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
Date of Panel Recommendation:	None
PMA Number:	P130029
Date of Notice of Approval:	June 17, 2014
Priority Review:	None

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.

III. Contraindications

None

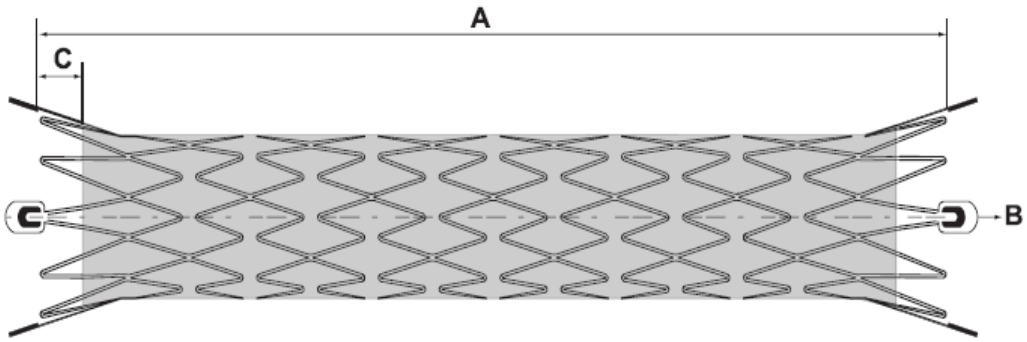
IV. Warnings and Precautions

The warnings and precautions can be found in the Fluency® Plus Endovascular Stent Graft labeling.

V. Device Description

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

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



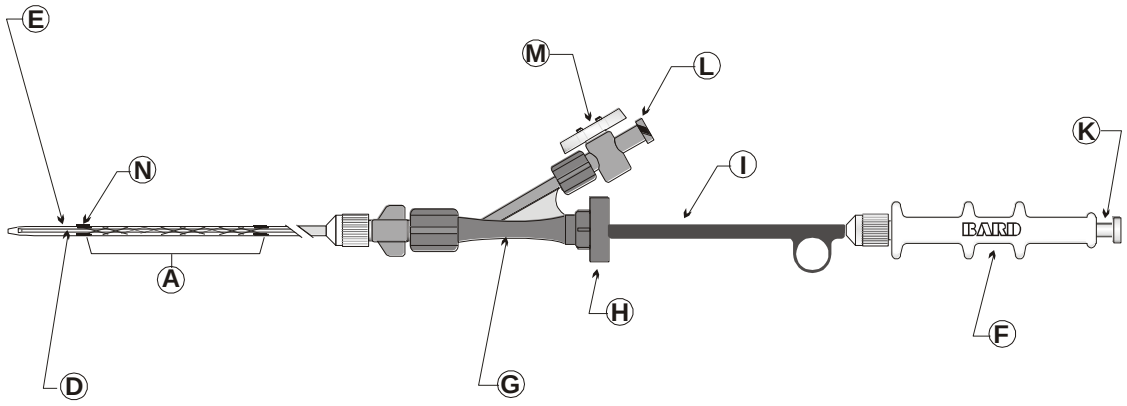
Legend:
A Stent Graft
B Tantalum Markers
C Uncovered Portion of Stent Graft

Table 1: Device Dimensions

Stent Graft Outer Diameter (mm)	Stent Graft Length (mm)					Delivery System French Size (F)	Delivery System Shaft Length (cm)
6	40	60	80	100	120	8	80 & 117
7	40	60				8	80 & 117
7			80	100	120	9	80 & 117
8	40	60	80	100	120	9	80 & 117
9	40	60	80	100	120	9	80 & 117
10	40	60	80	100	120	9	80 & 117
12	40	60	80	100	120	10	80 & 117
13.5	40	60	80	100	120	10	80 & 117

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

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



Legend:

A	Stent Graft (compressed)	**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 correction of in-stent restenotic lesions such as percutaneous transluminal angioplasty (PTA). 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.

The current standard treatment for stenosis in AV access patients is PTA. The average patient dialyzing with an AV fistula or graft will require approximately 0.5-3 PTA interventions per year.

