SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Coronary Drug Eluting Stent
Device Trade Name:	BioFreedom Drug Coated Coronary Stent System (BioFreedom DCS)
Device Procode:	NIQ
Applicant's Name and Address:	Biosensors International USA, Inc. 1013 Centre Rd. Suite 228 Wilmington, DE 19805
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P190020
Date of FDA Notice of Approval:	April 14, 2022

II. INDICATIONS FOR USE

The BioFreedom DCS is indicated for improving coronary luminal diameter in patients at high risk for bleeding with symptomatic ischemic heart disease due to de novo lesions of length ≤ 32 mm in native coronary arteries with a reference diameter ranging between 2.25 mm and 4.0 mm.

III. CONTRAINDICATIONS

The BioFreedom DCS is contraindicated for use in:

- Patients who cannot receive the recommended antiplatelet therapy (aspirin/$P2Y_{12}$ platelet inhibitor) and/or anticoagulation therapy (heparin or bivalirudin).
- Patients with lesion(s) that prevent(s) complete inflation of an angioplasty balloon.
- Patients with known hypersensitivity to the BA9 drug or its derivatives.
- Patients with known allergies to stainless steel, nickel or other metal ions found in 316L stainless steel.
- Patients with known sensitivity to contrast agents that cannot be controlled prophylactically prior to BioFreedom stent implantation.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the BioFreedom DCS labeling.

V. DEVICE DESCRIPTION

The BioFreedom DCS is a combination product consisting of two key components: the stent coated abluminally with the active ingredient Biolimus A9 (BA9), and the delivery system. The BioFreedom DCS is a polymer-free drug-coated coronary stent system.

The characteristics of the BioFreedom DCS are described in Table 1.

Table 1. BioFreedom DCS Product Characteristics

Stent Pattern	6-Crown model	9-Crown model
Stent Diameters (mm)	2.25, 2.5, 2.75, 3.0	3.5, 4.0
Stent Strut Thickness (mm)	0.119	0.114
Stent Lengths (mm)	8, 11, 14, 18, 24, 28	
Stent Material	Stainless Steel 316L	
Drug Component	An abluminal (outer surface of the stent) polymer-free coating of BA9 drug applied to the selectively micro-structured surface (SMS)	
Delivery System Working Length	142 cm	
Delivery System Design	Rapid Exchange (RX) compatible with guidewires ≤0.014”	
Stent Delivery System Balloon	Semi-compliant balloon with two radiopaque markers located on the catheter system balloon shaft to indicate balloon positioning and expanded stent length	
Guiding Catheter Compatibility	≥ 6F (min. guide catheter ID of 0.070”/1.78mm)	
Balloon Inflation Pressure	6-Crown model	9-Crown-model
Nominal Pressure	7atm/ 709 kPa	7 atm/ 709 kPa
Rated Burst Pressure	16 atm/ 1621 kPa	14 atm/ 1418 kPa
Catheter Shaft Outer Diameter	Distal: 0.034” (0.86 mm) Proximal: 0.020” (0.51 mm)	Distal: 0.037” (0.94 mm) Proximal: 0.020” (0.51 mm)
Shelf Life	9 months	

A. Device Component Description

The BioFreedom stent is made of stainless steel 316L. The stent is laser machined into two patterns that are differentiated by the number of crowns and the number of connectors. The 6-crown pattern is used for 2.25-3.0 mm diameter stents and the 9-crown stent pattern is used for 3.5-4.0 mm diameter stents. Each pattern is comprised of a series of corrugated rings aligned along a common longitudinal axis. Each ring is connected to an adjacent ring by two or three curved connectors oriented in the direction of the longitudinal axis. The outer (abluminal) surface of the stent is selectively micro-structured (SMS) prior to drug coating. Figure 1 illustrates a 9-crown BioFreedom stent.

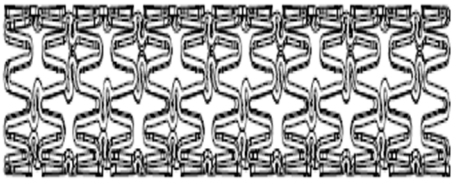

Figure 1. BioFreedom Stent Drawing

The stent is crimped onto the balloon of the Rapid Exchange (RX) Catheter that combines a single lumen proximal shaft with a single lumen mid-shaft and a coaxial lumen distal shaft to create the rapid exchange capability. Figure 2 provides a pictorial representation of the catheter delivery system.

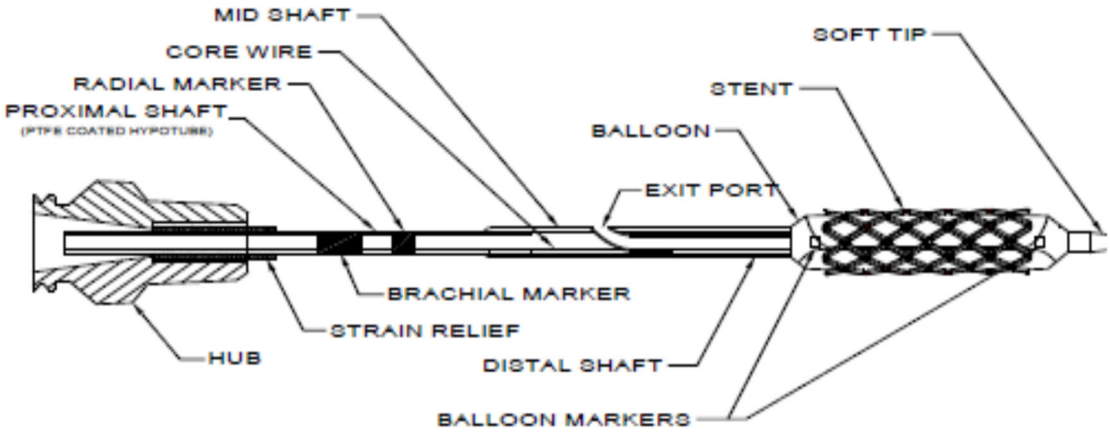

Figure 2. BioFreedom Delivery System, General View

The commercial size matrix is shown in Table 2.

Table 2. BioFreedom DCS Commercial Matrix

			Stent Length					
			8 mm	11 mm	14 mm	18 mm	24 mm	28 mm
Stent Model/Balloon Diameter	6-crown	2.25 mm	X	X	X	X	X	X
		2.50 mm	X	X	X	X	X	X
		2.70 mm	X	X	X	X	X	X
		3.00 mm	X	X	X	X	X	X
	9-crown	3.50 mm	X	X	X	X	X	X
		4.00 mm	X	X	X	X	X	X

B. Drug Component Description

The BioFreedom DCS is coated with BA9 (also referred to as Biolimus A9 or umirolimus).

1. BA9

The BA9 drug is the active pharmaceutical ingredient in the BioFreedom DCS. The BA9 chemical name is:

(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-4-(2-ethoxyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone

or

(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-Dihydroxy-12-[(1R)-2-[(1S,3R,4R)-4-(2-ethoxyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.04,9]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone.

The molecular formula of BA9 is C55H87NO14 and its molecular weight is 986.28 g/mol. The chemical structure of BA9 is depicted in Figure 3.

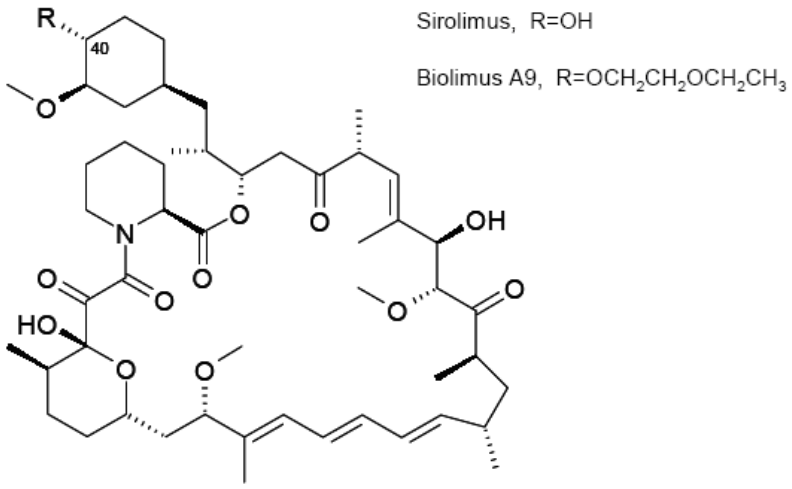

Figure 3. Chemical Structure of BA9

The nominal total loaded dose of BA9 per nominal stent length is shown in Table 3.

Table 3. Nominal BA9 Content (µg) per Nominal Stent Length

	8 mm	11 mm	14 mm	18 mm	24 mm	28 mm
All diameters (2.25-4.0 mm)	133	178	225	292	384	453

2. Mechanism of Action of BA9

Current understanding suggests that the mechanism of action of the BA9 drug on a molecular level is due to complex formation with cytoplasmic proteins that inhibit the cell cycle between the G0 and G1 phase. This results in interruption of the cascade governing

cell metabolism, growth, and proliferation, leading to a reversible inhibition of growth-factor-stimulated cell proliferation.

It is believed that the mechanism of action of the "limus family" is similar, with which the BA9 drug shares a common internal 'rapamycin' ring structure. This rapamycin ring structure is known to bind with the intracellular receptor FKBP-12. The resulting macrolide/FKBP-12 complex subsequently binds to a specific target protein known as mammalian target of rapamycin (mTOR) which is critical for cell cycle progression. Interaction of the macrolide/FKBP-12 complex with mTOR inactivates mTOR resulting in suppression of several specific signal transduction pathways and arrest of the cell cycle at the G1 to S phase.

