment Area Primary Patency			
12-Month rate (95% CI)	47.6% (0.389, 0.564)	24.8% (0.170, 0.325)	<0.001*
24-Month rate (95% CI)	26.9% (0.177, 0.360)	13.5% (0.068, 0.202)	<0.001*

* Statistical significance at the 0.05 level. p-value is from a Cox regression analysis using covariate of treatment group testing superiority of the **FLAIR® Endovascular Stent Graft** group to that of PTA

Statistical significance at the 0.05 level. A non-inferiority margin of 7 days was incorporated into the calculation of the p-value. A p-value <0.05 rejects the null hypothesis and concludes non-inferiority. p-value is from a Blackwelder t-test testing non-inferiority of the **FLAIR® Endovascular Stent Graft group to that of PTA.

***From the monthly rate to 6 months, the number of interventions to 6 months is calculated by multiplying the rate by 6. An analogous calculation has been made for the number of interventions to 12 months and 24 months. Estimates are from a Kaplan-Meier model.

4. Conclusion

The results from this multicenter, prospective, randomized, concurrently-controlled Post-Approval Study demonstrate the safety and effectiveness of the FLAIR® Endovascular Stent Graft for the treatment of stenoses at the venous anastomosis of ePTFE or other synthetic AV grafts through 12 months and 24 months and confirm the 6 month outcomes from the pivotal study upon which PMA approval was based. Due to the similarities between the FLAIR® Endovascular Stent Graft and the Fluency® Plus Endovascular Stent Graft stated above, these data are also informative for the expanded indication of the Fluency® Plus in the treatment of stenosis (not ISR) in the venous outflow of patients dialyzing with AV grafts.

OTHER CLINICAL INFORMATION

C. Meta-Analysis of Published Literature using the Fluency Plus Endovascular Stent Graft

Four (4) independent, peer-reviewed, clinical studies (both prospective and retrospective) examined the use of the Fluency® Plus Endovascular Stent Graft in the treatment of stented

and non-stented stenoses and occlusions in patients dialyzing with a synthetic AV graft. Cumulatively, these four studies included 144 patients that were treated with Fluency® Plus Endovascular Stent Grafts with 6-month ACPP rates ranging from 35% to 77% and Secondary Patency of 88% and 52%, respectively. (Table 10)

A meta-analysis of the peer-reviewed studies was completed based on a method by D'Agostino et. al. [5], which is a weighted average of the observed rates, where the weights are the inverse of the estimated variances of the observed rates (i.e., Meta-estimate = $\text{sum}(w_i * p_i)/\text{sum}(w_i)$; w_i is the weight of the i^{th} study and p_i is the observed rate in the i^{th} study). The 95% CI was based on normal approximation of the meta-estimate and was constructed using the meta-estimate and its standard error. The calculated 6-month ACPP rate was 49.1% (95% CI: 41.4%, 56.8%).

The Fluency® Plus Endovascular Stent Graft was placed following unsuccessful PTA, recurrent stenosis, complex stenoses and for AV access salvage when all other previous endovascular therapies were exhausted. As such, the data presented from these studies were gathered on patients with persistent, difficult-to-treat lesions.

Table 10: Summary of Literature

Study Author	Number of AVG patients	Technical Success[+]	FLUENCY® 6-month Access Circuit Primary Patency	FLUENCY® 6-month Access Circuit Secondary Patency
Karnabatitis et al. [1] (2013)	35	100%	77%	-
Dolmatch et al. [2] (2012)	58[#]	100%	35%	88%
Calsina et al. [3] (2013)	27	-	44%	52%
Schmelter et al.[4] (2014)	41*	99%**	41%	-

[+] Successful delivery of the stent graft to the intended site with a <30% residual stenosis after implantation.

* 24 FLUENCY® Stent Grafts, 16 other Stent Grafts and 1 patient with FLUENCY® Stent Graft and another Stent Graft (a total of 41 patients).

[#] 5 access types were unknown.

** Technical success rate includes 15 patients with AVF for a total of 65/66 with technical success.

[1] The authors declare that they have no conflict of interest

[2] Please note that Dr. Dolmatch is a speaker, consultant, and royalty recipient for Bard Peripheral Vascular, Inc.;

[3] Calsina et al: The authors declared that they have no conflicts of interest related to the contents of the referenced article

[4] Dr. Schmelter reports travel support from C. R. Bard GmbH outside the submitted work. Prof. Vorwerk reports personal fees (workshops) from C. R. Bard GmbH and personal fees (lectures) from W. L. Gore & Associates GmbH outside the submitted work. Dr. Dierk Vorwerk received an award from W. L. Gore & Associates outside the submitted work. The other authors certified that there is no conflict of interest.