When PTA fails to treat the stenosis, bare metal stent placement may be recommended (NKF KDOQI Guidelines, 2006). Bare metal stents are prone to neointimal proliferation leading to in-stent restenosis (Dolmatch, 2009). Despite its limited efficacy in clinical practice, PTA remains the most frequently utilized method for the treatment of in-stent restenosis. Although there is no clinical literature available on the clinical outcome of patients with in-stent restenosis, Yevzlin found in-stent restenosis to occur more frequently and with greater severity than *de novo* lesions. In a retrospective analysis of 76 hemodialysis patients seen for access dysfunction after the previous placement of a bare metal stent, 54% (n=41) had in-stent stenotic lesions while 46% (n=35) had *de novo* stenoses. The amount of luminal occlusion due to neointimal hyperplasia was 85% in the in-stent group and 80% in the *de novo* group (Yevzlin, 2009).

VII. Marketing History

The Fluency® Plus Vascular Stent Graft has been commercially available outside the United States since June 2005 with a vascular indication (iliac and femoral arteries). The Fluency® Plus Biliary Stent Graft has been available in Japan since April 2009. Additionally, the Fluency® Plus Tracheobronchial Stent Graft was cleared for use in the United States and is indicated for use in the treatment of tracheobronchial strictures produced by malignant neoplasms. The Fluency® Plus Tracheobronchcial Stent Graft has also been available in Canada since July 2005. The Fluency® Plus Vascular Stent Graft has never been withdrawn from any market as a result of risk of serious adverse health consequences.

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.

Previously reported complications include:

- Thrombotic occlusion
- Restenosis requiring reintervention
- 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 the specific adverse events that occurred in the clinical study, please see Section X below.

IX. Summary of Preclinical Studies

A. Biocompatibility

Biocompatibility testing on the materials used in the Fluency® Plus Endovascular Stent Graft was performed following the recommendations provided in International Organization for Standardization (ISO) 10993, *Biological Evaluation of Medical Devices* and FDA's *Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.* All biocompatibility testing was conducted on the Fluency® Plus device. The components of the stent graft and delivery system were categorized per ISO 10993-1, *Biological Evaluation of Medical Devices Part 1: Evaluation and Testing within a Risk Management Process* based on the intended duration and contact with or within the body.

Specific biocompatibility tests were performed based on the categorization of the stent graft and delivery system in accordance with ISO 10993, *Biological Evaluation of Medical Devices*. Table 2 provides a listing of the tests performed for both the implant and delivery system biocompatibility testing, along with the corresponding results. All biocompatibility tests were conducted in accordance with the Good Laboratory Practices (GLP) per 21 CFR, Part 58.

Table 2. Implant & Delivery System Biocompatibility Testing

Biocompatibility Test	Results		Biocompatibility Test	Results
Implant Testing			***Delivery System Testing***	
Cytotoxicity (Agarose Overlay)	PASS		Cytotoxicity (MEM Elution and Agarose Overlay)	PASS
Irritation/Intracutaneous Reactivity	PASS		Sensitization (Mouse Local Lymph Node Assay with both polar and non-polar extracts)	PASS
Sensitization (MLLNA)	PASS		Irritation (Intracutaneous Reactivity with both polar and non-polar extracts)	PASS
Acute Systemic Toxicity	PASS		Acute systemic toxicity (with both polar and non-polar extracts)	PASS
Subchronic Toxicity	PASS		Material-mediated Pyrogenicity	PASS
Genotoxicity (Bacterial Reverse Mutation Study)	PASS		Hemocompatibility (Hemolysis with polar extract)	PASS
Genotoxicity (Rodent Bone Marrow Micronucleus)	PASS		Hemocompatibility (direct contact Complement Activation C3a and SC5b-9)	PASS
Genotoxicity (Chromosomal Aberration)	PASS		Hemocompatibility (direct contact Plasma Recalcification)	PASS
Implantation (1 Week Intramuscular)	PASS		Hemocompatibility (*in vivo* Thrombogenicity)	PASS
Implantation (4 Week Intramuscular)	PASS		Genotoxicity (Ames Reverse Mutation Assay with both polar and non-polar extracts)	PASS

