



Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

April 26, 2016

Bard Peripheral Vascular, Inc.
Christoph Wagner von Hoff, BA, MBA
Regulatory Affairs Program Manager
1625 West 3rd St.
Tempe, Arizona 85281-1740

Re: P130029/S002
Trade/Device Name: Fluency[®] Plus Endovascular Stent Graft
Filed: May 1, 2015
Amended: January 27, 2016
Product Code: PFV

Dear Mr. Wagner von Hoff:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement for the Fluency[®] Plus Endovascular Stent Graft. This device 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. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84. This is a reminder that as of

September 24, 2014, class III devices are subject to certain provisions of the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. For more information on these requirements, please see the UDI website, <http://www.fda.gov/udi>.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm>.

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or
2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at <http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm>.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to:

- (1) reduce a risk to health posed by the device; or
- (2) remedy a violation of the act caused by the

device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at <http://www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm>.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm>. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in 6 copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Ifeanyi Uwemedimo at 240-402-5243 or Ifeanyi.Uwemedimo@fda.hhs.gov.

Sincerely yours,

Kenneth J. Cavanaugh -S

for

Bram D. Zuckerman, M.D.

Director

Division of Cardiovascular Devices

Office of Device Evaluation

Center for Devices and Radiological Health

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.

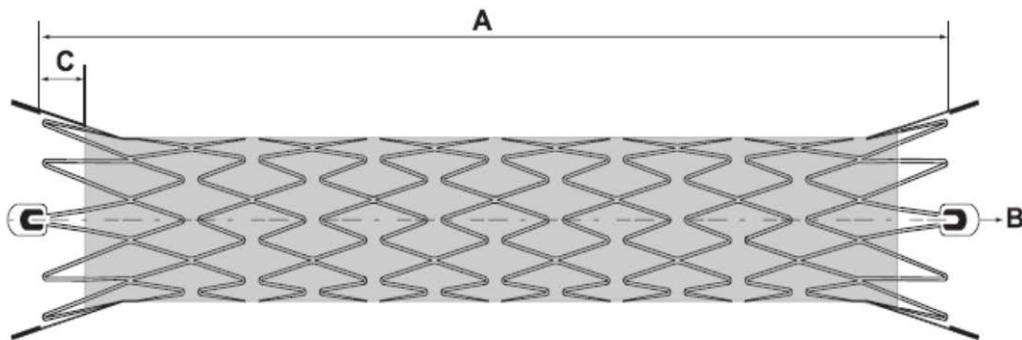
IV. WARNINGS AND PRECAUTIONS

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

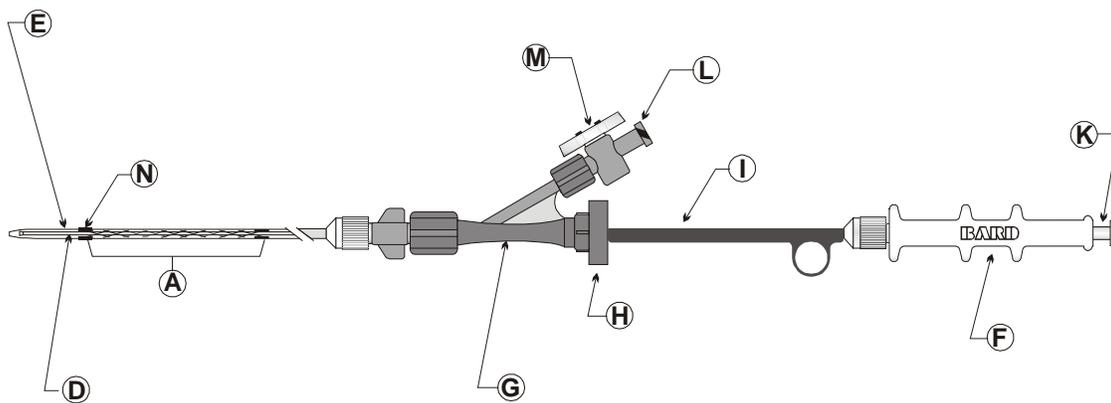
Table 1: Device Dimensions

Stent Graft Outer Diameter (mm)	Stent Graft Length (mm)					Delivery System French Size (F)	Delivery System Shaft Length (cm)
	40	60	80	100	120		
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-adaptor with a Tuohy-Borst valve.

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



Legend:

- | | | | |
|---|--------------------------|---|--------------------------|
| A | Stent Graft (compressed) | H | Tuohy-Borst Valve |
| B | Reference Figure 1 | I | Safety Clip |
| C | Reference Figure 1 | J | Intentionally Left Blank |
| D | Inner Catheter | K | Female Luer Port |
| E | Outer Sheath | L | Female Luer Port |
| F | Hand Grip | M | 2-Way Stopcock |
| G | Y-Injection Adapter | 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/cellulitis 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)	FLUENC Y[®] 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 ($\geq 50\%$ 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 = $\sum(w_i * p_i) / \sum(w_i)$; 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 (TAPP).

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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FLUENCY[®] PLUS

Endovascular Stent Graft

Instructions For Use



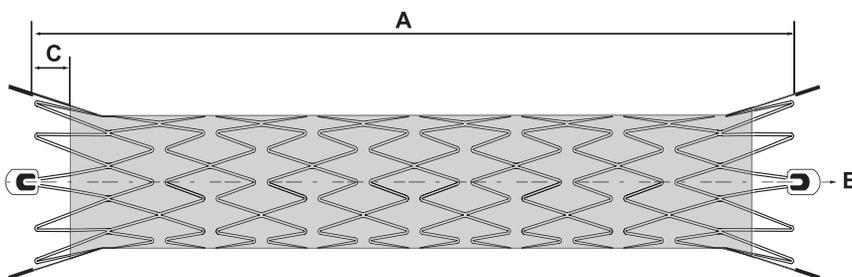
INFORMATION FOR USE

Caution: Federal law (U.S.) restricts the use of this device to sale by or on the order of a physician.

Device Description

The **FLUENCY[®] Plus Endovascular Stent Graft** implant (Figure 1) is a flexible, self-expanding vascular prosthesis (**A**) comprised of expanded polytetrafluoroethylene (ePTFE) encapsulating a Nitinol stent framework, except the flared stent graft ends with the four radiopaque Tantalum markers (**B**). The inner lumen of the stent graft surface (blood contacting surface) is carbon impregnated. The length of the uncovered portion of the stent graft is approximately 2 mm at each end (**C**).

Figure 1: Implant



The **FLUENCY[®] Plus Endovascular Stent Graft** is available in diameters 6 mm, 7 mm, 8 mm, 9 mm, 10 mm, 12 mm and 13.5 mm and in lengths of 40 mm, 60 mm, 80 mm, 100 mm and 120 mm.

Endovascular System (Figure 2)

The stent graft (**A**) is supplied premounted between the inner catheter (**D**) and the outer sheath (**E**) on the distal end of the endovascular system. In this compressed configuration, the Nitinol stent struts lie close together and the radiopaque markers appear as a contiguous band at each end of the stent graft.

The endovascular system is a coaxial catheter system consisting of an inner catheter (**D**), which connects to the handgrip (**F**) via a metal tube and an outer sheath (**E**), which connects to a Y-injection-adaptor (**G**) with a Tuohy-Borst valve (**H**).

The endovascular system has two female Luer-lock ports: one (**K**) at the proximal end of the handgrip, and the second (**L**) on top of the Y-injection-adaptor.