The BA9 drug coated on the BioFreedom DCS has an ancillary function as an anti-proliferative and anti-restenotic agent due to its ability to interrupt smooth muscle cell migration and proliferation.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of coronary artery disease. These may include exercise, diet, smoking cessation, drug therapy, percutaneous coronary interventions (such as angioplasty and placement of other coronary stents), and coronary artery bypass graft surgery (CABG). 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.

VII. MARKETING HISTORY

As of March 2020, approximately 339,000 BioFreedom DCS devices have been distributed outside the United States (OUS). The countries where the BioFreedom DCS is commercially available are listed below. No products have been withdrawn from the market in any of the following countries.

- Algeria
- Argentina
- Armenia
- Austria
- Bangladesh
- Belarus
- Bolivia
- Bosnia-Herz.
- Brazil
- Brunei Daruss.
- Bulgaria
- Burma
- Chile
- Colombia
- Costa Rica
- Croatia
- Cyprus
- Czech Republic
- Denmark
- Dominican Rep.
- Ecuador
- Egypt
- El Salvador
- Estonia
- Finland
- France
- Georgia
- Germany
- Greece
- Honduras
- Hong Kong
- Hungary
- India
- Indonesia
- Iran
- Ireland
- Israel
- Italy
- Japan
- Jordan
- Kazakhstan
- Latvia
- Lebanon
- Libya
- Liechtenstein
- Lithuania
- Macau
- Macedonia
- Malaysia
- Mexico
- Montenegro
- Morocco
- Norway
- Oman
- Palestine
- Pakistan

- Panama
- Portugal
- Singapore
- South Korea
- Switzerland
- The Netherlands
- United Kingdom
- Vietnam
- Peru
- Romania
- Slovakia
- Spain
- Syria
- Tunisia
- Utd. Arab Emir.
- Philippines
- Saudi Arabia
- Slovenia
- Sri Lanka
- Taiwan
- Turkey
- Uzbekistan
- Poland
- Serbia
- South Africa
- Sweden
- Thailand
- Ukraine
- Venezuela

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events (in alphabetical order) that may be associated with the use of a stent in native coronary arteries include but are not limited to:

- Access site complications (including arteriovenous fistula, hematoma, infection, nerve injury, pain, peripheral ischemia, phlebitis, pseudoaneurysm)
- Acute myocardial infarction
- Allergic reaction or hypersensitivity to anti-coagulation and/or anti-thrombotic therapy, contrast media, or stent components and/or delivery system materials
- Aneurysm
- Angina pectoris (stable or unstable)
- Bleeding complications which may require transfusions or surgical repair
- Cardiac arrhythmias, including ventricular fibrillation and ventricular tachycardia
- Cardiac failure
- Cardiac tamponade
- Cardiogenic shock
- Coronary artery complications (incl. abrupt closure, dissection, embolism, injury, perforation, plaque rupture/shift, restenosis, rupture, spasm, thrombosis, total occlusion)
- Death
- Delayed endothelialization
- Distal emboli
- Endocarditis
- Failure to deliver the stent to the intended site
- Need for emergent or non-emergent coronary artery bypass grafting (CABG)
- Fever or pyrogenic reactions
- Hypotension/hypertension
- Infections
- Myocardial ischemia
- Nausea and vomiting
- Palpitations
- Perforation of the heart or great vessels
- Pericardial effusion
- Pulmonary failure
- Renal failure

- Stent compression
- Stent misplacement/migration/ embolization
- Stent thrombosis
- Stroke/cerebrovascular accident (CVA)/ transient ischemic attack (TIA)
- Vasovagal reaction
- Vessel spasm
- Volume overload

There may be other potential adverse events that are unforeseen at this time.

Potential adverse events that may be associated with exposure to the BA9 drug include but are not limited to (Steudel et al. 2011):

- Chest heaviness
- Lymphadenopathy
- Nausea
- Mouth ulcers

BA9 drug administration experience is limited to intra-coronary stent delivery. Patient exposure to BA9 is directly related to the total surface area of stents implanted. Consequently, adverse drug effects have not been fully characterized especially at significantly higher systemic doses than what would be delivered via the BioFreedom DCS.

For the specific adverse events that occurred in clinical studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A series of non-clinical laboratory studies and pharmacokinetic studies related to the product were performed. Studies included those performed on the drug substance (BA9), the bare metal stent alone, the coated stent alone, the delivery system, and the finished combination product.

A. Laboratory Studies

1. In Vitro Engineering Testing

In vitro engineering testing, in accordance with FDA's "Guidance for Industry and FDA Staff: Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems", was conducted on test samples representative of the BioFreedom DCS. Specific in vitro engineering tests were performed on the representative uncoated, bare metal version of the BioFreedom stent and the delivery system.

Table 4 summarizes this testing. "Pass" denotes that the test results met product specifications and/or the recommendations in the above referenced guidance document.

Table 4. Summary of Engineering Testing

Test	Purpose	Acceptance Criteria	Results
Material Characterization			
Stent Material Composition	To confirm the chemical composition of the 316L stainless steel tubing.	Per ASTM F138	Pass
Stent Mechanical Properties	To determine raw material quality and uniformity and predict subsequent thermochemical effects.	Per established standard requirements	Pass
Stent Corrosion Resistance	To determine resistance to galvanic and pitting corrosion.	Per ASTM F2129 and ASTM G71 standards	Pass
Stent Dimensional and Functional Attributes			
Dimensional Verification	To ensure accurate stent dimensions.	Meet established design specifications	Pass
Percent Surface Area	To determine the surface coverage of the bare stent in the vessel.	The percent contact surface area of the stent at any deployed diameter must not be >20%	Pass
Foreshortening	To ensure the foreshortening of the stent falls within acceptable limits.	Foreshortening ≤10%	Pass
Recoil	To ensure the amount of elastic recoil after deployment falls within acceptable limits.	Recoil ≤5%	Pass
Stent Integrity	To ensure stent defects do not contribute to clinical complications.	No fractures, cracks, or scratches	Pass
Radial Stiffness and Radial Strength	To ensure the stent can resist collapse under short-term or long-term external loads.	Radial strength ≥500 mmHg Minimum compression resistance of 0.1 N/mm of stent length at 0.5 mm of stent compression	Pass
Stress/Strain and Fatigue Analysis	To determine the stent durability when exposed to worst case physiological loads and configuration by means of a Finite Element Analysis.	N/A	N/A
Accelerated Durability	To determine the long-term integrity of the stent under cyclical loading conditions.	No complete segment breakage after 400 million cycles (equivalent to 10 years of implantation)	Pass
Particulate Evaluation	To ensure acceptable levels of particulate generated after simulated use.	≤6000 particles ≥10 µm ≤600 particles ≥25 µm	Pass

Test	Purpose	Acceptance Criteria	Results
Magnetic Resonance Imaging (MRI) Safety and Compatibility	To determine the effect of MR on the position and temperature of the stent, and to determine the extent of image artifact during MRI.	See product labeling for safe MRI use conditions	Pass
Radiopacity	To ensure adequate visibility on X-ray and angiography.	Stents must be adequately visualized on angiogram and have an acceptable contrast value on X-ray	Pass
Delivery System Dimensional and Functional Attributes			
Dimensional Verification	To ensure accurate delivery system dimensions.	Meet established design specifications	Pass
Delivery, Deployment and Retraction	To verify the delivery catheter can safely and reliably deliver the stent to the intended location according to the instructions for use, without damage to the stent.	Per validated test protocols	Pass
Balloon Rated Burst Pressure	To determine the rated burst pressure (RBP) of the balloon when used with the stent.	6-crown: ≥16 atm 9-crown: ≥14 atm with 95%/99.9% confidence/reliability	Pass
Balloon Fatigue	To ensure the balloon can withstand repeated inflation/deflation cycles.	Withstand 10 cycles at RBP	Pass
Balloon Compliance	To determine the relationship between the stent diameter and the balloon inflation pressure.	See compliance chart in device labeling	Pass
Balloon Inflation and Deflation Time	To ensure the balloon inflation and deflation time are within acceptable limits for clinical use.	6-crown: Inflation ≤10 s Deflation ≤15 s 9-crown: Inflation ≤15 s Deflation ≤20 s	Pass
Catheter Bond Strength and Tip Pull Test	To ensure the bond strength of the joints and/or fixed connections, including the distal tip of the delivery system, are adequate for clinical use.	Per ISO 10555-1	Pass
Flexibility and Kink Test	To ensure the device can withstand flexural forces that are typical of clinical use.	The catheter inflation lumen must be able to flex at the radius of curvature of 15 mm without kinking or exhibiting a diameter of reduction >50%	Pass
Catheter Torque	To demonstrate that the delivery	System must withstand ≥2	Pass

Test	Purpose	Acceptance Criteria	Results
Strength	system can withstand torsional forces that are typical of clinical use.	rotations without losing its functional integrity	
Coating Integrity	To evaluate the ability of the delivery system coatings to resist damage during clinical use.	For characterization only	Pass
Stent Securement	To demonstrate the stent will not dislodge from the delivery system when subjected to forces experienced in typical clinical use.	Force required to dislodge mounted stent ≥1.5 N	Pass

2. Drug Coating Characterization Testing

The drug coating characterization testing conducted on the BioFreedom DCS is summarized in Table 5.

Table 5. Drug Coating Characterization Testing

Test	Purpose	Acceptance Criteria	Results
Acute Coating Integrity	To evaluate drug coating integrity of the stent.	Characterization only	Pass
Coating Thickness and Uniformity	To demonstrate that drug coating thickness is uniform along the length of the stent.	Characterization only	Pass
Longitudinal Coating Uniformity	To characterize the coating uniformity along the length of the stent.	Characterization only	Pass
Acute Coating Durability Test	To demonstrate the ability of the coating to resist delamination when subjected to simulated clinical use conditions.	Characterization only	Pass

3. Chemistry Manufacturing and Controls (CMC) Testing

Where applicable, International Conference on Harmonization (ICH) guidelines were followed for the testing routinely performed on the BioFreedom DCS system. This testing is summarized in Table 6.