Biocompatibility Test	Results		Biocompatibility Test	Results
Implant Testing			***Delivery System Testing***	
Implantation (13 Week Intramuscular)	PASS		Genotoxicity (Chromosomal Aberration Assay with McCoy's 5A Medium)	PASS
Hemocompatibility (i.e. Hemolysis)	PASS		Genotoxicity (Rodent Bone Marrow Micronucleus Assay with polar extract)	PASS
Hemocompatibility (Complement Activation)	PASS			
Hemocompatibility (*in vivo* Thrombogenicity)	N/A			
Pyrogenicity: Material Mediated	PASS			
Chronic Toxicity & Carcinogenicity	N/A			

B. Bench Testing

In vitro bench testing was conducted as part of the design verification and validation to support the safety and effectiveness of the Fluency® Plus Endovascular Stent Graft and Delivery System. This testing was conducted based on recommendations from risk assessments with consideration to FDA and industry recognized voluntary standards. The bench test results are summarized in Table 3.

Table 3: Summary of *In Vitro* Bench Testing

Test	Purpose/Objective	Results
Material Composition	To verify the chemical composition of the nitinol (nickel-titanium) and tantalum of the implant.	Pass
Shape Memory and Superelasticity	To ensure incoming tubing used in the manufacture of the implant's base stent complies with visual, dimensional, and performance specifications.	Pass
Mechanical Properties	To characterize the implant's base stent raw material mechanical properties (for uniaxial tensile strength and fatigue strength) to support stress/strain and fatigue analyses.	N/A
Corrosion Resistance – Post 10 Year Pulsatile Accelerated Durability	To verify the implant's ability to resist corrosion (pitting and crevice) and determine the presence of toxic byproducts released due to corrosion.	Pass
Corrosion Resistance – Galvanic Corrosion.	To verify the implant's ability to resist corrosion (galvanic) when coupled with other metals such as present in bare metal stents commonly encountered in the intended indication.	Pass
Dimensional Verification - Implant	To verify that critical implant dimensions (outer diameter and length) are met post-deployment under simulated physiological conditions.	Pass

Test	Purpose/Objective	Results
Percent Surface Area	To verify that the length of the uncovered ends meet their pre-determined acceptance criteria; and to characterize the implant's base stent percent free surface area (not including the covering).	Pass
Foreshortening	To quantify the relationship between length and diameter for the implant from its crimped to deployed form as well as in the freely expanded state, in the presence of a bare metal stent.	Pass
Integrity (post-deployment)	To evaluate the integrity of the implant in the presence of a bare metal stent post- deployment. To verify that the implant shows no defects that would render it unsuitable for the intended use.	Pass
Tantalum Marker Weld Strength	To verify that the strength of the tantalum marker bonds meets the performance requirements post-deployment.	Pass
Strength of Graft to Stent / Attachment System Bond	To verify that the force required to separate the two bonded ePTFE layers of the implant encapsulation is acceptable for the indication.	Pass
Radial Outward Force	To characterize force exerted by the implant as a function of implant diameter.	Pass
Accelerated Durability / Radial Fatigue	To evaluate the durability (maintenance of structural integrity) of the implant under arterial pulsatile fatigue conditions simulating 10 years of use.	Pass
Focal Compression Fatigue	To characterize the behavior of the implant in focal compression fatigue conditions.	N/A
MRI Safety and Compatibility	To evaluate MRI safety and compatibility.	Pass
Radiopacity	To evaluate the radiopacity of the implant with radiographic and angiographic imaging.	Pass
Crush Resistance	To evaluate the ability of the implant to resist permanent deformation following collapse between parallel plates. .	Pass
Kink Resistance	To evaluate the implant's flexibility in its deployed configuration.	Pass
Encapsulation Porosity	To characterize the stent graft covering porosity.	Pass
Local Compression	To characterize elastic deformation of the implant in response to localized compressive force.	Pass