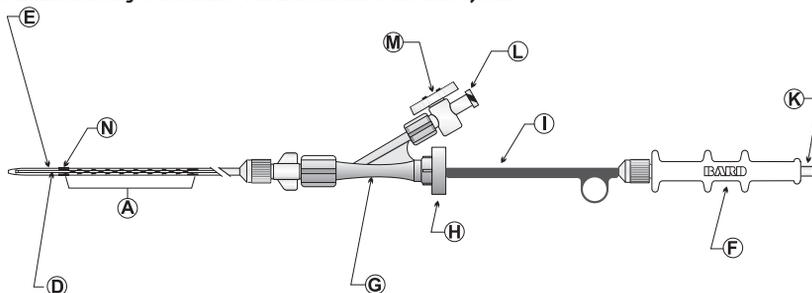
Prior to loading the endovascular system over a guide wire, both ports must be flushed with sterile saline to eliminate any air bubbles that may be trapped in the inner catheter lumen and/or the stent graft lumen. Flushing these lumens will also facilitate stent graft deployment. When flushing the stent graft lumen via the top port, ensure that the 2-way stopcock (**M**) is open, and that the Tuohy-Borst valve is closed.

Tightening the Tuohy-Borst valve (by turning it clockwise) prevents movement of the outer sheath relative to the inner catheter. There is also a removable safety clip (**I**) that prevents premature outer sheath retraction. The safety clip can be removed by pressing down on the top of the clip above the finger hole. In order to deploy the stent graft, the Tuohy-Borst valve must be open and the safety clip must be removed.

There is a radiopaque marker band (**N**) on the outer sheath of the endovascular system. Before stent graft deployment, this marker band overlaps with the radiopaque markers on the distal stent graft end. During stent graft deployment the marker band on the outer sheath will retract (towards the handgrip). When the moving marker band is past the proximal stent graft end by approximately 10 mm, the stent graft is fully released. The radiopaque markers on the proximal (inflow) end of the stent graft will have visually separated when the stent graft is released.

The **FLUENCY[®] Plus Endovascular Stent Graft** System is available in working lengths of 80 cm and 117 cm and it is compatible with 0.035" guidewires.

Figure 2: Itemized Drawing of the FLUENCY® PLUS Endovascular Stent Graft System



LEGEND for Figures 1 & 2

Reference	Corresponding Information
A	FLUENCY® PLUS Endovascular Stent Graft
B	Tantalum markers
C	Uncovered portion of stent graft
D	Inner catheter
E	Co-axial outer sheath
F	Handgrip
G	Y-injection-adaptor
H	Tuohy-Borst valve
I	Removable safety clip
J	Intentionally left blank in IFU
K	Endovascular system female Luer port on proximal end of handgrip
L	Endovascular system female Luer port top of the Y-injection adaptor
M	2-way stopcock
N	Radiopaque marker band

How Supplied:

The FLUENCY® PLUS Endovascular Stent Graft is supplied sterile (by ethylene oxide gas). For single use only.

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.

Contraindications:

There are no known contraindications for the FLUENCY® PLUS Endovascular Stent Graft.

Warnings:

- This device should only be used by physicians who are familiar with the complications, side effects, and hazards commonly associated with dialysis access shunt revisions and endovascular procedures.
- Do not expose the stent graft to temperatures higher than 500 °F (260 °C). ePTFE decomposes at elevated temperatures, producing highly toxic decomposition products.
- Examine the packaging and endovascular system to determine if there is any damage, defects or if the sterile barrier is compromised. Do not use the device if any of these conditions are observed.
- Do not resterilize. After resterilization, the sterility of the product is not guaranteed because of an indeterminable degree of potential pyrogenic or microbial contamination which may lead to infectious complications. Cleaning, reprocessing and/or resterilization of the present medical device increases the probability that the device will malfunction due to potential adverse effects on components that are influenced by thermal and/or mechanical changes.
- Do not reuse. This device has been designed for single use only. Reusing this medical device bears the risk of cross-patient contamination as medical devices, particularly those with long and small lumina, joints, and/or crevices between components are difficult or impossible to clean once body fluids or tissues with potential pyrogenic or microbial contamination have had contact with the medical device for an indeterminate period of time. The residue of biological material can promote the contamination of the device with pyrogens or microorganisms which may lead to infectious complications.

- **Do not use in patients with uncorrectable coagulation disorders.**
- **Do not use in patients with bacteremia or septicemia.**
- **Do not use in patients that cannot be adequately premedicated and have a known allergy or sensitivity to contrast media.**
- **Do not use in patients with known hypersensitivity to nickel-titanium.**
- **Do not use in patients whose AV access graft/fistula is infected.**
- **Do not use in patients with an AV access graft that has been implanted for less than 30 days.**
- **Do not use in patients with an immature AV fistula.**
- **Do not use the device in patients where full expansion of an appropriately sized angioplasty balloon could not be achieved during pre-dilation.**
- **Do not use the device after the "Use By" date specified on the label.**
- **Do not use if packaging/pouch is damaged.**
- **Do not use the device if the endovascular system cannot be flushed prior to use. Flushing is required prior to insertion or reinsertion.**
- **The delivery catheter is not intended for any use other than stent graft deployment.**
- **Placing a stent graft across a vessel side branch may impede blood flow and hinder or prevent future procedures.**
- **The stent graft (implant) cannot be repositioned within the vessel after total or partial deployment.**
- **Once partially or fully deployed, the stent graft cannot be retracted or remounted onto the delivery system.**
- **Do not attempt to move the implant during or after deployment.**
- **The effects of direct cannulation on the stent graft have not been evaluated in a clinical study.**
- **Notify the patient that the stent graft should not be cannulated and applying pressure to the implant area should be avoided.**

Precautions:

- Prior to stent graft deployment, refer to the Stent Graft Sizing Table (Table 1) and read the Instructions for Use.
- Faulty placement techniques may lead to stent graft deployment failure.
- A 0.035" guidewire is required for the introduction of the endovascular system. The guidewire must remain in place during the introduction, manipulation and removal of the endovascular system.
- Careful attention should be paid to ensure the device is appropriately sized to the achievable lumen, taking into account any change to the stated treatment area diameter that may have resulted from previous interventions. Under-sizing the device may result in device migration.
- The appropriate length device(s) should be selected so that the stent graft extends at least 10 mm distally (outflow) and 10 mm proximally (inflow) beyond the lesion into the non-diseased vessel.
- The safety and effectiveness of the device when placed across a tight bend including the terminal cephalic arch or across a joint has not been evaluated.
- The safety and effectiveness of the device when placed across an aneurysm or a pseudoaneurysm has not been evaluated.
- The safety and effectiveness of the device when used in the Superior Vena Cava has not been evaluated.
- The safety and effectiveness of the device when used in central lesions (including the thoracic outlet) where a stent was not previously placed has not been evaluated.
- The safety and effectiveness of the device when placed across a fractured bare metal stent has not been evaluated.
- The device has not been tested for use when used around a tight bend such as an AV loop graft.
- The device has not been tested for use in an overlapped condition with another FLUENCY® Plus Stent Graft.
- Do not kink the delivery catheter or use excessive force during delivery to the target lesion.
- In the case of in-stent restenosis, post dilation of the stent graft must be performed with a PTA balloon catheter no larger than the previously placed bare metal stent.
- The stent graft implant cannot be expanded with an angioplasty balloon beyond its stated diameter.
- Ensure that the Tuohy-Borst valve on the Y-injection-adaptor is closed during insertion and manipulation of the endovascular system.
- Prior to stent graft deployment, ensure that the proximal (inflow) stent graft end is positioned in a straight section of the lumen to reduce the risk of higher deployment forces and possible endovascular system failure.
- The endovascular system will function after the safety clip is removed and the Tuohy-Borst valve is loosened. This should not be undertaken until the stent graft is at the target location and ready to be deployed.
- Higher deployment force may be encountered with longer length stent grafts.
- If unusual resistance or high deployment force is encountered during stent graft deployment, abort the procedure, remove the delivery system and use an alternative device.
- If resistance is encountered when removing the delivery system, it is recommended to remove the delivery system, introducer and guidewire as a single unit.
- Careful attention of the operator is warranted to mitigate the possibility of distal (central venous system) migration of the stent graft during deployment. After deployment of approximately 15 mm of the stent graft, wait for the distal end the stent graft to fully expand.