Table 6. CMC Release Testing

Test	Test Description
Drug content	Assay is conducted to quantitatively verify that the total amount of drug on the stent is within the specifications established for the finished product.
BA9 Identification, Degradation Products & Impurities	Assay is conducted to verify the identity of the drug substance (BA9) and quantitatively verify the amount and type of degradation products on the stent are within the specifications established for the finished product.
Drug Release	The *in vitro* release profile for BA9 is measured on the stent to

Test	Test Description
	verify that the drug release is within the specifications established for the finished product.
Endotoxin	The amount of bacterial endotoxins is verified to be within the specification limits established for the finished product.
Particulates	Particulate levels are measured to verify that they remain below the specifications established for the finished product.
Appearance	A visual inspection is conducted to verify that the product's appearance specifications are met.
Content Uniformity	Multiple stents are assayed to verify the uniformity of the drug content between individual stents is within the specifications established for the finished product.
Residual Solvent: Acetone	The amount of acetone on the BioFreedom DCS is determined to verify that the residual level of the solvent used in the manufacturing process is within the specification limits established for the finished product.

4. Stability and Shelf Life

Stability/shelf-life studies were conducted to establish a shelf life for the BioFreedom DCS. The stability testing included BA9 drug content, identification, degradation products and impurities, drug release, endotoxin, particulates, drug weight loss, appearance, content uniformity, and residual solvent testing. Appropriate mechanical engineering tests were also performed on aged product and packaging to ensure that the finished product continues to meet specifications throughout its expiration dating. The data generated supports a product shelf life of 9 months.

5. Packaging and Sterilization

Packaging verification testing was performed to demonstrate that the design of the BioFreedom DCS packaging can withstand the hazards of the distribution environment and that the sterility of the device is maintained throughout the labeled shelf life. The BioFreedom DCS is sterilized using electron beam (E-beam) irradiation. The sterilization validation and dose audit verifications were performed per ISO 11137-1 "Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices" and ISO 11137-2 "Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose". The validation and dose audit verifications confirm that the E-beam sterilization process achieves a minimum sterility assurance level (SAL) of 10^{-6}. In addition, the quantity of bacterial endotoxins was verified to be within the specification limits.

6. Biocompatibility

A series of Good Laboratory Practice (GLP) biocompatibility tests were conducted to demonstrate that the components of the BioFreedom DCS are non-toxic and biocompatible. Tests were conducted on final, E-beam-sterilized BioFreedom DCS, selectively-microstructured bare metal stents, and stent delivery systems. These test articles were processed in the same manner as the finished BioFreedom DCS. The

results of the biocompatibility studies indicated that the BioFreedom DCS was biologically safe and acceptable for clinical use.

All biocompatibility testing was conducted in accordance with one or more of the following general regulations, standards and guidance documents:

- Good Laboratory Practices Regulations (21 CFR § 58)
- Guidance for Industry: "Coronary Drug-Eluting Stents-Nonclinical and Clinical Studies" (March 2008)
- Guidance for Industry and FDA Staff: "Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems"
- Guidance for Industry and FDA Staff: "Use of International Standard ISO 10993-1, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" (April 2013)
- ISO 10993-1, "Biological Evaluation of Medical Devices: Evaluation and Testing within a Risk Management Process"
- ISO 14971, Medical devices: "Application of Risk Management to Medical Devices"

Table 7 provides a summary of the biocompatibility testing conducted to support the BioFreedom DCS.

Table 7. Summary of Biocompatibility Testing

Test Name	Test Description	Test Article	Results
Cytotoxicity	ISO 10993-5: Direct Contact Cytotoxicity (L929 MEM Elution)	• Drug coated stent • SMS bare metal stent • Delivery system	Pass (non-cytotoxic)
	ISO 10993-5: MEM Elution Assay with L-929	• SMS bare metal stent • Delivery System	Pass (non-cytotoxic)
	ISO 10993-5: MEM Endpoint Dilution Using L-929	• Drug coated stent	Pass (non-cytotoxic)
Pyrogenicity	ISO 10993-11: Materials Mediated Rabbit Pyrogenicity Test	• Drug coated stent • SMS bare metal stent • Delivery System	Pass (non-pyrogenic)
Sensitization	ISO 10993-10: Sensitization (Guinea Pig Maximization)	• Drug coated stent • SMS bare metal stent • Delivery System	Pass (non-sensitizing)
	MHLW Sensitization (Guinea Pig Maximization)	• SMS bare metal stent	Pass (non-sensitizing)
Intracutaneous Reactivity	ISO 10993-10: Irritation Test	• Drug coated stent • SMS bare metal stent • Delivery System	Pass (non-irritant)
Subchronic/ Subacute Toxicity	ISO 10993-11: Subchronic Intravenous Toxicity Study in	• Drug coated stent • SMS bare metal stent	Pass (non-toxic)

Test Name	Test Description	Test Article	Results
	Mice (14 Dose Exposure)		
	ISO 10993-11: Subacute Intraperitoneal Toxicity Study in Mice (14 Dose Exposure)	• Drug coated stent • SMS bare metal stent	Pass (non-toxic)
Acute Systemic Toxicity	ISO 10993-11: Acute Systemic Injection Test	• Drug coated stent • SMS bare metal stent • Delivery System	Pass (non-toxic)
Hemocompatability /Hemolysis	ASTM F756 Hemolysis Assay – Direct Contact Method	• Drug coated stent • SMS bare metal stent • Delivery system	Pass (non-hemolytic)
	ASTM F756 Hemolysis Assay – Extract Method	• Drug coated stent • SMS bare metal stent • Delivery system	Pass (non-hemolytic)
Complement Activation	IS0 10993-4: Complement Activation Test (C3a and SC5b-9)	• Drug coated stent • SMS bare metal stent • Delivery system	Pass
Implantation	IS0 10993-6: Intramuscular Implantation with Histopathology (2 week)	• Drug coated stent	Pass
	ISO 10993-6: Intramuscular Implantation with Histopathology (13 week)	• Drug coated stent	Pass
Genotoxicity	ISO 10993-3: Bacterial Mutagenicity Test – Ames Assay	• Drug coated stent • SMS bare metal stent	Pass (non-mutagenic)
	ISO 10993-3: *In Vitro* Mouse Lymphoma Assay with Extended Treatment	• Drug coated stent • SMS bare metal stent	Pass (non-mutagenic)
	ISO 10993-3: *In Vivo* Mouse Micronucleus Assay	• Drug coated stent • SMS bare metal stent	Pass (non-mutagenic)
	MHLW Bacterial Mutagenicity Test – Ames Assay	• SMS bare metal stent	Pass (non-mutagenic)
	MHLW *In Vitro* Chromosome Aberration Analysis	• SMS bare metal stent	Pass (non-mutagenic)
	ISO 10993-3: *In Vitro* Chromosome Aberration Analysis	• SMS bare metal stent	Pass (non-mutagenic)
	MHLW *In Vivo* Mouse Micronucleus Assay with Exhaustive Extraction	• SMS bare metal stent	Pass (non-mutagenic)
Subchronic/Chronic Toxicity, Genotoxicity, Carcinogenicity	Chemical Characterization Testing and Toxicological Risk Assessment	• Drug coated stent	Pass

A risk assessment was performed for the potential toxicity of the BioFreedom DCS. No major concerns regarding the BioFreedom DCS toxicity were found.

B. Animal Studies

Detailed arterial histopathology and histomorphometry are not obtainable through human clinical trials. Consequently, a series of animal studies were conducted to evaluate safety, efficacy (proof of concept dosing), and overall product performance.

Animal studies (feasibility, safety, and acute) were conducted in accordance with §21CFR 58 (Good Laboratory Practices). The results of these studies support the safety and biocompatibility of the BioFreedom DCS. Table 8 includes summaries of the major animal studies performed to support product safety.

Table 8. Summary of Major Supportive Animal Studies

Study Type	# of Stents	Testing Summary	Results
GLP Safety and PK Study	Histo-pathology cohort: Test: 25 DCS Control: 24 BioFlex II 37 Cypher PK cohort: 12 DCS.	Single (non-overlapped) stents were implanted into 51 Yucatan mini swine. Histopathology was performed at day 28, 90, and 180. In the PK cohort, BA9 concentrations were measured in the systemic circulation and the myocardium.	At 28 days, all DCS stents showed the anti-proliferative coatings to be efficacious compared to bare metal stent controls while maintaining a similar safety profile. At 90 and 180 days, DCS stents had less stenosis than the Cypher DES. In the PK cohort, BA9 concentrations reached a maximum within 1 to 2 hours following implantation and dropped to near undetectable levels within 2 days. At 180 days all samples from blood and myocardium were below the limit of quantitation.
GLP Overlapped Safety Study	Test: 12 DCS Control: 12 BioFlex II	To evaluate the vascular response to overlapped BioFreedom stents, 19 Yucatan mini swine were implanted with either DCS or bare metal stents in overlapped configurations. Histo-pathology was evaluated at 28 and 180 days.	Medial area, neointimal area, and neointimal thickness were similar between groups, with percent stenosis lower in the overlapped portions of DCS stents compared to bare metal controls at 28 days. At 180 days, the two groups demonstrated comparable vascular responses.
GLP Acute PK Study	42 DCS	To assess coronary tissue and residual BA9 concentrations on the stent, 14 Yorkshire swine were implanted with DCS in each of the three main coronary arteries and evaluated at 1, 2, 4, and 24 hours, and 2, 3, and 7	BA9 reached maximum concentration in the target tissue within 2 hours. Tissue concentrations dropped approximately 88% by 4 hours and remained constant for the remainder of the 7 days.