Test	Purpose/Objective	Results
Migration Resistance	To verify that the stent graft adequately resists displacement when overlapped by a bare metal stent during simulated use conditions.	Pass
Dimensional Verification – Delivery System	To verify that the delivery system meets it dimensional pre- and post- deployment.	Pass
Delivery, Deployment and Retraction	To characterize the system with respect to flushability / leakproofness and luer lock compatibility; trackability, pushability, torqueability, tip morphology; premature deployment; deployment force and accuracy; stent graft conformability and ability to withdraw.	Pass
Bond Joint Strength	To determine the bond strength of the joints and/or fixed connections of the delivery system and verify that the strength of the bond joints are adequate for the intended use.	Pass
Tubing Tensile Strength	To determine the longitudinal tensile strength of catheter tubing used in the delivery system and verify that it has sufficient strength for the intended use.	Pass
Flexibility / Kinkability	To ensure that the system does not kink during delivery, deployment or withdrawal to and from the target deployment site under anticipated use conditions.	Pass
Torque Strength	To evaluate the resistance to torque of the proximal Luer Lock to Guiding Tube joint and to verify that this joint can withstand the anticipated torsional forces during use.	Pass
Stability of Product for Labeled Shelf Life	To ensure that the product performance characteristics are maintained for the stated shelf life of the product.	Pass
Packaging Integrity	To evaluate the stress resistance of the packaging during transportation and conditioning.	Pass

C. Sterility, Packaging and Shelf-Life Testing

The Fluency® Plus Endovascular Stent Graft is a single-use device that is distributed sterile to the end user. Sterilization and validation (in accordance with AAMI/ANSI/ISO 11135-1:2007 "Sterilization of Health Care Products – Ethylene Oxide – Part 1: Requirements for the Development, Validation, and Routine Control of Ethylene Oxide Sterilization Process for Medical Devices) for the Fluency® Plus Endovascular Stent Graft demonstrates a Sterility Assurance Level (SAL) of 10^{-6}. Stability testing of the device and sterile packaging was performed and validated to ensure a 3-year shelf life.

D. Animal Testing

The animal model used in the evaluation of the Fluency® Plus Endovascular Stent Graft was the Ovine carotid artery to jugular vein shunt model (AV graft shunt). Follow-up time-points were at 3-days (n=5) and 28-days (n=7) post device implantation. Placement of the device across a graft-to-vein anastomosis allowed for the evaluation of the device in both an AV graft and a fistula (native vessel) model. The control in this study was the FLAIR™ Endovascular Stent Graft (P060002) and was evaluated to help determine a baseline of clinical acceptability.

The Fluency® Plus Endovascular Stent Graft demonstrated similar findings to the control device, which was used to help establish a clinically acceptable baseline. Additionally, the stent graft and delivery performance was classified as "good" (a rating of 4) or "excellent" (a rating of 5) in all areas evaluated. The results of this study lead to the conclusion that the Fluency® Plus Endovascular Stent Graft behaves similarly to the FLAIR Endovascular Stent Graft.

X. Summary of Primary Clinical Study

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of an endovascular procedure with the Fluency® Plus Endovascular Stent Graft 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 in the US under IDE #G100281. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between February 2, 2010 and October 07, 2013. The database for this PMA reflected data collected through August 13, 2013 and included 265 patients. There were 23 investigational sites.

The study was a prospective, multi-center, randomized, concurrently-controlled clinical study.

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.

Binary Restenosis at 90 days, defined as lesions with a ≥50% diameter stenosis, was calculated using quantitative angiographic methods by an independent core laboratory. In addition, the location of the target lesion was determined by both the site (at Baseline) and the Core Lab (at the 90-day follow-up).
All site-reported AEs and/or UADEs were adjudicated by a Clinical Events Committee (CEC). This was a multidisciplinary group of individuals not otherwise involved in the

trial. The CEC members were independent from both the sponsor and the study investigators. The committee was responsible for the review and validation of all AEs and the subsequent classification of these events by level of seriousness and relationship to the device or procedure. The definitions and the committee charter were documented in a CEC Manual of Operations. A Data Safety Monitoring Board (DSMB) was also responsible for safety oversight. The DSMB was comprised of four members that were not directly involved in the conduct of the study: one biostatistician, two interventional radiologists, and one interventional nephrologist. The DSMB was responsible for independently evaluating interim safety and effectiveness analyses as described in the clinical protocol. The DSMB independently conducted evaluations of subject safety during the study and, if necessary, made recommendations to Bard that the trial be continued, amended, or terminated to ensure the safety of subjects.