- When passing a PTA balloon catheter through the deployed stent graft for post dilation, advance the PTA balloon catheter under fluoroscopy to ensure that the stent graft is not dislodged.
- Do not attempt to re-sheath the delivery system after stent graft release.
- Clinical investigations regarding the safety and effectiveness of the device have been limited to implants placed within AV grafts/fistula located in the upper extremities.

Potential Complications:

Complications and Adverse Events associated with use of the **FUENCY® Plus Endovascular Stent Graft** may include the usual complications associated with endovascular stent and stent graft placement and dialysis shunt revisions. These may include the following: Allergic reaction, aneurysm, arm or hand edema, bleeding at access site, blood leakage from delivery system (hemostasis), bond joint failures, cellulitis, cerebrovascular accident, congestive heart failure, death, delivery system kinking, detachment of part, face or neck edema, failure to deploy, fever, hematoma, hemoptysis, hemorrhage, high deployment forces, inability to track to target location, inaccurate deployment, incompatibility with accessory devices, infection, insufficient stent graft expansion, no visibility under fluoroscopy, pain, perforation, premature deployment, prolonged bleeding, pseudoaneurysm, rash, reaction to contrast, restenosis requiring reintervention, sepsis, steal syndrome, stent graft embolism, stent graft fracture, stent graft kinking, stent graft migration, stent graft misplacement, thrombotic occlusion, ventricular fibrillation, or vessel rupture.

The above complications may be associated with adverse events, medical or surgical intervention and/or death.

MR Conditional Information:

Non-clinical testing and analysis has demonstrated that the **FUENCY® Plus Endovascular Stent Graft** alone or in combination with a bare metal stent is MR Conditional as defined in ASTM F2503-13. Patients with this implant can be scanned safely under the following conditions:

- Static magnetic field of 1.5-Tesla or 3-Tesla.
- Spatial gradient field of 2500 Gauss/cm (25 T/m) or less.
- Maximum whole-body-averaged specific absorption rate (SAR) of 1 W/kg for 15 minutes of scanning for stent graft placement in the arms. For stent graft placement in the torso, the whole body SAR may be 2 W/kg for 15 minutes of scanning.
- In a configuration where the patients arms are not in contact with each other or touching the body.
- Normal mode operation of the MR system.
- A radiofrequency (RF) head transmit coil may be used. The safety of other MR local coils has not been evaluated.

Summary of Nonclinical Tests:

3 Tesla (128 MHz). Temperature rises of the **FUENCY® Plus Endovascular Stent Graft** alone or in combination with bare metal stents was determined based on heating tests according to ASTM F2182-11a using a GE Signa HDx whole body active shield MR scanner using software version 14/ LX/MR and a phantom designed to simulate human tissue. The maximum temperature rise after 15 minutes of scanning was 1.7 °C when scaled to a local background SAR of 1 W/kg. An analysis based on measured temperature rises and the electric fields in the body during MRI yielded a maximum projected in-vivo rise of 6 °C. This rise is conservative because blood flow and perfusion in the tissues surrounding the stent were not considered.

1.5 Tesla (64 MHz). Temperature rises of **FUENCY® Plus Endovascular Stent Graft** alone or in combination with bare metal stents were measured in a nonclinical configuration according to ASTM F2182-11a using a GE Signa whole body coil and a phantom designed to simulate human tissue. The maximum temperature rise after 15 minutes of power application was 2.6 °C when scaled to a local background SAR of 1 W/kg. An analysis based on measured temperature rises and the electric fields in the body during MRI yielded a maximum projected in-vivo rise of less than 8 °C for the SAR limits above. This rise is conservative because blood flow and perfusion in the tissues surrounding the stent were not considered.

Image artifact was evaluated according to ASTM F2119-07(2013) in the same GE Signa HDx MR system used for the 3T heating tests. Maximum artifact beyond the **FUENCY® Plus Endovascular Stent Graft** in combination with a bare metal stent made from Nitinol was determined to be less than 5 mm for the spin echo sequence and 8 mm for the gradient echo sequence. The lumen of **FUENCY® Plus Endovascular Stent Graft** and/or the bare metal stent is expected to be partially obscured. The artifact may be greater for a bare metal stent made from materials other than Nitinol. It may be necessary to optimize MR imaging parameters for the presence of this metallic implant.

Magnetic force was measured with the deflection technique of ASTM F2052-14 in the GE Signa HDx MR system. The deflection angle of the **FUENCY® Plus Endovascular Stent Graft** in combination with a bare metal stent made from Nitinol was less than 2° at the edge of the bore of the scanner, where the spatial gradient was 4.7 T/m and the static field intensity was 1.7 T. The magnetic force may be greater for a bare metal stent made from materials other than Nitinol.

NOTE: The effect of heating in the MRI environment for stent grafts with fractured struts is not known.

Storage:

Store in a cool, dry place. Keep away from sunlight. Use by the "Use By" date specified on the label.

Disposal Instructions:

After use, this product may be a potential biohazard. Handle and dispose of in accordance with accepted medical practice and applicable local, state and federal laws and regulations.

Stent Graft Sizing and Selection:

Special care must be taken to ensure that the appropriate size **FLUENCY® Plus Endovascular Stent Graft** is selected prior to introduction. In order to ensure sufficient wall apposition, it is recommended to oversize the stent graft relative to the healthy (non-diseased) portion of the vessel.

Table 1: Stent Graft Sizing and Selection Table

Reference Vessel Diameter*	Recommended Stent Graft Diameter	Stent Graft Oversizing
5.0 mm – 5.5 mm	6 mm	0.5 mm – 1.0 mm
5.0 mm – 6.0 mm	7 mm	1.0 mm – 2.0 mm
6.0 mm – 7.0 mm	8 mm	1.0 mm – 2.0 mm
7.0 mm – 8.0 mm	9 mm	1.0 mm – 2.0 mm
8.0 mm – 9.0 mm	10 mm	1.0 mm – 2.0 mm
9.0 mm – 11.0 mm	12 mm	1.0 mm – 3.0 mm
11.0 mm – 12.0 mm	13.5 mm	1.5 mm – 2.5 mm

*The largest diameter (post balloon angioplasty) of the healthy vessel segment adjacent to the lesion.