Study Type	# of Stents	Testing Summary	Results
		days post-implantation	
GLP Acute & Short-term Safety Study	Test: 5 DCS Control: 3 BioFlex II	To demonstrate the rapid drug release profile of the BioFreedom DCS does not cause local cellular toxicity at the stented site, 8 Yorkshire swine were implanted with non-overlapping DCS or bare metal control stents and evaluated at 3 and 28 days.	All animals survived to the designated timepoint. No evidence of necrosis or toxicity or adverse reaction was observed within the myocardium or organs.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study, LEADERS FREE II (LFII) to establish a reasonable assurance of safety and effectiveness of the BioFreedom DCS in patients considered high bleeding risk (HBR) in the US, Canada, Denmark, France, Germany, Italy, and the United Kingdom under IDE G130034. Data from this study was the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were enrolled between February 14, 2017 and September 5, 2017. The database for this PMA reflected data collected through February 18, 2019 and included 2449 patients. There were 66 investigational sites.

This study was a prospective, single arm, multi-center, multi-national, open label trial to evaluate the safety and effectiveness of the BioFreedom DCS in patients with coronary artery disease who were at high risk of bleeding. Patients received percutaneous coronary intervention (PCI) with the BioFreedom DCS followed by one month of dual antiplatelet therapy (DAPT).

The results were compared to a historical control, the Gazelle bare metal stent (BMS) used as the control arm in the earlier LEADERS FREE (LFI) trial (described further in Section XI). Identical inclusion/exclusion criteria, case report forms, angiographic core laboratory, and clinical events committee (CEC) adjudication rules, processes and committee members as the LFI trial were utilized. A 5-strata level propensity analysis was utilized for the statistical analysis plan comparing the LFII DCS cohort to the LFI BMS historical control.

Choice of Control: In most pivotal trials, the control treatment represents a contemporary standard of care that is approved in the US. However, the Gazelle BMS used as the historical control is not an FDA-approved device and has never been used in the US. The applicant believed that conducting a randomized trial with a BMS arm would present an equipoise problem and safety concern as the results of LFI in

Europe had already initially demonstrated superiority of the BioFreedom DCS to the BMS control, and at the time the LFII trial was being planned, no drug eluting stents (DES) marketed in the US had been studied for use in patients at high risk of bleeding, making any DES also unsuitable as a control.

Nonclinical and clinical information about the Gazelle BMS, as well as a white paper defending the choice of the Gazelle BMS as a historical control for the LFII study, were reviewed as part of the PMA. In summary, the Gazelle BMS uses a very similar stainless-steel platform as the BioFreedom DCS, with the same strut thickness of 120 μm. Apart from the lack of drug coating, the only difference between the platforms is a modification of the connectors, which are straight in the Gazelle BMS, and S-shaped in the BioFreedom DCS. Gazelle received CE-mark approval in 2005 and has been commercialized by the applicant since then in Europe, Asia, and Latin America. Gazelle was used as the control in the LFI study, and because it cannot be distinguished from the BioFreedom DCS by the naked eye, that trial was able to be performed in a double-blind fashion (further discussed in the Supplemental Clinical Information section below). To demonstrate that the thicker struts of the Gazelle BMS compared to more modern BMS would not bias LFII in favor of the BioFreedom DCS arm, the applicant provided analyses that favorably compared the performance of the Gazelle BMS in LFI with that of other contemporary BMS used in similar patient cohorts (Mehran et al. 2009; Räber et al. 2012; Sabaté et al. 2014; Spaulding et al. 2011; Valgimigli et al. 2015).

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the LEADERS FREE II study was limited to patients who met the following inclusion criteria:

   Any indication for PCI in patients deemed at high risk for bleeding and candidates for 1-month DAPT. This includes candidates with stable angina, silent ischemia, acute coronary syndrome (ACS) including ST-segment elevation myocardial infarction (STEMI) and non-STEMI, non-native lesions, and in-stent restenosis. Reasons for unsuitability for >1 month DAPT included at least one of the following:

   1. Adjunctive oral anticoagulation treatment planned to continue after PCI
   2. Age ≥75 years old
   3. Baseline Hemoglobin (Hgb) <11 g/dl (or anemia requiring transfusion during the 4 weeks prior to the index procedure)
   4. Any prior intracerebral bleed
   5. Any stroke in the last 12 months
   6. Hospital admission for bleeding during the prior 12 months
   7. Non-skin cancer diagnosed or treated <3 years with a perceived increased risk of bleeding
   8. Planned daily non-steroidal anti-inflammatory drugs (NSAID) (other than aspirin) or steroids for >30 days after PCI

9. Planned surgery that would require interruption of DAPT (within next 6 months)
10. Renal failure defined as creatinine clearance <40 ml/min
11. Thrombocytopenia (platelet count (PLT) <100,000/mm^3)
12. Severe chronic liver disease defined as patients who have developed any of the following: variceal hemorrhage, ascites, hepatic encephalopathy or jaundice
13. Expected non-compliance to prolonged DAPT for other medical reasons

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

1. Pregnant and breastfeeding women
2. Patients expected not to comply with 1-month DAPT
3. Patients requiring a planned staged PCI procedure more than one week after the index procedure
4. Procedure planned to require non-study stents, or stand-alone balloon angioplasty (POBA) or stand-alone atherectomy
5. Active bleeding at the time of inclusion
6. Reference vessel diameter <2.25 mm or >4.0 mm
7. Cardiogenic shock
8. Compliance with long-term single anti-platelet therapy unlikely
9. A known hypersensitivity or contraindication to aspirin, clopidogrel (or prasugrel, or ticagrelor if applicable), stainless steel, zinc, Biolimus A9 or a sensitivity to contrast media, which cannot be adequately pre-medicated
10. PCI during the previous 12 months for a lesion other than the target lesion of the index procedure
11. Participation in another clinical trial (12 months after index procedure)
12. Patients with a life expectancy of <12 months

To support the propensity analysis comparing the LFII cohort to the historical BMS arm of LFI, study enrollment caps were placed on the criteria listed in Table 9.

Table 9. Enrollment Caps in LFII

Inclusion Criteria	Max # Patients
Candidates with STEMI	50
Candidates meeting only the criteria: Age ≥75 years old	250
Candidates meeting only the criteria: Expected non-compliance to prolonged DAPT for other medical reasons	10

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 30 days, 6 months, and 1 year after the index procedure. Telephone contact was initiated with the patients at 2 months and will also be conducted at 2- and 3-years post-procedure.

Preoperatively, patients received physical examinations, angina status was recorded, routine laboratory tests including Creatine kinase (CK) and/or Creatine kinase myocardial band (CK-MB) or troponin were conducted, and 12-lead electrocardiograms were performed. Postoperatively, an ECG was performed prior to discharge, with a 12-lead ECG required to document any suspicious cardiac ischemic episode. Troponin or CK and CK-MB (per institutional standard) were measured in the case of signs/symptoms of MI and at least once post-procedure with one of the measurements at 18-24 hours post-procedure. At follow-up visits, angina assessment, any adverse events, cardiovascular and other important medication intake, and any hospitalizations were recorded.

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 the composite of cardiac death and MI at 6 months. Secondary safety endpoints were assessed at all follow-up time points and included:

- Composite of cardiac death and MI at 1 and 2 months and 1, 2 and 3 years
- The composite of cardiac death, myocardial infarction (MI) and stent thrombosis (Definite/Probable)
- Bleeding per Bleeding Academic Research Consortium (BARC) criteria (BARC 3 to 5, all BARC, by access site)
- All individual components of the primary endpoint
    - Cardiac death
    - Myocardial infarction (according to the Third Universal Definition[1])
        - Q wave, Non-Q wave, and all myocardial infarction
- Stent thrombosis per Academic Research Consortium (ARC) definition[2]
- All-cause mortality

With regards to effectiveness, the primary effectiveness endpoint was the incidence of clinically-driven target lesion revascularization (CD-TLR) at 6 months. Secondary effectiveness endpoints were assessed at all follow-up time points and included:

- Urgent TLR
- CD-TLR at time points other than the primary endpoint
- Clinically-driven target vessel revascularization

With regard to success/failure criteria, non-inferiority testing of the primary safety and primary effectiveness endpoints was planned. If non-inferiority was shown, both

1 Third Universal Definition (Thygesen et al. 2012)
2 Stent thrombosis was evaluated as per the ARC definition provided by Cutlip et al. (2007).

the primary safety and primary effectiveness endpoints would be then tested for superiority (first safety, then effectiveness).

Protocol Definition of MI: The protocol definition of MI was the third Universal Definition and included Q wave, non-Q wave, and all myocardial infarctions. Periprocedural PCI was defined as detection of a rise of troponin > 3X of the upper reference limit (URL) or a rise in CK-MB > 3X URL. Spontaneous MI was defined as the detection of a rise in troponin > URL or CK-MB >URL (Cutlip et al. 2007).

B. Accountability of PMA Cohort

At the time of database lock, of 1203 patients enrolled and found to be eligible for the PMA study, 91.4% patients are available for analysis at the completion of the study, the 12-month post-index procedure visit. The disposition of the patients is summarized in Table 10.

Table 10. Patient Disposition

Parameter	LFII DCS	LFI BMS
Signed Informed Consent (enrolled)	2449	1227
Screen Failures	1246	16
Intention-to-Treat (ITT) Population*	1203	1211
30-Day Landmark Analysis Population‡	87.7% (1055/1203)	85.1% (1031/1211)
Deaths prior to 12-Month Visit	7.6% (91/1203)	8.7% (105/1211)
Withdrawals Prior to 12-Month Visit	1.1% (13/1203)	0.9% (11/1211)
Completed 12-Month Visit	91.4% (1099/1203)	90.4% (1095/1211)

** The intention-to-treat (ITT) population includes patients who met all the study eligibility criteria. The lesions were deemed treatable and the guidewire crossed the lesion. All subsequent percentages are based on this population.*
‡ All ITT patients who were event-free through 30 days and followed up thereafter.