The control group was treated with percutaneous transluminal angioplasty (PTA), the standard of care treatment. PTA was performed using legally marketed PTA catheters.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the RESCUE study was limited to patients who met the following inclusion criteria:

   - Subject must have had an AV access graft (implanted for ≥ 30 days) or mature fistula located in an arm, and must have undergone at least one successful dialysis session prior to the index procedure.
   - Subject must have had angiographic evidence of a previously-placed bare metal stent located in the venous outflow of the AV access circuit in which a ≥ 50% stenosis originates.
   - The target lesion must have been located in the restenosed bare metal stent and extend to no more than 3 cm outside of the bare metal stent.
   - The target lesion must have been ≤10 cm in length.
   - After angiography, the Investigator must have judged that the lesion was amenable to angioplasty.
   - The reference vessel diameter at the restenosed bare metal stent must have been between 5.0 mm and 12.0 mm.
   - Additional stenotic lesions (≥ 50%) in the venous outflow that were >3cm from the edge of the target lesion must have been successfully treated (defined as <30% residual stenosis) prior to the index procedure.

   Patients were not permitted to enroll in the RESCUE study if they met any of the following exclusion criteria:

   - The target lesion had a corresponding thrombosis treated within 7 days prior to the index procedure.
   - The target lesion had a reference vessel diameter that is larger than 12.0 mm.
   - The subject had an infected AV access graft/fistula or uncontrolled systemic infection.
   - A pseudoaneurysm was present within the target lesion.
   - The location of the target lesion required that the FLUENCY® PLUS Endovascular Stent Graft be deployed across the elbow joint.

- The location of the target lesion required that the FLUENCY® PLUS Endovascular Stent Graft be deployed at or across the segment of graft or fistula utilized for dialysis needle puncture (i.e., "cannulation zone").
- The location of the target lesion required that the FLUENCY® PLUS Endovascular Stent Graft cross the cephalic arch (perpendicular portion of the cephalic vein in the region of the deltopectoral groove before its junction with the axillary vein).
- The location of the target lesion required that the FLUENCY® PLUS Endovascular Stent Graft be placed in the Superior Vena Cava.
- The location of the target lesion required that the FLUENCY® PLUS Endovascular Stent Graft be placed across an angle that is greater than 90 degrees (i.e., tight bend or loop).
- The restenosed bare metal stent was fractured, as verified by angiography per investigational site's standard of care.
- The subject had a known uncontrolled blood coagulation disorder.
- The subject had a known hypersensitivity to nickel-titanium.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 30 days, 90 days, 6 months, 12 months, 18 months, and 24 months postoperatively. The following table summarizes the objective parameters measured during the preoperative screening and postoverative study follow-up examinations:

Table of Assessments

Study Interval	Study Timeframe								
	Screening	Index Procedure	Hospital Discharge	F/U Contact 1 (30 Days Post Procedure (+/- 7 days))	F/U Contact 2 (90 Days Post Procedure (+/- 15 days))	F/U Contact 3 (6 Months Post Procedure (+/- 30 days))	F/U Contact 4 (12 Months Post Procedure (+/- 30 days))	F/U Contact 5 (18 Months Post Procedure (+/- 30 days))	F/U Contact 6 (24 Months Post Procedure (+/- 30 days))
Informed Consent	X								
Medical History	X								
Clinical Evaluation	X		X		X	X			
Medications Assessment	X	X	X	X	X	X	X	X	X
Angiography		X			X				
Randomization and Study Procedure		X							
Adverse Events*		X	X	X	X	X	X	X	X
Telephone Contact or Return Office Visit**				X	X**	X****	X	X	X
Return Office Visit					X	X****			
Study Completion									X

* Includes all re-interventions to the access circuit post the index procedure
**A telephone contact should occur with both the subject and his/her dialysis center.
***A telephone contact should occur with the dialysis center.
****A return office visit is the preferred method of follow-up at the 6 Month time point. If the subject is unable to return, he/she may be contacted by phone.

Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

With regards to safety, the primary safety endpoint was non-inferiority over PTA through 30 days. Safety was defined as freedom through 30 days from any localized or systemic adverse events, 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.

With regards to effectiveness, the primary effectiveness endpoint was superiority of Access Circuit Primary Patency (ACPP) over PTA at 6 months. ACPP was defined as the interval following the index procedure until the next access thrombosis or reintervention. ACPP ends with a reintervention anywhere within the access circuit, from the arterial inflow to the superior vena cava-right atrial junction. Venous rupture caused by PTA is not an ACPP failure unless achieving hemostasis also causes thrombosis. The secondary effectiveness endpoint was superiority of post-intervention lesion patency (PLP) through 6 Months. PLP was defined as the interval after the index intervention until the next re-intervention at the original treatment site or until the extremity (access) is abandoned for permanent access. Percutaneous or surgical treatments of new arterial or venous outflow stenoses or occlusions that do not involve the original lesion are compatible with lesion patency. Creation of a new graft or fistula that incorporates the original lesion into the new access circuit is also compatible with lesion patency.