NOTE:

- **In order to ensure safe stent graft placement and lesion coverage, it is recommended that the stent graft extends a minimum of 10 mm distally (outflow) and 10 mm proximally (inflow) beyond the lesion at both ends.**
- **If a stent graft is oversized per Table 1, there will be minimal foreshortening (<10%) of the stent graft during deployment.**
- **Keep in mind that approximately 2 mm of each stent graft end is uncovered.**

Materials required for the Fluency® Plus Endovascular Stent Graft Procedure:

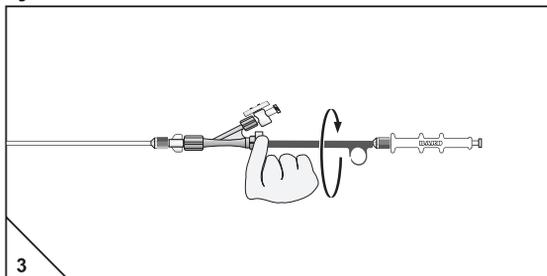
- Heparinized saline
- Sterile syringes
- 0.035" (0.889 mm) guidewire with a length at least twice as long as the endovascular system
- Introducer sheath with appropriate inner diameter
- Balloon angioplasty catheter for pre and/or post dilation
- Inflation device
- Diagnostic catheters and accessories
- Contrast Medium

DIRECTIONS FOR USE

Preparation:

1. Carefully remove the endovascular system from its packaging and inspect packaging and system for any damage or defects. Do not use if the sterile barrier is compromised.
2. The use of an appropriately sized introducer sheath is recommended.
3. Prepare a stiff 0.035" guidewire per its Instructions for Use and advance the guidewire under fluoroscopy to the target location.
4. Select an appropriate stent graft diameter and stent graft length based on the Stent Graft Sizing and Selection Table listed above (Table 1).
5. Pre-dilate the lesion and confirm that the stenosed lumen can be dilated to the desired diameter. In case of in-stent restenosis, the balloon diameter for pre-dilation should be no larger than the previously placed bare metal stent diameter.
6. Remove the endovascular system from the packaging and tighten the Tuohy-Borst valve on the Y-injection-adaptor by turning it clockwise. (see figure 3)

Figure 3

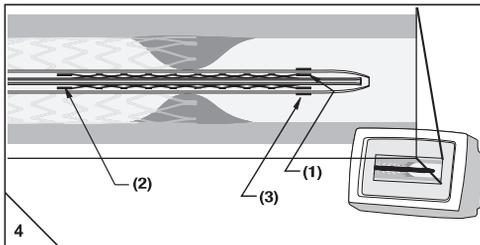


7. Flush the stent graft lumen with sterile saline by using a small volume syringe.
 - a) Attach the syringe to the Luer port at the back of the endovascular system and flush the endovascular system until saline leaks from the distal tip of the catheter.
 - b) Attach the syringe to the Luer port on the Y-adapter, open 2 way stopcock (in line with Y-adapter) and flush the endovascular system until saline leaks from the distal end of the endovascular system. Close the stopcock when flushing is complete and remove the syringe from the Luer port.

Introduction of the endovascular system:

8. Under radiographic guidance, advance the stent graft across the lesion. Use the radiopaque stent graft ends to center the stent graft. It is recommended to advance the endovascular system past the lesion and then pull back slightly on the entire system to attain correct positioning of the radiopaque markers and ensure slack is removed from the endovascular system.
9. Ensure the delivery catheter is straight and the stent graft extends a minimum of 10 mm distally (outflow) and 10 mm proximally (inflow) beyond the lesion into the non-diseased vessel.
10. Confirm the position of the radiopaque markers on the stent graft ends (see figure 4). It is recommended that the position of the stent graft ends (1, 3) and (2) should be marked on the screen.

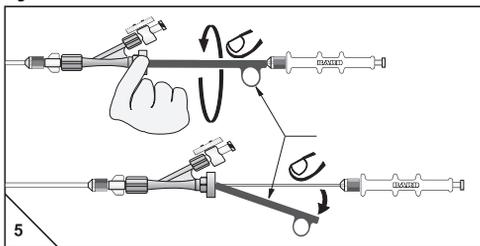
Figure 4



Stent Graft Deployment:

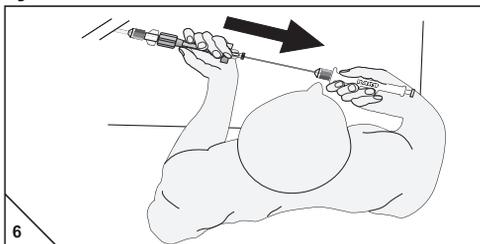
11. When the stent graft is ready for deployment, open the Tuohy-Borst valve by turning it counter clockwise and remove the safety clip by pressing down on the top of the grip surface with the thumb and pulling downward. (see figure 5).

Figure 5



12. Confirm that the stent graft position remains unchanged by examining the radiopaque markers.
13. To deploy the implant, pin the handgrip on a stable surface with your back hand and slowly pull the Y-injection-adapter with your front hand towards the handgrip. This action retracts the outer sheath and exposes a corresponding portion of the stent graft. The back hand should stay fixed in position with slight adjustments as necessary to allow for proper deployment (see figure 6).

Figure 6



14. Deploy the first 15 mm of the stent graft slowly until the distal stent graft end has expanded. Once the distal (outflow) portion has fully expanded, deploy the remainder of the stent graft slowly.

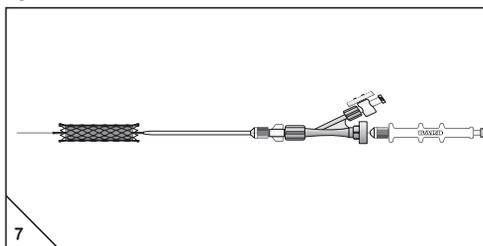
NOTE: Higher deployment force may be encountered with longer length stent grafts or in tortuous anatomy.

IMPORTANT:

- **When deploying the stent graft, the delivery system should be kept as straight as possible. Slight back tension on the handgrip is recommended to ensure that the delivery system is stationary and straight.**
 - **Do not hold or kink the outer sheath of the delivery catheter.**
 - **Ensure the Y-injection-adaptor and outer sheath move during stent graft deployment and the handgrip is stationary.**
 - **If unusual resistance or high deployment force is encountered during stent graft deployment, abort the procedure, remove the delivery system and use an alternative device of the same size.**
15. The stent graft is fully deployed when the Tuohy-Borst valve touches the handgrip (see figure 7).

Additionally, the radiopaque markers on the proximal end of the stent graft will have separated once fully deployed. After full stent graft deployment, wait for complete device expansion before removing the delivery system over the guidewire.

Figure 7

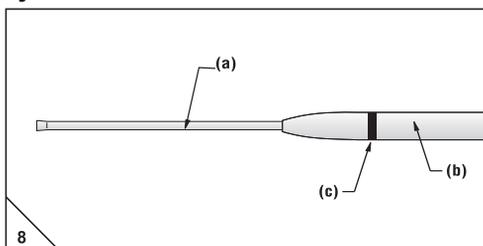


16. Remove the delivery system under fluoroscopy while maintaining guidewire access. Do not attempt to re-sheath the delivery system after the stent graft has been deployed.

NOTE: If resistance is encountered removing the delivery system, it is recommended to remove the delivery system, introducer and guidewire as a single unit.

17. After removing the delivery system, visually confirm that the complete system has been removed. (see figure 8)
 - (a) inner catheter with distal flared end
 - (b) outer sheath with radiopaque marker band (c)

Figure 8



18. Post dilate the stent graft with an angioplasty balloon sized appropriately as to ensure complete wall apposition to the reference vessel.
19. Examine the implanted stent graft under fluoroscopy to verify final stent graft position.