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 information provided above does not raise any questions about the reliability of the data.

XII. 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.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

- Results from the RESCUE Study demonstrated that the Fluency® Plus Endovascular Stent Graft was superior to the PTA Control for in-stent restenosis with respect to six-month Access Circuit Primary Patency and was no different than the PTA Control with respect to safety. Additionally, ISR may be considered worst case compared to stenosis in patients with unstented AV grafts. Therefore, the data from the RESCUE study also supports the effectiveness of the Fluency® Plus Endovascular Stent Graft for the expanded indication of treatment of stenosis in the venous outflow of hemodialysis patients dialyzing by an AV graft.

- Due to the device similarities, clinical data from the FLAIR® studies (FLAIR and RENOVA) were leveraged as supplemental information to support the expanded indication of stenosis in patients with AV grafts. The results of the FLAIR® Clinical Study demonstrated that the FLAIR Endovascular Stent Graft was superior to the PTA Control with respect to six-month Treatment Area Primary Patency (T APP).

B. Safety Conclusions

- Results from the RESCUE Study and the leveraged pre-clinical data from PMA P130029 provides reasonable assurance that the Fluency® Plus Endovascular Stent Graft is safe for use in the treatment of in-stent restenosis in the venous outflow of hemodialysis patients dialyzing by either an arteriovenous (AV) fistula or AV graft when used in accordance with its labeling. Considering that in-stent restenosis is more challenging to treat due to the presence of a metallic stent, the safety results for the RESCUE Study were appropriately leveraged to support the expanded indication.

- Leveraged data from PMA P130029 non-clinical testing along with FLAIR® (P060002) and post-approval (RENOVA) clinical studies did not show any difference in the safety profile when compared to treatment using PTA alone. This provides additional assurance that the Fluency® Plus Endovascular Stent Graft is safe for treatment of stenosis in hemodialysis patients dialyzing by an AV graft.

- It is important to note that although the leveraged studies evaluated treatment of ISR in both AV grafts and AV fistulas, the expanded indication only includes treatment of AV grafts. Treatment of *de novo* stenosis in AV fistulas is currently not well-understood. Treatment of *de novo* stenosis (not ISR) in an AV fistula could result in unanticipated clinical complications, such as complete thrombosis of the fistula. Considering that the ability to salvage a fistula is relatively low in comparison to AV grafts, treatment of *de novo* stenosis in an AV fistula could result in undesirable outcomes for high-risk hemodialysis patients. In summary, treatment of native AV Fistula raises additional concerns that were not fully addressed by the clinical data; therefore, the leveraged clinical studies are only sufficient to support the expanded use of Fluency® Plus Endovascular Graft for stenosis in the venous outflow of patients with AV Grafts.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in clinical studies conducted to support PMA approvals as described above. The probable benefits compared to PTA alone are improved AV access patency, decreased need for re-interventions, the ability to save the existing AV graft access circuit and avoiding the need for AV access circuit abandonment and subsequent creation of a new AV access. The risks are similar to PTA alone, which is currently the standard of care.

In conclusion, given the available information above, the leveraged clinical data demonstrate that the probable benefits outweigh the probable risks for the Fluency® Plus Endovascular Stent Graft for treatment of stenosis in the venous outflow of hemodialysis patients dialyzing by an AV graft.

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 indications for use.

The leveraged non-clinical studies indicate that the Fluency® Plus Endovascular Stent Graft meets safety and performance specifications.

Results of the randomized, prospective, multi-center clinical trial (RESCUE) demonstrated that the FLUENCY® PLUS Endovascular Stent Graft was superior to the PTA Control with respect to six-month Access Circuit Primary Patency (ACPP), the primary effectiveness endpoint, and no different than the PTA Control with respect to safety.

Overall, non-clinical testing was leveraged from PMA P130029, the RESCUE clinical trial, published literature, as well as those drawn from the pivotal and post-market studies of the FLAIR® Endovascular Stent Graft, a device similar to the Fluency® Plus Endovascular Stent Graft. Considering that treatment of in-stent restenosis is a worse-

case condition to treat, pre-clinical and clinical data obtained for treatment of in-stent restenosis was adequately leveraged to support the treatment of stenosis in AV Grafts. Thus, the leveraged data provides reasonable assurance that the Fluency® Plus Endovascular Stent Graft is safe and effective for use in the treatment of in-stent restenosis in the venous outflow of an AV fistula or AV graft and stenosis in the venous outflow of patients dialyzing by an AV graft when used in accordance with its labeling.

XIV. CDRH DECISION

CDRH issued an approval order on April 26, 2016.

The applicant's manufacturing facility has been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See the 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.

XVI. REFERENCES

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