C. Study Population Demographics and Baseline Characteristics

Table 11 presents demographics for the BioFreedom DCS ITT population and the historical control group. The mean age of the DCS patients was 74.6 years and 31.3% were female. Subjects were predominantly white (at least 75.0%; race data not available for approximately 20% of DCS patients) and overweight (mean body mass index (BMI) 28.7).

Table 11. LFII and Historical Control Demographics

Characteristic	LFII DCS (N=1203)	LF1 BMS (N=1211)
Sex		
Male	68.7% (826/1203)	69.1% (837/1211)
Female	31.3% (377/1203)	30.9% (374/1211)
Age (years)	74.6 ± 9.7 (1203) (43.0, 96.0)	75.7 ± 9.3 (1211) (37.8, 99.5)
Race		

Characteristic	LFII DCS (N=1203)	LF1 BMS (N=1211)
American Indian or Alaska Native	0.25% (3/1203)	0% (0/1211)
Asian	0.7% (8/1203)	7.3% (88/1211)
Black or African American	3.7% (45/1203)	0.1% (1/1211)
Native Hawaiian or Other Pacific Islander	0% (0/1203)	0.1% (1/1211)
White	75.0% (902/1203)	51.8% (627/1211)
Other	0.7% (9/1203)	0.1% (1/1211)
Not permitted to collect*	19.9% (239/1203)	40.8% (494/1211)
Ethnicity		
Hispanic or Latino	1.6% (19/1203)	NA**
Not Hispanic or Latino	76.4% (919/1203)	NA
Not permitted to collect*	22.0% (265/1203)	NA
BMI (kg/m^2)	28.66 ± 5.83 (1200)	27.18 ± 4.56 (1188)

*LFII and LFI were partially conducted in regions outside of the US that do not permit the collection of racial demographic data.
**Ethnicity demographic data for LFI was not provided.

Table 12 shows the baseline clinical characteristics and medical history for the patient population. Thirty-four percent of BioFreedom DCS patients had diabetes, 24.1% had prior MI, and 45.2% presented with an acute coronary syndrome (ACS). In general, baseline clinical characteristics were comparable between the BioFreedom DCS and historical control groups. Any imbalances were mitigated after propensity score stratification.

Table 12. Baseline Clinical Characteristics

Parameter	LFII DCS (N=1203)	LFI BMS (N=1211)
Current Smoker	12.2% (144/1180)	11.4% (137/1203)
Diabetes Mellitus	34.5% (414/1201)	32.3% (391/1210)
Diabetic (Medically Treated)	30.7% (369/1201)	29.4% (356/1210)
Diabetic (Insulin Dependent)	11.2% (135/1201)	11.3% (137/1210)
Hypercholesterolemia	74.4% (892/1199)	62.7% (746/1189)
Hypertension	86.5% (1039/1201)	79.6% (961/1208)
Renal Insufficiency at Screening†	21.2% (255/1201)	23.1% (278/1206)
History of MI	24.1% (287/1189)	21.4% (258/1203)
Prior CABG	15.5% (186/1202)	10.1% (122/1209)
ACS at Presentation	45.2% (544/1203)	43.1% (522/1211)
STEMI	2.33% (28/1203)	4.0% (48/1211)
NSTEMI	22.4% (270/1203)	23.2% (281/1211)
Unstable angina	20.4% (246/1203)	15.9% (193/1211)
History of Stroke	14.6% (175/1200)	9.1% (110/1208)
History of Malignancy	9.4% (112/1194)	9.8% (119/1210)

Parameter	LFII DCS (N=1203)	LFI BMS (N=1211)
Congestive Heart Failure	19.7% (237/1201)	12.4% (150/1211)
Previous PCI	38.1% (456/1198)	21.9% (265/1208)
Stent in Target Lesion	11.4% (137/1198)	NA
Peripheral Vascular Disease	17.4% (209/1198)	15.8% (190/1201)
Single vessel disease	23.8% (283/1189)	38.4% (460/1198)
Multiple vessel disease	76.2% (906/1189)	61.6% (738/1198)
Blood Disorder	16.5% (198/1202)	9.3% (112/1208)
Anemia	12.2% (147/1203)	6.9% (83/1211)
Thrombocytopenia	1.7% (20/1203)	1.2% (14/1211)
Other	2.6% (31/1203)	1.2% (15/1211)
Atrial Fibrillation	35.0% (420/1201)	34.6% (418/1209)
Chronic Obstructive Pulmonary Disease	14.0% (168/1201)	11.7% (141/1202)

NA= Not Available
† Per lab normal for creatinine

Key Baseline Lesion Characteristics: In BioFreedom DCS patients, visually estimated mean reference vessel diameter was 3.0 ± 0.5 mm, mean lesion length was 18.6 ± 10.6 mm, and mean percent diameter stenosis was 83.7 ± 12.4%. The target lesion location distribution is generally reflective of patients presenting for PCI with approximately 50% in the LAD, 29% in the LCX, and 34% in the RCA. Approximately half of lesions were classified as complex (B2/C). Additional baseline lesion characteristics can be found in Table 13.

Table 13. Baseline Lesion Characteristics

	LFII DCS (N=1203 Subjects N=1945 Lesions)	LFI BMS (N=1211 Subjects N=1909 Lesions)
Pre-Procedure		
Target Vessel		
Left Anterior Descending (LAD)	49.9% (641/1284)	51.8% (666/1287)
Left Circumflex Artery (LCX)	29.1% (374/1284)	28.9% (371/1287)
Right Coronary Artery (RCA)	33.9% (435/1284)	35.1% (451/1287)
Left Main	5.0% (64/1284)	3.9% (50/1287)
Graft	0.2% (2)	0.2% (2)
Mean Lesion Length (mm)	18.56 ± 10.59 (1945)	17.22 ± 9.07 (1905)
Mean RVD (mm)	3.01 ± 0.52 (1945)	2.99 ± 0.49 (1905)
% Diameter Stenosis (DS)	83.69 ± 12.42 (1945)	81.65 ± 12.31 (1907)
TIMI Flow		
0	9.2% (178/1945)	7.2% (138/1909)
1	4.5% (87/1945)	3.6% (68/1909)
2	7.9% (154/1945)	6.2% (119/1909)

	LFII DCS (N=1203 Subjects N=1945 Lesions)	LFI BMS (N=1211 Subjects N=1909 Lesions)
3	82.9% (1613/1945)	86.4% (1650/1909)
B2/C Lesion	52.0% (1011/1945)	46.1% (881/1909)
In-stent Restenosis	8.2% (160/1945)	2.0% (38/1909)
Bifurcation	13.4% (261/1945)	12.6% (240/1907)
Total Occlusion	5.0% (98/1945)	3.4% (64/1907)
Post-Procedure		
Lesion Success*	96.7% (1880/1945)	98.0% (1841/1878)
Dissection	0.9% (11/1203)	1.0% (13/1211)
Perforation	0.2% (2/1203)	0.0% (0/1211)

*Lesion success was defined as the attainment of <20% residual stenosis by visual estimate and either TIMI flow 3 or consistent TIMI flow 2 before and after the procedure with any percutaneous method.

Key Procedural Characteristics: The majority of the BioFreedom DCS patients had one lesion treated (64.1%) and one vessel treated (77.9%). Approximately half of patients had one stent implanted (53.2%). Additional procedural characteristics can be found in Table 14.

Table 14. Procedural Characteristics

	LFII DCS (N=1203 Subjects N=1287 Procedures)	LFI BMS (N=1211 Subjects N=1287 Procedures)
Type of Procedure		
Index	93.5% (1203)	94.1% (1211)
Staged	6.5% (84)	5.9% (76)
Number Lesions Treated/Subject	1.57 (1203)	1.59 (1211)
0	0.2% (3/1203)	0% (0/1211)
1	60.4% (727/1203)	61.4% (744/1211)
2	25.6% (308/1203)	25.7% (311/1211)
3	9.4% (113/1203)	8.7% (105/1211)
4 or more	4.3% (52/1203)	4.2% (51/1211)
Number of Vessels Treated/Subject	1.32 (1203)	1.07 (1211)
0	0.2% (3/1203)	0% (0/1211)
1	71.9% (865/1203)	73.2% (886/1211)
2	22.9% (276/1203)	22.5% (273/1211)
3	4.9% (59/1203)	3.8% (46/1211)
4	0% (0/1203)	0.5% (6/1211)
Number of Stents Placed/Subject	1.8 (1203)	1.7 (1211)
0	1.0% (12/1203)	0.5% (6/1211)

	LFII DCS (N=1203 Subjects N=1287 Procedures)	LFI BMS (N=1211 Subjects N=1287 Procedures)
1	53.2% (683/1203)	55.3% (712/1211)
2	26.2% (337/1203)	27.4% (352/1211)
3	12.1% (155/1203)	11.6% (149/1211)
4	4.2% (54/1203)	3% (38/1211)
5 or more	3.4% (44/1203)	2.3% (30/1211)
Total Stent Length (mm)/Subject	34.6 ± 23.3 (1275)	31.60 ± 20.98 (1269)
Any overlapping stent	18.6% (239/1284)	13% (167/1283)

HBR Characteristics of Patients Enrolled in LFII: Table 15 below provides an overview of the study HBR criteria met by all registered subjects. The mean number of HBR criteria met per BioFreedom DCS patient was 1.74. The most common HBR criteria met were age ≥75 years (64.1% of all DCS patients) and adjunctive oral anticoagulation treatment planned to continue after PCI (35.6% of all DCS patients). Most of the HBR criteria in LFII are very similar to the LFI BMS historical control arm.