Post Procedure Precaution:

The effects of direct cannulation of the **FLUENCY® PLUS Endovascular Stent Graft** have not been determined. Notify the patient that the stent graft should not be directly cannulated and that applying pressure to the implant area should be avoided.

Patient Implant Information Card:

A Patient Implant Information Card is provided with this device. The Patient Data, Implant Data, and Hospital Data should be carefully recorded on the card and given to the patient.

Apply one of the peel-off stickers found on the product labels on the product carton box or on the pouch to the indicated area on the Patient Implant Information card. This peel-off sticker contains important information about the patient's stent graft implant. The patient should carry this card with them and provide to any medical personnel caring for the patient in the future.

SUMMARY OF CLINICAL STUDY

In the RESCUE study, a total of 265 patients were treated at 23 U.S. investigational sites in this prospective, multi-center, randomized, concurrently-controlled clinical study designed to assess the safety and effectiveness of the **FLUENCY® Plus Endovascular Stent Graft**. A total of 781 subjects were screened for eligibility, while 265 subjects were randomized and treated. The primary reason for exclusion from the study was the subjects' failure to meet the target lesion angiographic specific criteria. 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 patients 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.

At the time of this interim analysis, the 265 patients randomized into the Intent-to-Treat (ITT) group were evaluated for the primary and secondary endpoints. Of this group, the ITT analyses were conducted on patients who had reached pre-specified follow-up time points. As such, evaluation of the primary safety endpoint at 30 days included 244 patients (118 in the treatment arm and 126 in the control arm), while evaluation of the primary effectiveness endpoint at six months included 220 patients (109 in the treatment arm and 111 in the control arm). Patients will be followed through 24 months.

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, data was leveraged from the RESCUE study that supported the original PMA approval for treatment of in-stent restenosis to support treatment of stenosis in the venous outflow of hemodialysis patients dialyzing by an AV graft. 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 the Supplementary Data Section for summaries of those clinical studies (FLAIR and RENOVA).

Study Endpoints

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. The primary safety endpoint was evaluated based on the incidence of safety events observed through 30 days.

Secondary endpoints included: (1) Post-Intervention Lesion Patency at 30 days, 90 days and 12 months; (2) Access Circuit Primary Patency at 30 days, 90 days, 12 months, 18 months and 24 months; (3) Index of Patency Function at 30 days, 90 days, 6 months, 12 months, 18 months and 24 months; (4) Index of Patency Function – Target Lesion at 30 days, 90 days, 6 months, 12 months, 18 months and 24 months; (5) Secondary Patency at 30 days, 90 days, 6 months, 12 months, 18 months and 24 months; (6) Binary Restenosis at 90 days; (7) Technical and Procedural Success; and (8) Safety at 90 days, 6 months, 12 months, 18 months and 24 months.

Patients studied

Eligible patients had a hemodynamically significant stenosis $\geq 50\%$ and clinical evidence of AV graft or AV fistula dysfunction (without thrombotic occlusion), with angiographic evidence of a previously placed bare metal stent located in the venous outflow of the AV access circuit. To be included in the study, the target lesion must have been located in the restenosed bare metal stent extending no more than 3 cm beyond the bare metal stent end, and must have been ≤ 10 cm in length. The AV access graft must have been implanted at least 30 days, or the AV fistula located in the arm must have been mature, and must have undergone at least one successful hemodialysis session.

Patients were excluded from the study if they had a thrombosis treated within 7 days before the index procedure, or if the restenosed bare metal stent was determined by angiography to be fractured. Patients were also excluded for a variety of conditions which would make the implantation procedure more difficult or would confound the interpretation of the study results.

Methods

Patients were prospectively randomized to treatment with the **FLUENCY® Plus Endovascular Stent Graft** or PTA. Cross-overs were not allowed. Clinical follow-up visits were conducted at thirty and ninety days, and at six months after the index procedure. Interim visits were conducted as clinically indicated. Qualitative angiography was conducted in conjunction with the 90-day follow-up visit. Antiplatelet and anticoagulation therapy was at the discretion of the physician. Patients were monitored for adverse events throughout the trial.

An independent Clinical Events Committee (CEC) adjudicated all adverse events and serious 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.

For effectiveness, the primary endpoint was measured by percentage of subjects with Access Circuit Primary Patency (ACPP) through 6 months and was estimated using the Kaplan-Meier method. The primary effectiveness endpoint comparing PTA to **FLUENCY® Plus Endovascular Stent Graft** (stratified by access type) was tested, using a stratified log rank test at a two-sided significance level of 0.05.

For safety, the non-inferiority of **FLUENCY® Plus Endovascular Stent Graft** to PTA in the primary safety endpoint was tested using a Farrington and Manning Exact Test at a one-sided significant level of 0.05.

Additionally, similar to the analysis of the primary effectiveness endpoint, the secondary effectiveness endpoint of Post-intervention Lesion Patency (PLP) was compared between **FLUENCY® Plus Endovascular Stent Graft** and PTA using a stratified log rank test at a two-sided significance level of 0.05. This test was conducted after both primary tests were successful to control for multiplicity.

Results

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Tables 2 - 4 summarize the patient demographics, medical history, and the AV Access circuit description.

Table 2: Patient Demographics

	PTA Alone (N=137)	FLUENCY® Plus (N=128)	All Patients (N=265)
Age (years) [1]	p=0.691 [2]		
Mean (SD)	62.2 (13.55)	61.5 (13.42)	61.9 (13.47)
Min, Max	27, 93	34, 89	27, 93
Sex	p=0.741 [3]		
Female	67 (48.9)	60 (46.9)	127 (47.9)
Male	70 (51.1)	68 (53.1)	138 (52.1)

[1] Age is calculated as the date of informed consent minus date of birth.

[2] P value is from t test

[3] P value is from z test

Table 3: Medical History

	PTA Alone (N=137)	FLUENCY® Plus (N=128)	All Patients (N=265)
	n (%)	n (%)	n (%)
Congestive Heart Failure	38 (27.7)	37 (28.9)	75 (28.3)
Coronary Heart Disease	42 (30.7)	52 (40.6)	94 (35.5)
Diabetes Mellitus	86 (62.8)	87 (68.0)	173 (65.3)
Hypercoagulation	3 (2.2)	1 (0.8)	4 (1.5)
Hypertension	130 (94.9)	116 (90.6)	246 (92.8)
Glomerulonephritis	4 (2.9)	5 (3.9)	9 (3.4)
Peripheral Vascular Disease	17 (12.4)	14 (10.9)	31 (11.7)
Steal Syndrome	2 (1.5)	3 (2.3)	5 (1.9)
Cerebrovascular Accident	19 (13.9)	26 (20.3)	45 (17.0)
Transient Ischemic Attack	7 (5.1)	5 (3.9)	12 (4.5)
Other Pre-Existing Conditions	133 (97.1)	127 (99.2)	260 (98.1)

Table 4: Description of the Access Circuit

	PTA Alone (N= 137)	FLUENCY® Plus (N= 128)	All Patients (N= 265)
AV Access Type	n (%)	n (%)	n (%)
Graft	63 (46.0)	59 (46.1)	122 (46.0)
Mature Fistula	74 (54.0)	69 (53.9)	143 (54.0)
Location	n (%)	n (%)	n (%)
Right Arm	44 (32.1)	47 (36.7)	91 (34.3)
Left Arm	93 (67.9)	81 (63.3)	174 (65.7)
Position	n (%)	n (%)	n (%)
Forearm	17 (12.4)	21 (16.4)	38 (14.3)
Upper Arm	120 (87.6)	107 (83.6)	227 (85.7)
Time Since Implantation/Creation (Months)			
n	130	119	249
Mean (SD)	41.0 (27.09)	34.8 (23.95)	38.0 (25.77)
Min, Max	2, 154	6, 159	2, 159

TARGET LESION CHARACTERISTICS

Table 5 summarizes target lesion characteristics at baseline of the test and control groups.