B. Accountability of PMA Cohort

A total of 781 subjects were screened for eligibility, only 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. Of the 265 subjects that were randomized, two-hundred forty-four (244) subjects were included in the 30 day primary safety endpoint analysis and 220 subjects in the six month primary effectiveness endpoint analysis. At the time of database lock, of 220 patients enrolled in the PMA study had reached the 6 month follow-up evaluation. Of these 220, 91% (200) of subjects were available for analysis.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a dialysis access study performed in the US.

Table 4: 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)

	PTA Alone (N=137)	FLUENCY® PLUS (N=128)	All Patients (N=265)
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 5: 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 6: 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

Table 7: 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			

	PTA Alone (N= 137)	FLUENCY® PLUS (N= 128)	All Patients (N= 265)
Yes	78 (56.9)	65 (50.8)	143 (54.0)
No	59 (43.1)	63 (49.2)	122 (46.0)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the ITT cohort of 265 patients available for the 30 day evaluation. The key safety outcome for this study is presented below in tables 8 to 9. Adverse effects are reported in tables 10 to 11.

Table 4: 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 5: Incidence of Primary Safety Endpoint in First 30 Days

	PTA Alone (n=137)	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/cellulitus 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 FLUENCY® PLUS Endovascular Stent Graft (non-inferiority p-value = 0.007). Thus, the non-inferiority ($\delta = 0.075$) of FLUENCY® PLUS Endovascular Stent Graft to PTA alone with regard to this primary safety endpoint is confirmed.

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 3.

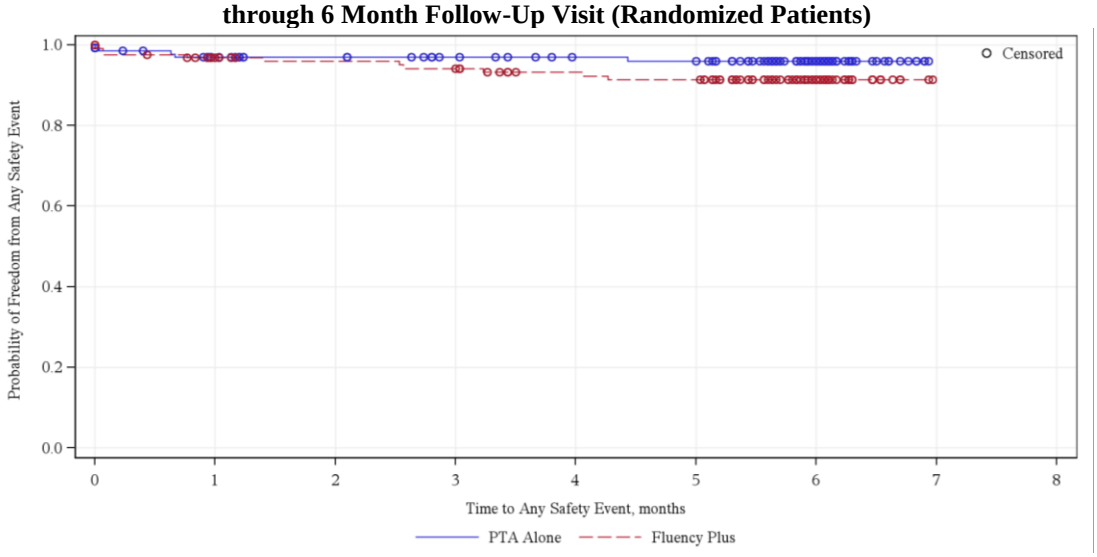
Table 6: Safety Events through 6 months (Randomized Patients)

Parameter	PTA Alone (N=137)	Fluency® 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)

Parameter	PTA Alone (N=137)	Fluency® Plus (N=128)	Overall (N=265)
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)

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

Figure 3: 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 7: All Device and/or Procedure Related Adverse Events through 6 months (inclusive of reported Safety Events in Table 6)

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

Treatment Group	Description of AE
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)

2. Effectiveness Results

The analysis of effectiveness was based on the ITT cohort of 220 patients available for the 6 month evaluation. Key effectiveness outcomes for this study are presented below in tables 12 to 15.