Table 15. **Patients Meeting One or More of the HBR Inclusion Criteria**

HBR Inclusion Criteria	LFII DCS (N=1203)	LFI BMS (N=1211)
Patients satisfying one or more of the following criteria:		
Oral anticoagulation after PCI	34.1% (410/1203)	35.6% (431/1211)
≥ 75 years old	60.7% (730/1203)	64.1% (776/1211)
Anemia or recent transfusion	16.3% (196/1203)	16.0% (194/1211)
Prior intracerebral bleed	1.2% (15/1203)	1.6% (19/1211)
Stroke <1 year	2.3% (28/1203)	2.0% (24/1211)
Hospital for bleeding <1 year	3.9% (47/1203)	2.7% (33/1211)
Non-skin cancer <3 years	7.8% (94/1203)	9.9% (120/1211)
NSAID or steroids ≥30 days post PCI	9.2% (111/1203)	2.8% (34/1211)
Planned major surgery <6 months	12.1% (146/1203)	17.4% (211/1211)
Renal failure (Cr. Clearance <40 ml/min)	14.7% (177/1203)	20.2% (245/1211)
Thrombocytopenia (<100,000 mm^3)	2.7% (32/1203)	1.5% (18/1211)
Severe chronic liver disease	1.2% (14/1203)	0.8% (10/1211)
Expected DAPT non-compliance	3.5% (42/1203)	3.9% (47/1211)
Number of HBR criteria met (mean)	1.74	1.78 (all LFI patients)

Antiplatelet Medication Usage: Use of dual antiplatelet therapy (aspirin plus a $P2Y_{12}$ inhibitor) at discharge, 1 month, 6 months, and 12 months is summarized in Table 16. All

patients were required to be on DAPT for one month and single antiplatelet therapy indefinitely (either aspirin or any $P2Y_{12}$ inhibitor). Antiplatelet compliance was generally good, with 1.2% (15/1203) BioFreedom DCS patients discontinuing DAPT prior to 23 days and 7.1% (86/1203) prolonging DAPT beyond 37 days. Clopidogrel was the predominant $P2Y_{12}$ inhibitor (78.9% usage) used at discharge in DCS patients. In all, 84.1% of DCS patients (1012/1203) were on DAPT at the time of discharge. At discharge, 33.5% of DCS patients (403/1203) were on oral anticoagulants. The date of DAPT discontinuation was recorded differently in the two studies, however, the percentage of patients who had discontinued DAPT within the acceptable window (30 ± 7 days) was similar in the two groups (86.9% of LFII DCS patients and 90.2% of BMS).

Table 16. Antiplatelet Medication Usage

	LFII DCS (N=1203)	**LFI BMS (N=1211)**
Discharge		
$P2Y_{12}$ Inhibitor	93.1% (1120/1203)	99.5% (1205/1211)
Clopidogrel	78.9% (949/1203)	93.8% (1134/1211)
Prasugrel	1.4% (17/1203)	1.3% (16/1211)
Ticagrelor	12.8% (154/1203)	4.5% (54/1211)
Aspirin	84.6% (1018/1203)	97% (1173/1211)
DAPT (Aspirin and $P2Y_{12}$)	84.1% (1012/1203)	96.9% (1172/1211)
Oral Anticoagulation	33.5% (403/1203)	34.6% (418/1211)
1 month		
$P2Y_{12}$ Inhibitor	98.2% (1156/1177)	77.1% (921/1196)
Clopidogrel	84.8% (998/1177)	73.9% (866/1196)
Prasugrel	1.6% (19/1177)	1.2% (14/1196)
Ticagrelor	12.4% (146/1177)	3.4% (40/1196)
Aspirin	93.8% (1104/1177)	93.1% (1091/1196)
DAPT (Aspirin and $P2Y_{12}$)	92.3% (1086/1177)	72.7% (852/1196)
Oral Anticoagulation	36.7% (432/1177)	32.7% (383/1196)
6 months		
$P2Y_{12}$ Inhibitor	31.4% (348/1110)	NA*
Clopidogrel	27.8% (309/1110)	NA
Prasugrel	0.4% (4/1110)	NA
Ticagrelor	3.2% (36/1110)	NA
Aspirin	74.1% (822/1110)	NA
DAPT (Aspirin and $P2Y_{12}$)	8.6% (95/1110)	NA
Oral Anticoagulation	37.9% (421/1110)	NA
12 months		
$P2Y_{12}$ Inhibitor	31.5% (341/1083)	21.2% (235/1088)
Clopidogrel	27.4% (297/1083)	19.8% (215/1088)
Prasugrel	0.8% (9/1083)	0.6% (6/1088)
Ticagrelor	3.5% (38/1083)	1.3% (14/1088)
Aspirin	75.6% (819/1083)	81.3% (884/1088)

DAPT (Aspirin and $P2Y_{12}$)	12.0% (130/1083)	9.7% (106/1088)
Oral Anticoagulation	38.0% (412/1083)	36.5% (397/1088)

*NA=Not Available

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the 1203 ITT patients. Key safety outcomes are presented in Table 17. Adverse effects are reported in Table 18 and Table 19.

Primary Endpoint (Safety): The primary safety endpoint of cardiac death and MI was met. Non-inferiority of the primary endpoint of cardiac death or all MI (3rd Universal Definition) 6 months following BioFreedom DCS implantation in HBR patients compared to the LF II Gazelle BMS historical control arm was demonstrated after propensity score adjustment (as pre-specified in the LF II SAP). Propensity score stratification was performed by an independent statistician.

The 6-month Kaplan-Meier (KM) estimated rate for cardiac death/all MI was 6.5% for the BioFreedom DCS group and 9.7% for the BMS historical control group. Based on the number of patients and observed rates in each stratum, the results show that the stratified difference between BioFreedom DCS and Gazelle BMS KM estimated rates of cardiac death/all MI at 6 months was -3.5% with a 97.5% confidence interval upper limit of -1.2%, which was well below the prespecified non-inferiority margin of 3.92%. The -3.5% difference was also statistically significant for superiority, with the upper limit of the 2-sided 95% confidence interval (-5.8%, -1.2%) less than zero.

Secondary Endpoints (Safety): At 1-year follow-up, the composite safety endpoint (cardiac death and MI) occurred at a 9.3% KM estimated rate in the BioFreedom DCS group, and at a 12.4% KM estimated rate in the BMS group (p=0.0150, log-rank test) with a hazard ratio of 0.72 (95% CI 0.55, 0.94), as shown in the propensity-stratified adjusted KM curves below (Figure 4).

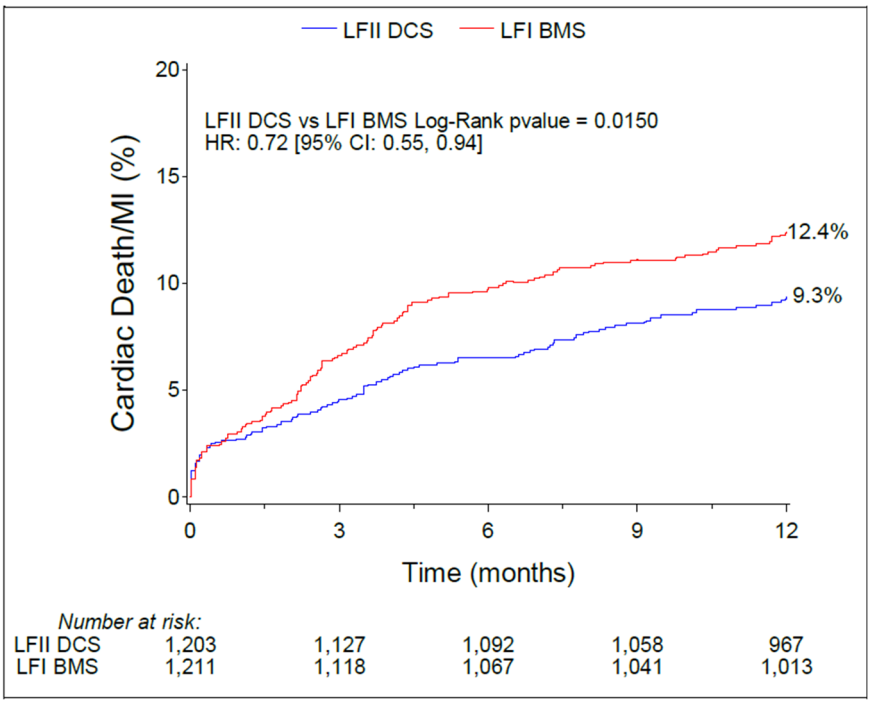

Figure 4. Kaplan-Meier Plot of Cardiac Death and MI Through 1 Year

Other supportive individual and composite safety endpoints between 1 and 12 months are listed in Table 17. The values provided are KM estimated rates without propensity score adjustment. Major bleeding (BARC 3-5) at 1 year was high but similar in both groups, occurring in 82 BioFreedom DCS patients (7.0%) vs. 85 BMS patients (7.3%). ARC definite/probable stent thrombosis occurred in 22 patients (1.9%) receiving BioFreedom DCS stents, versus 26 patients (2.2%) in the BMS historical control arm.