Table 5: Target Lesion Characteristics at Index Procedure

	PTA Alone (N= 137)	FLUENCY® Plus (N= 128)	All Patients (N= 265)
Target Lesion Location	n (%)	n (%)	n (%)
Central Vein	52 (38.0)	41 (32.0)	93 (35.1)
Peripheral Vein	83 (60.6)	86 (67.2)	169 (63.8)
Target Lesion Length (cm)			
Mean (SD)	2.92 (1.67)	3.17 (1.80)	3.04 (1.73)
Min, Max	0.5, 8.0	0.5, 10.0	0.5, 10.0
Percentage of Stenosis (%)			
Mean (SD)	69.75 (13.87)	71.25 (13.13)	70.48 (13.51)
Min, Max	50.0, 100.0	50.0, 100.0	50.0, 100.0
Reference Vessel Diameter at the Restenosed Bare Metal Stent (mm)			
Mean (SD)	9.51 (1.97)	9.18 (1.69)	9.35 (1.85)
Min, Max	5.0, 14.5	5.0, 12.0	5.0, 14.5
Additional Stenotic Lesions in the Venous Outflow that were > 3 cm from the Edge of the Target Lesion			
Yes	78 (56.9)	65 (50.8)	143 (54.0)
No	59 (43.1)	63 (49.2)	122 (46.0)

Patient Accountability

Investigators treated 265 patients at 23 sites. Two-hundred forty-four (244) patients were included in the 30 day primary safety endpoint analysis and 220 patients in the six month primary effectiveness endpoint analysis. At the time of this interim analysis, a total of 21 patients did not yet have their 30 day follow up visit or had discontinued within 30 days without a safety event and were excluded from the safety analysis. A total of 45 active patients had not yet reached their 6 month follow up visit and were excluded from the effectiveness analysis.

Summary of Safety

The primary safety endpoint for this study was noninferiority of **FLUENCY® Plus Endovascular Stent Graft** to PTA alone for freedom from safety events through 30 days. 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. Analyses are presented for safety events as adjudicated by the blinded Clinical Endpoint Committee (CEC). Tables 6 and 7 show the results of the analyses for Freedom from any Safety Events / Adverse Events through 30 days.

Table 6: 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 7: Incidence of Primary Safety Endpoint in First 30 Days

	PTA Alone (N=111)	FLUENCY® Plus (N=128)
Number of Patients 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/cellulitis of both legs/sepsis	0	1 (0.8)
Ventricular fibrillation	1 (0.7)	0
Infolded covered stent	1 (0.7)	0

The percentage of patients (AV graft and fistula patients) free from safety events through 30 days was 96.8% (95% CI: 92.07, 99.13) for patients with PTA alone, and 96.6% (95% CI: 91.55, 99.07) for patients with **FLUCENCY® Plus Endovascular Stent Graft** (non-inferiority p-value = 0.007). Thus, the non-inferiority ($\delta = 0.075$) of **FLUCENCY® Plus Endovascular Stent Graft** to PTA alone with regard to this primary safety endpoint is confirmed.

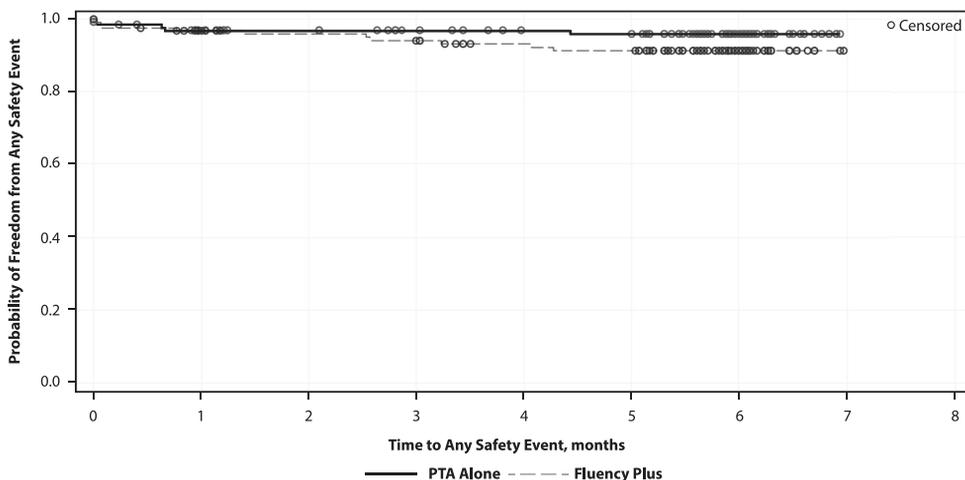
A list of Safety Events observed in the Clinical Study through six months can be found in Table 8, and a list of device and/or procedure related AEs can be found in Table 9. AEs are defined as those that reasonably suggest the involvement of the AV access circuit (not including stenosis or thrombosis). A Clinical Events Committee (CEC) and Data Safety Monitoring Board (DSMB) reviewed all AEs and safety trends. The Kaplan-Meier analysis of freedom from any safety event through 6 Month follow-up is provided in Figure 9.

Table 8: Safety Events through 6 months (Randomized Patients)

Parameter	PTA Alone (N=137)	FLUCENCY® PLUS (N=128)	Overall (N=265)
Number of Safety Events Reported	8	11	19
Number(%) of Patients Reporting Safety Events	5 (3.6)	10 (7.8)	15 (5.7)
Diagnosis/Event Name			
Hemorrhage	0	2 (1.6)	2 (0.8)
Infection	2 (1.5)	2 (1.6)	4 (1.5)
Pain	1 (0.7)	0	1 (0.4)
Arm or Hand Edema	0	2 (1.6)	2 (0.8)
Pseudoaneurysm	0	2 (1.6)	2 (0.8)
Vessel Rupture	2 (1.5)	0	2 (0.8)
Other	3 (2.2)	2 (1.6)	5 (1.9)
Other: Allergic reaction. to uncertain source; rash on right arm	0	1 (0.8)	1 (0.4)
Other: Fever/cellulitis of both legs/sepsis	0	1 (0.8)	1 (0.4)
Other: Infolded covered stent	1 (0.7)	0	1 (0.4)
Other: Prolonged Bleeding	1 (0.7)	0	1 (0.4)
Other: Ventricular Fibrillation	1 (0.7)	0	1 (0.4)
Other: Hemoptysis	0	1 (0.8)	1 (0.4)

Note: Patients with multiple events may be counted more than once (in more than one category).