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 8. 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.

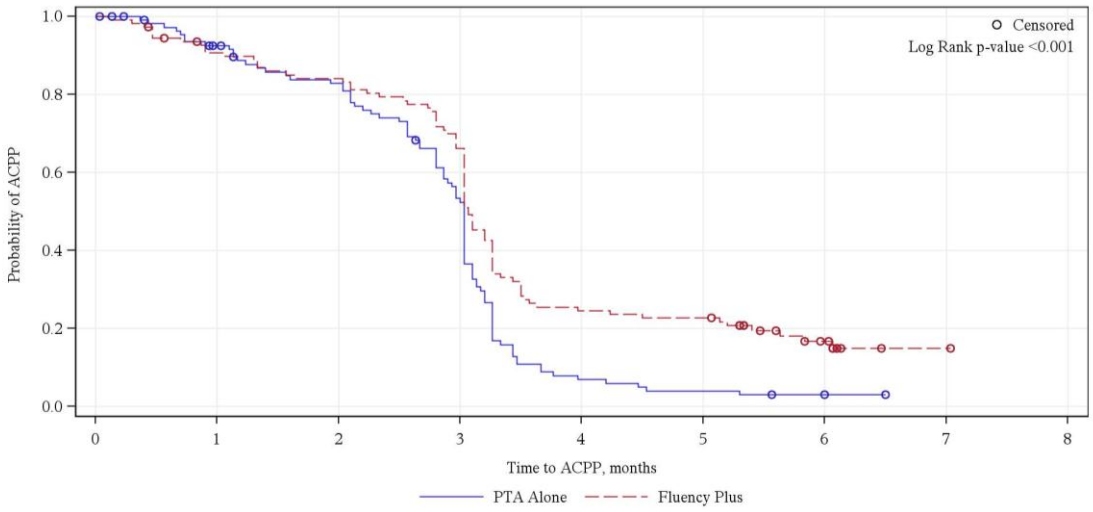
Table 8: Access Circuit Primary Patency through Six Months (ITT)

	PTA Alone (n=111)	**FLUENCY® PLUS (n=109)**
Percentage of ACPP at 6 months (%)	**3.0**	**16.7**
95% CI for Rate [1]	(0.00, 6.27)	(9.24, 24.16)
Time to event (days)		
Median	91.0	92.0
95% CI for Median [2]	(86.00, 91.00)	(91.00, 98.00)
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 4 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 4: Kaplan Meier Analysis for Access Circuit Primary Patency through 6 Month Follow Up (ITT)



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 9. 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.

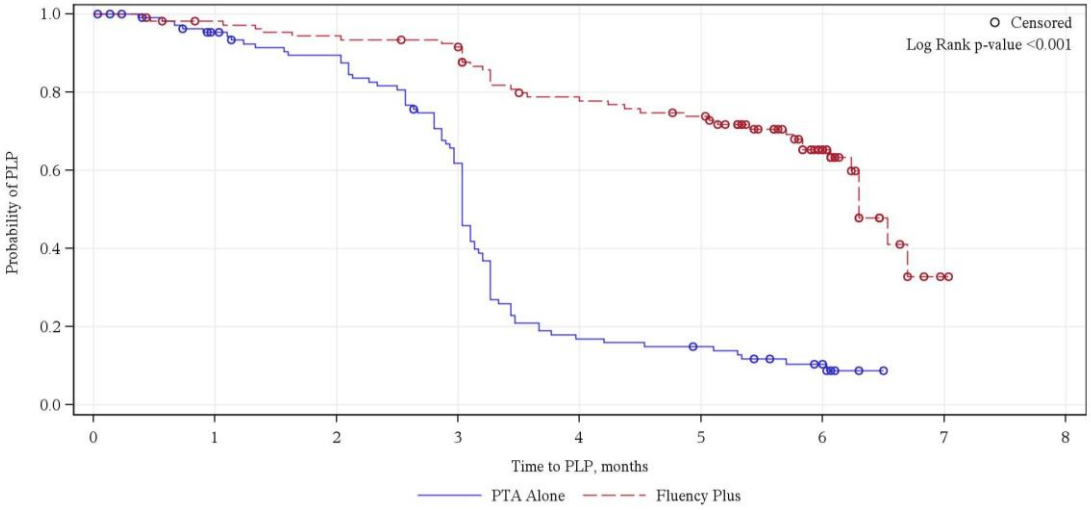
Table 9: Post Intervention Lesion Patency at 6 Months (ITT)

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.