Table 17. Summary of Secondary Safety Endpoints

Endpoints	Study Device	KM Estimated Event Rate (N=1203)			
		1 Month	2 Months	6 Months	12 Months
Cardiac Death or MI (3rd Universal)	LFII DCS	2.7% (33)	3.6% (43)	6.5% (78)	9.3% (110)
	LFI BMS	3.2% (39)	4.5% (54)	9.7% (117)	12.3% (147)
Cardiac Death, MI or Stent Thrombosis (ARC Definite/Probable)	LFII DCS	2.7% (33)	3.6% (43)	6.6% (79)	9.4% (111)
	LFI BMS	3.4% (41)	4.6% (56)	9.9% (119)	12.6% (150)
All Death	LFII DCS	1.0% (12)	2.1% (25)	4.6% (55)	7.6% (91)
	LFI BMS	1.0% (12)	1.8% (22)	NA	8.7% (105)
Cardiac Death	LFII DCS	0.9% (11)	1.1% (13)	2.5% (30)	3.5% (41)
	LFI BMS	0.8% (10)	1.4% (17)	NA	5.1% (61)
Non-cardiac Death	LFII DCS	0.1% (1)	1.0% (12)	2.1% (25)	4.3% (50)
	LFI BMS	NA	NA	NA	NA
All MI (3rd Universal)	LFII DCS	1.9% (23)	2.7% (32)	4.4% (52)	6.5% (75)
	LFI BMS	2.6% (31)	3.7% (44)	5.9% (70)	8.8% (103)
Target Vessel MI	LFII DCS	1.8% (22)	2.1% (25)	3.4% (40)	4.5% (52)

Endpoints	Study Device	KM Estimated Event Rate (N=1203)			
		1 Month	2 Months	6 Months	12 Months
	LFI BMS	1.5% (18)	2.5% (30)	4.1% (48)	6.3% (73)
All Bleeding	LFII DCS	10.1% (121)	12.6% (151)	16.7% (198)	21.2% (249)
	LFI BMS	10.5% (126)	11.9% (142)	14.5% (173)	19.1% (225)
Major Bleeding (BARC 3-5)	LFII DCS	3.2% (38)	4.5% (54)	5.4% (64)	7.0% (82)
	LFI BMS	3.0% (36)	3.3% (40)	4.9% (58)	7.3% (85)
Stent Thrombosis (ARC Definite/Probable)	LFII DCS	1.1% (13)	1.3% (16)	1.5% (18)	1.8% (21)
	LFI BMS	1.1% (13)	1.6% (19)	1.6% (19)	2.2% (26)

Adverse effects that occurred in the PMA clinical study:

A summary of adverse events is presented below in Table 18. Adverse events were reported using MedDRA preferred terms. Only adverse events occurring at a rate of ≥1% in either treatment group are reported.

There was a total of 3301 adverse events reported in 860 patients in the BioFreedom DCS group, compared to a total of 2325 adverse events reported in 822 patients in the historical control BMS group. The frequency and nature of adverse events observed in the LEADERS FREE II trial were similar to those observed for other drug-eluting stents approved in the US. Note that events were not always coded consistently across the LFII and LFI trials, so direct comparisons are not necessarily informative. The below table combines related terms where appropriate.

Table 18. All Adverse Events Occurring in >1% of Patients

	LF II DCS (N=1203 Subjects) % Subjects (# of Events)	LFI BMS (N=1211 Subjects) % Subjects (# of Events)
Any Adverse Event to 365 Days	71.5% (3301)	67.9% (2325)
Blood and lymphatic system disorders		
Anaemia	2.8% (37)	2.9% (44)
Cardiac disorders		
Acute myocardial infarction	4.1% (55)	4.8% (79)
Angina pectoris	2.7% (34)	4.3% (59)
Angina unstable	1.0% (12)	1.9% (25)
Atrial fibrillation	5.7% (78)	3.4% (42)
Bradycardia	1.3% (17)	0.6% (7)
Cardiac failure	1.7% (24)	3.7% (55)
Cardiac failure congestive	3.2% (46)	1.3% (20)
Coronary artery dissection	0.9% (11)	1.0% (13)
Coronary artery stenosis	4.6% (61)	0.2% (2)
Dizziness	3.4% (44)	1.0% (12)
Myocardial infarction	2.2% (31)	2.1% (29)

	LF II DCS (N=1203 Subjects) % Subjects (# of Events)	LFI BMS (N=1211 Subjects) % Subjects (# of Events)
Palpitations	1.0% (12)	0.4% (5)
Gastrointestinal disorders		
Abdominal pain	1.6% (19)	0.3% (4)
Abdominal pain upper	1.2% (18)	0.7% (8)
Diarrhoea	2.1% (27)	0.9% (11)
Gastrointestinal haemorrhage	1.8% (23)	1.3% (16)
Nausea	1.5% (20)	0.3% (4)
Rectal haemorrhage	1.2% (16)	1.3% (22)
General disorders and administration site conditions		
Asthenia	1.4% (18)	0.7% (9)
Chest pain	11.1% (167)	6.5% (89)
Coronary artery restenosis	0.2% (5)	4.0% (60)
Death	1.4% (17)	1.0% (13)
Fatigue	2.0% (25)	0.7% (8)
Non-cardiac chest pain	1.2% (14)	0.7% (9)
Oedema peripheral	1.8% (22)	0.9% (12)
Pain	1.2% (15)	0.0% (0)
Thrombosis in device or Vascular stent thrombosis	1.8% (35)	2.3% (32)
Infections and infestations		
Bronchitis	1.1% (15)	0.7% (8)
Lower respiratory tract infection	0.3% (4)	1.0% (12)
Pneumonia	2.1% (30)	2.3% (30)
Respiratory tract infection	0.4% (5)	1.2% (14)
Upper respiratory tract infection	1.1% (13)	0.1% (1)
Urinary tract infection	2.9% (39)	2.3% (28)
Injury, poisoning and procedural complications		
Fall	1.2% (15)	0.9% (11)
Post procedural myocardial infarction	0.3% (4)	1.2% (16)
Vascular access site haemorrhage	1.3% (17)	0.0% (0)
Vessel puncture site haematoma or Vascular access site haematoma	2.2% (27)	2.1% (25)
Investigations		
Cardiac enzymes increased or Myocardial necrosis marker increased	0.9% (12)	1.8% (23)
Troponin I increased or Troponin T increased or Troponin increased	0.8% (10)	1.3% (16)
Metabolism and nutrition disorders		
Hypokalaemia	1.1% (14)	0.1% (1)
Musculoskeletal and connective tissue disorders		

	LF II DCS (N=1203 Subjects) % Subjects (# of Events)	LFI BMS (N=1211 Subjects) % Subjects (# of Events)
Arthralgia	1.7% (24)	0.3% (4)
Back pain	2.8% (34)	0.6% (7)
Musculoskeletal discomfort or Musculoskeletal pain or Musculoskeletal stiffness or Myalgia	1.8% (13)	0.7% (2)
Pain in extremity	1.9% (26)	1.0% (13)
Nervous system disorders		
Cerebrovascular accident	0.5% (6)	1.2% (15)
Headache	1.6% (19)	0.3% (4)
Ischaemic stroke or Brain stem infarction or Cerebellar infarction or Cerebral infarction or Cerebral ischaemia or Ischaemic cerebral infarction	1.1% (13)	0.9% (11)
Syncope	2.3% (29)	0.9% (13)
Renal and urinary disorders		
Acute kidney injury or Renal injury	2.8% (37)	0.1% (1)
Haematuria (blood in urine)	2.0% (28)	1.7% (23)
Renal failure or Renal failure acute or Renal failure chronic	0.7% (9)	2.7% (35)
Respiratory, thoracic and mediastinal disorders		
Acute pulmonary oedema or Pulmonary oedema	1.2% (16)	1.7% (21)
Chest discomfort	2.1% (28)	0.0% (0)
Chronic obstructive pulmonary disease	1.9% (26)	0.7% (14)
Cough	1.7% (23)	1.2% (14)
Dyspnoea	8.0% (102)	6.1% (79)
Dyspnoea exertional	1.1% (14)	0.5% (6)
Epistaxis (nosebleed)	2.1% (30)	2.7% (42)
Respiratory failure	1.2% (17)	0.1% (1)
Skin and subcutaneous tissue disorders		
Cellulitis	1.2% (14)	0.1% (1)
Contusion	1.8% (22)	0.0% (0)
Laceration	1.5% (19)	0.0% (0)
Rash or Rash generalized or Rash popular	1.2% (14)	0.4% (5)
Surgical and medical procedures		
Coronary revascularization or Percutaneous coronary intervention or Vascular stent restenosis	3.5% (46)	1.7% (22)
Vascular disorders		
Haematoma or Traumatic haematoma	1.6% (19)	0.9% (11)
Hypertension	2.7% (33)	0.8% (10)

	LF II DCS (N=1203 Subjects) % Subjects (# of Events)	LFI BMS (N=1211 Subjects) % Subjects (# of Events)
Hypotension	2.3% (28)	0.9% (12)
Peripheral arterial occlusive disease	1.0% (16)	0.4% (9)

A summary of device/procedure-related serious adverse events is presented below in Table 19. A serious adverse event either resulted in death, was life-threatening, required inpatient hospitalization or caused prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or required intervention to prevent permanent impairment or damage. Serious adverse events were reported using MedDRA preferred terms. Only serious adverse events occurring at a rate of ≥1% in either treatment group are reported.

There was a total of 210 device/procedure-related serious adverse events reported in 134 patients in the BioFreedom DCS group, compared to a total of 376 serious adverse events reported in 211 patients in the historical control BMS group. The below table combines related terms where appropriate.

Table 19. Device or Procedure-Related Serious Adverse Events

	LF II DCS (N=1203 Subjects) % Subjects (# of Events)	LFI BMS (N=1211 Subjects) % Subjects (# of Events)
Any Device/Procedure-Related Serious Adverse Event to 365 Days	11.1% (210)	17.4% (376)
Acute myocardial infarction or Acute coronary syndrome or Myocardial infarction or Post procedural myocardial infarction	3.4% (44)	5.1% (77)
Angina pectoris or Angina unstable or Chest pain	1.1% (14)	4.3% (56)
Coronary angioplasty or Coronary artery bypass or Coronary artery restenosis or Coronary revascularisation or Percutaneous coronary intervention or Vascular stent restenosis	2.7% (35)	5.1% (75)
Coronary artery thrombosis or Thrombosis in device or Vascular stent thrombosis	1.9% (33)	2.2% (32)

2. Effectiveness Results

The analysis of effectiveness was based on the 1203 ITT patients. Key effectiveness outcomes are presented in Table 20 to Table 22.