Figure 9: Kaplan Meier Analysis for Freedom from Any Safety Event through 6 Month Follow-Up Visit (Randomized Patients)



The rate of freedom from any safety event through 90 days in the randomized patient population was 97.0% (95% CI: 94.09, 99.90) for PTA alone, and 94.2% (95% CI: 89.99, 98.37) for **FLUENCY® Plus Endovascular Stent Graft**. The rate of freedom from any safety event through 6 months in the randomized patient population was 96.0% (95% CI: 92.62, 99.46) for PTA alone, and 91.3% (95% CI: 86.19, 96.49) for **FLUENCY® Plus Endovascular Stent Graft**.

Table 9: All Device and/or Procedure Related Adverse Events through 6 months (inclusive of reported Safety Events in Table 8)

Treatment Group	Description of AE
PTA	Vessel Rupture: Right Axillary Vein
	Contrast Reaction
	Prolonged Bleeding
	Pain: Access Arm – Left Upper Arm
	Infolded Covered Stent
	Pain: Left Shoulder
	Vessel Rupture: Cephalic Vein in Left Shoulder Area
FLUENCY® Plus	Pseudoaneurysm: Basilic Vein Adjacent To Stent
	Pseudoaneurysm: Cannulation Zone of Access
	Bilateral Face Edema
	Pain: Shoulder and Neck
	Infection (Old Stent in Fistula)
	Arm or Hand Edema (Left Arm Swelling)
	Pain: All Over Body
	Allergic Reaction to Uncertain Source (Rash on Right Arm)
	Arm or Hand Edema (Entire Left Upper Extremity)

Primary Effectiveness Results

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.

ACPP was defined as the interval following placement of the **FLUENCY® Plus Endovascular Stent Graft** until thrombosis or re-intervention of the AV access circuit. ACPP ended with a re-intervention anywhere within the access circuit, from the arterial inflow to the superior vena cava-right atrial junction. The primary effectiveness endpoint of ACPP through 6 months is a binary endpoint and reflects the percentage of patients who are free from thrombosis or re-intervention for at least 6 months.

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 10. 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 10: Access Circuit Primary Patency at 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)
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.

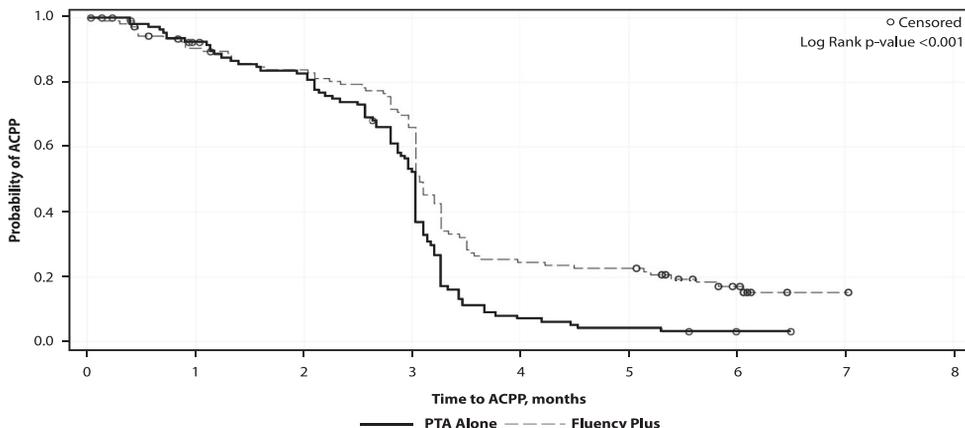
[2] The 95% confidence interval about median uses the Brookmeyer and Crowley method.

[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.

Figure 10 presents the Kaplan-Meier curves for Access Circuit Primary Patency through 6 months in the ITT group. The analysis shows a difference in survivorship curves between the treatment groups, with a steeper decline in survivorship for PTA than for **FLUENCY® Plus Endovascular Stent Graft**, particularly after approximately 3 months.

Figure 10: Kaplan-Meier Analysis for Access Circuit Primary Patency through 6 Month Follow Up (ITT)



SECONDARY EFFECTIVENESS RESULTS

Hypothesis Tested Secondary Effectiveness Result

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 11. 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 11: Post Intervention Lesion Patency at 6 Months (ITT)

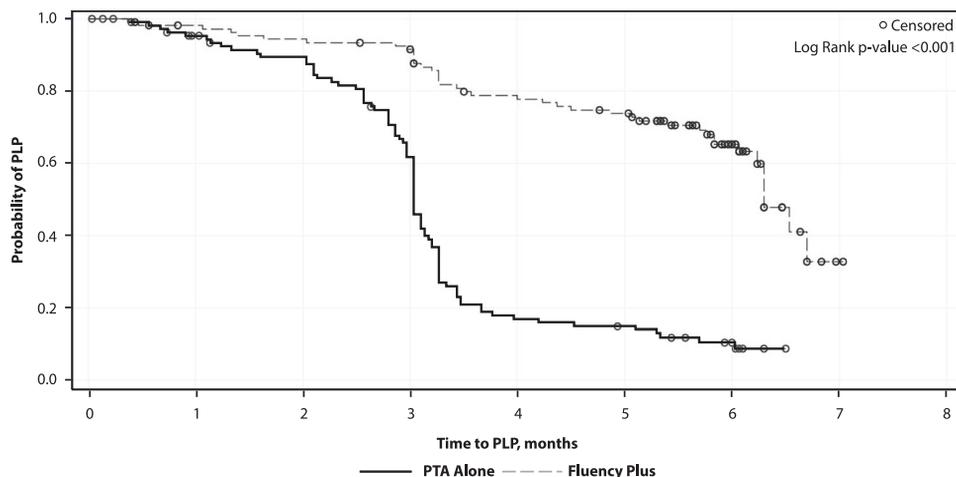
Overall (AV Graft and AV Fistula)		
	PTA Alone (N=111)	FLUENCY® PLUS (N=109)
Percentage of Post-Intervention Lesions Patency at 6 months (180 days)	10.4	65.2
95% CI for Rate [1]	(4.30, 16.57)	(55.59, 74.86)
Time to event (days)		
Median	91.0	189.0
95% CI for Median [2]	(91.00, 94.00)	(187.00, NE)
25% 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. NE = Not estimable.

The Kaplan-Meier analysis for PLP through 6 months (ITT population) is shown in Figure 11. The analysis shows a difference in survivorship curves between the treatment groups, with a noticeably steeper decline in survivorship from 2 months on for the PTA group.

Figure 11: Kaplan-Meier Analysis for Post Intervention Lesion Patency at 6 months (ITT)



Non Hypothesis Tested Secondary Effectiveness Results

The results for the non-hypothesis tested secondary endpoints are listed in Tables 12 and 13.