The Kaplan Meier analysis for PLP through 6 months (ITT population) is shown in Figure 5. 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 5: Kaplan Meier Analysis for Post Intervention Lesion Patency at 6 months (ITT)



Non-Hypothesis Tested Secondary Effectiveness Result

The results for the non-hypothesis tested secondary endpoints are listed in Table 10 and Table 11.

Table 10: 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 11: Acute Secondary Effectiveness Results without hypothesis testing

	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.

E. 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. Panel Recommendations

In accordance with the provisions of section 515(c)(2) 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.

XII. Conclusions Drawn from Preclinical and Clinical Studies

A. Effectiveness Conclusions

The primary effectiveness endpoint was superiority for access circuit primary patency (ACPP). The superiority of FLUENCY® PLUS to PTA alone for ACPP through 6 months was confirmed. For the overall population (both AV Graft and Fistula subjects combined), the ACPP rate at 6 months was 3.0% for subjects with PTA alone, and 16.7% for subjects with FLUENCY® PLUS ($p < 0.001$). For AV Graft subgroup, the ACPP rate at 6 months was 0.0% for subjects with PTA alone, and 16.3% for subjects with FLUENCY® PLUS ($p = 0.022$). For Fistula subgroup, the ACPP rate at 6 months was 5.6% for subjects with PTA alone, and 17.2% for subjects with FLUENCY® PLUS ($p = 0.002$). There was no significant difference in ACPP rates at 6 months between AV Graft and Fistula groups ($p = 0.428$) or between central vs. peripheral vein locations ($p = 0.428$).

A secondary effectiveness endpoint was superiority for post-intervention lesion patency (PLP) through 6 months. The superiority of FLUENCY® PLUS to PTA alone for PLP through 6 months was confirmed. For the overall population (both AV Graft and Fistula subjects combined), the percentage of PLP at 6 months was 10.4% for subjects with PTA alone, and 65.2% for subjects with FLUENCY® PLUS ($p < 0.001$). For AV Graft subgroup, the percentage of PLP at 6 months was 5.2% for subjects with PTA alone, and 57.7% for subjects with FLUENCY® PLUS ($p<0.001$). For Fistula subgroup, the percentage of PLP at 6 months was 14.7% for subjects with PTA alone, and 72.0% for subjects with FLUENCY® PLUS ($p<0.001$).

B. Safety Conclusions

The primary safety endpoint was non-inferiority for safety events through 30 Days. The non-inferiority ($\delta = 0.075$) of FLUENCY® PLUS to PTA alone for freedom from specified safety events through 30 days was confirmed. For the overall population (both AV Graft and Fistula subjects combined), the percentage of subjects free from safety events through 30 days was 96.8% for subjects with PTA alone, and 96.6% for subjects with FLUENCY® PLUS (non-inferiority p-value = 0.007). For AV Graft subgroup, the percentage of subjects free from safety events through 30 days was 98.2% for PTA alone, and 100% for FLUENCY® PLUS. For Fistula subgroup, the percentage of subjects free from safety events through 30 days was 95.7% for PTA alone, and 93.8% for FLUENCY® PLUS

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The device improves AV access patency, decreases the need for re-interventions, allows for saving the existing AV access circuit and avoids 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 data support that for the Fluency® Plus Endovascular Stent Graft 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 probable benefits outweigh the probable risks.

D. Overall Conclusions

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.

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

Data from non-clinical testing and the clinical trial 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 circuit of hemodialysis patients dialyzing by either an arteriovenous (AV) fistula or AV graft when used in accordance with its labeling.

XIII. CDRH Decision

CDRH issued an approval order on June 17, 2014.
The applicant's manufacturing facility has been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. 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 labeling.

Postapproval Requirements and Restrictions: See approval order.