Table 12: Secondary Effectiveness Results without hypothesis testing (ITT)

	PTA alone (N=111)	FLUENCY® PLUS (N=109)
Index of Patency Function [1]	n=100	n=88
30 Days – mean number of days (SD)	29.5 (3.25)	30.0 (0.00)
90 Days – mean number of days (SD)	84.4 (17.61)	86.4 (13.60)
6 Months – mean number of days (SD)	125.7 (53.79)	137.9 (49.64)
Index of Patency Function at Target Lesion [2]	n=100	n=88
30 Days – mean number of days (SD)	29.5 (3.25)	30.0 (0.00)
90 Days – mean number of days (SD)	84.8 (17.16)	87.6 (11.34)
6 Months – mean number of days (SD)	136.1 (51.67)	153.8 (42.60)
Post-Intervention Secondary Patency [3]		
30 Days – Rate (no. events/no. at risk)	100.0 (0/103)	100.0 (0/105)
90 Days – Rate (no. events/no. at risk)	100.0 (0/100)	100.0 (0/102)
6 Months – Rate (no. events/no. at risk)	100.0 (0/54)	98.8 (1/55)
Binary Restenosis at 90 Days [4]	74.8% (83/111)	19.3% (21/109)

- [1] Index of Patency Function (IPF) was defined as the time from the index study procedure to complete AV graft or AV fistula abandonment divided by the number of visits for a reintervention performed on the AV access circuit in order to maintain vascular access for hemodialysis
- [2] Index of Patency Function at Target Lesion (IPF-T) was defined as the time from the index study procedure to complete access abandonment divided by the number of visits for a reintervention performed at the target lesion in order to maintain vascular access for hemodialysis
- [3] Post-Intervention Secondary Patency (PSP) was defined as the interval after the index intervention until the access undergoes surgical thrombectomy or revision, or until the access is abandoned.
- [4] Lesions with a ≥50% diameter stenosis at 90 days follow-up were characterized as restenotic. If a study patient returned for a reintervention prior to the 90 day (+/- 15 days) Follow-Up Visit, angiographic images were submitted to the Core Lab for Qualitative Vessel Analysis (QVC). If this occurred, a repeat 90 day Follow-Up angiogram was not performed.

Table 13: Acute Secondary Effectiveness Results without hypothesis testing (Randomized Patients)

	PTA alone (N=137)	FLUENCY® PLUS (N=128)
Technical Success (Device Delivery Success) [1]	N/A	99.2% (127/128)
Procedure Success [2]	95.6% (131/137)	96.9% (124/128)

- [1] Technical success was defined as deployment of the implant to the intended location assessed at the time of the index procedure.
- [2] Procedure Success was defined as anatomic success and resolution of the pre-procedural clinical indicator(s) of a hemodynamically significant stenosis.

Patient Death Summary

There were sixteen (16) deaths among the randomized patients, including 8 patients in the test group and 8 patients in the control group. None of these deaths were attributed to the study device.

The eight (8) deaths in the study device group occurred between 13 days and 158 days following the index procedure. Causes of death included: hemorrhagic shock with multi-organ failure (day 97), myocardial infarction (day 158), septic shock and pneumonia (day 16), one unknown cause of death (day 13), end stage renal disease (day 134), cardiac arrest (day 133), metastatic pancreatic carcinoma (day 129), and sepsis secondary to cellulitis (day 17).

The eight (8) deaths in the PTA Control group occurred between 01 and 145 days following the index procedure. Causes of death included: ventricular fibrillation (day 1), access rupture, exsanguination (day 145), five events of cardiac arrest (one at day 7, one at day 33, one at day 64, one at day 79, and one at day 12), end stage renal disease (day 120).

Observed Device Malfunctions

There were zero (0) device malfunctions reported.

Supplementary Data

Selected AV Access Publications

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 (4) studies included 144 patients that were treated with **FLUENCY® Plus Endovascular Stent Grafts** with 6-month ACP rates ranging from 35% to 77% and Secondary Patencies of 88% and 52%, respectively (Table 14).

A meta-analysis of the peer-reviewed studies was completed based on a method by D'Agostino and Weintraub (1995), 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 = $\sum(w_i * p_i) / \sum(w_i)$; 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 ACP rate was 49.1% (95% CI: 41.4%, 56.8%).

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

Table 14: 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. (2013)	35	100%	77%	-
Dolmatch et al. (2012)	58 [#]	100%	35%	88%
Calsina et al. (2013)	27	-	44%	52%
Schmelter et al. (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.

SUMMARY OF CLINICAL STUDIES WITH THE FLAIR® ENDOVASCULAR STENT GRAFT

The **FLAIR® Endovascular Stent Graft** implant is similar in design and materials to the **FLUENCY® Plus Endovascular Stent Grafts** implant. The results from two multicenter, prospective, randomized, concurrently-controlled clinical studies demonstrated the safety and effectiveness of the **FLAIR® Endovascular Stent Graft** for the treatment of stenoses at the venous anastomosis of ePTFE or other synthetic arteriovenous (AV) through 6 months, 12 months and 24 months and were the basis upon which PMA approval was granted. The clinical data from the studies served as additional support for the extension of the **FLUENCY® Plus Endovascular Stent Grafts** indication to include non-stented stenoses and occlusions in patients dialyzing with a synthetic AV graft.

In the two studies, the **FLAIR® Endovascular Stent Graft** Pivotal study and the **FLAIR® Endovascular Stent Graft** Post Market Study (RENOVA), the eligible patients had a hemodynamically significant stenosis ($\geq 50\%$ reduction of normal vessel diameter) accompanied by a hemodynamic, functional or clinical abnormality (defined by K/DOQI, 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.

FLAIR® ENDOVASCULAR STENT GRAFT PIVOTAL STUDY

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.

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:

- 1) The ability to successfully deliver the **FLAIR® Endovascular Stent Graft**;
- 2) Procedural success;
- 3) Treatment area primary patency (at 2 months);
- 4) Access circuit primary patency (at 2 and 6 months);
- 5) Assisted access circuit primary patency(at 2 and 6 months);
- 6) Access circuit cumulative (i.e., secondary) patency (at 2 and 6 months); and
- 7) Percent stenosis of the treatment area (at 2 and 6 months).

Results

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.

Summary of Safety

Adverse Event rates (through 210 days) for randomized and “roll-in” patients are presented in Table 15. The statistical comparisons and p-values presented in Table 15 are from the randomized population only.

Table 15: 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

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 16.

Table 16: 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.

Conclusions

Data from the clinical trial provide a reasonable assurance that the FLAIR® Endovascular Stent Graft is safe and effective for the treatment of stenoses at the venous anastomosis of ePTFE or other synthetic arterio-venous (AV) access grafts when used in accordance with its labeling.

A PROSPECTIVE, RANDOMIZED, CONCURRENTLY-CONTROLLED 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 (\pm 30 days) post-index procedure.

Study Endpoints

The primary objectives of this Post Approval study were to:

- 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;
- Demonstrate that the 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,
- 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.

Secondary Endpoints included:

- 1) The number of re-interventions to the access circuit until graft abandonment or through 12 months post-index procedure;
- 2) Post-Intervention Assisted Primary Patency (PAPP) at 6, 12 and 24 months;
- 3) Post-intervention Secondary Patency at 6, 12 and 24 months;
- 4) Procedural success;
- 5) Demonstrate the effectiveness of the BPV 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
- 6) 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.

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.

Summary of Safety

A summary of all adverse events through 24 months is presented in Table 17.

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 17: 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.

Summary of Effectiveness

Primary and secondary effectiveness endpoint results are presented in Table 18.

Table 18: 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.

Conclusions

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 arteriovenous (AV) through 12 months and 24 months and confirm the 6 month outcomes from the pivotal study upon which PMA approval was based.

CONCLUSIONS DRAWN FROM STUDIES

Results of the randomized, prospective, multi-center clinical trial 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 for treatment of in-stent restenosis.

Data from the non-clinical testing, the clinical trial, those drawn from 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**, provide a 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 arteriovenous (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.

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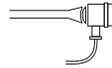
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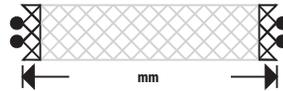
MR Conditional



Stent Graft Diameter



Contents: (1)



Stent Graft Length



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