Primary Endpoint (Effectiveness): The primary effectiveness endpoint of CD-TLR was met (Table 20). Non-inferiority of the primary endpoint of CD-TLR 6 months following BioFreedom DCS implantation in HBR patients compared to the LF II Gazelle BMS historical control arm was demonstrated after propensity score adjustment (as pre-specified in the LF II SAP). The same propensity score stratification as the primary safety endpoint analysis was used.

The 6-month Kaplan-Meier (KM) estimated rate for CD-TLR was 3.7% for the BioFreedom DCS group and 6.1% for the BMS historical control group. Based on the number of patients and observed rates in each stratum, the results show that the stratified difference between BioFreedom DCS and Gazelle BMS KM estimated rates of CD-TLR at 6 months was -2.2% with a 97.5% confidence interval upper limit of -0.4%, which was well below the prespecified non-inferiority margin of 2.48%. The -2.2% difference was also statistically significant for superiority, with the upper limit of the 2-sided 95% confidence interval (-4.1%, -0.4%) less than zero.

Table 20. Analyses of Primary Endpoints at 6 Months

Endpoint	LFII DCS KM Estimate (N=1203)	LFI BMS KM Estimate (N=1211)	Stratified KM Difference	P value
Cardiac Death and MI at 6 Months	6.5%	9.7%	Non-inferiority -3.5% [-1.2%]*	<0.0001
			Superiority -3.5% [-5.8%, -1.2%]**	0.0033
Clinically Driven Target Lesion Revascularization	3.7%	6.1%	Non-inferiority -2.2% [-0.4%]*	<0.0001
			Superiority -2.2% [-4.1%, -0.4%]**	0.0175

*Upper 97.5% confidence interval
**95% confidence interval

To examine events occurring after DAPT discontinuation at one month, the 30-day landmark analysis population, consisting of all ITT patients that did not experience any events prior to 30 days, was also evaluated for the primary endpoints (Table 21).

Table 21. 30-Day Landmark Population Primary Endpoints at 6 Months

Endpoint	LFII DCS KM Estimate (N=1054)	LFI BMS KM Estimate (N=1031)	Stratified KM Difference	P value
Cardiac Death and MI	3.8%	6.9%	Non-inferiority -3.5% [-1.47%]*	<0.0001
			Superiority -3.5% [-5.53%, -1.47%]**	0.0013

Clinically Driven Target Lesion Revascularization	2.9%	5.4%	Non-inferiority -2.41% [-0.53%]*	<0.0001
			Superiority -2.41% [-4.3%, -0.53%]**	0.0157

*Upper 97.5% confidence interval
**95% confidence interval

Secondary Endpoints (Effectiveness): At 1-year follow-up, the effectiveness endpoint (CD-TLR) occurred at a 7.2% KM estimated rate in the BioFreedom DCS group, and at a 9.2% KM estimated rate in the BMS historical control group (p=0.0388, log-rank test) with a hazard ratio of 0.72 (95% CI 0.52, 0.98), as shown in the propensity-stratified adjusted KM curves below (**Figure 5**).

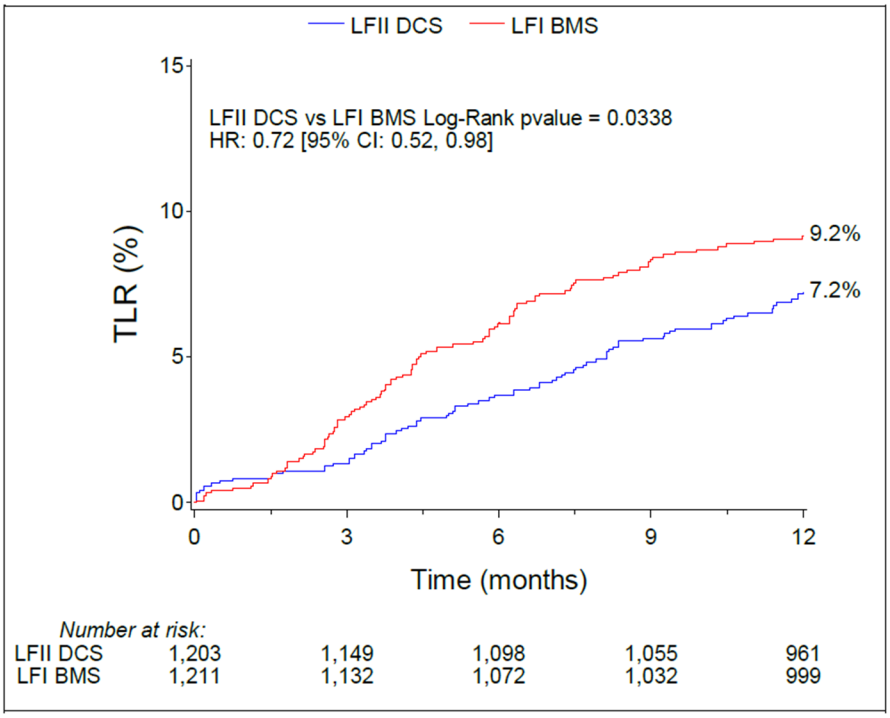

Figure 5. Kaplan-Meier Plot of CD-TLR Through 1 Year

Other supportive composite effectiveness endpoints between 1 and 12 months are listed in Table 22. The values provided are KM estimated rates without propensity score adjustment. Revascularization rates after 2 months consistently favored the DCS group compared with the historical BMS control.

Table 22. Secondary Effectiveness Endpoints

Endpoints	Study Device	KM Estimated Event Rate (N=1203)			
		1 Month	2 Months	6 Months	12 Months
Urgent TLR	LFII DCS	0.7% (9)	0.9% (11)	2.6% (30)	3.9% (45)
	LFI BMS	0.5% (6)	1.3% (16)	4.4% (52)	5.6% (65)
Clinically Driven TLR	LFII DCS	0.8% (10)	1.1% (13)	3.7% (43)	7.2% (82)
	LFI BMS	0.5% (6)	1.4% (17)	6.1% (71)	9.3% (107)

Endpoints	Study Device	KM Estimated Event Rate (N=1203)			
		1 Month	2 Months	6 Months	12 Months
Clinically Driven TVR	LFII DCS	1.1% (13)	1.4% (17)	4.1% (48)	7.7% (88)
	LFI BMS	0.5% (6)	1.4% (17)	6.3% (73)	10.0% (115)

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes:

Sex/Gender
Although not powered to evaluate safety or effectiveness of the BioFreedom DCS in sex- or gender-specific subgroups, outcomes for male and female patients from the LFII trial at one year are available (Table 23).

The composite rate of cardiac death/all MI in LFII DCS patients at one year was 9.62% in male patients and 8.72% in female patients.

The stent thrombosis rate at one year was 1.96% in males and 1.94% in females. The major bleeding rate (BARC 3-5) was 6.09% in male patients and 9.77% in female patients.

Table 233. Primary and Secondary Endpoints by Sex/Gender

Endpoint	Male (N=826)	Female (N=377)
Cardiac Death / All MI	78 (9.62%)	32 (8.72%)
All Death	62 (7.59%)	29 (7.78%)
Cardiovascular Death	28 (3.46%)	13 (3.54%)
Non-cardiac Death	34 (4.27%)	16 (4.4%)
All MI	53 (6.62%)	22 (6.08%)
Target-Vessel MI	37 (4.61%)	15 (4.11%)
Major Bleeding (BARC 3-5)	49 (6.09%)	36 (9.77%)
Definite or Probable Stent Thrombosis	16 (1.96%)	7 (1.94%)
Clinically-indicated Target Lesion Revascularization	60 (7.66%)	22 (6.19%)
Clinically-indicated Target Vessel Revascularization	64 (8.14%)	24 (6.75%)
Target Lesion Failure	97 (12.04%)	38 (10.36%)
Target Vessel Failure	100 (12.41%)	40 (10.91%)

The overall conclusions of the trial regarding the safety and effectiveness of the BioFreedom DCS when used with one month of DAPT in patients at high risk of bleeding can be generalized to males and females.

Age
Of the 1203 patients in LFII, 988 were >65 years old at the time of registration. The rates of cardiac death/all MI, BARC 3-5 bleeding, and stent thrombosis at one year in patients >65 years old were 9.52%, 7.99%, and 2.08%, respectively.

These rates were comparable to those observed in the overall LFII population. Table 24 summarizes event rates at one year in patients >65 and ≤65 years old in the LFII study.

Table 24. Primary and Secondary Endpoints By Age

Endpoint	≤65 (N=215)	>65 (N=988)
Cardiac Death / All MI	18 (8.49%)	92 (9.52%)
All death	11 (5.21%)	80 (8.19%)
Cardiovascular Death	6 (2.86%)	35 (3.63%)
Non-cardiac Death	5 (2.42%)	45 (4.73%)
All MI	13 (6.18%)	62 (6.51%)
Target-Vessel MI	9 (4.25%)	43 (4.5%)
Major Bleeding (BARC 3-5)	8 (3.83%)	77 (7.99%)
Definite or Probable Stent Thrombosis	3 (1.41%)	20 (2.08%)
Clinically-indicated Target Lesion Revascularization	12 (5.74%)	70 (7.52%)
Clinically-indicated Target Vessel Revascularization	15 (7.16%)	73 (7.82%)
Target Lesion Failure	20 (9.44%)	115 (11.99%)
Target Vessel Failure	23 (10.84%)	117 (12.19%)

Race and Ethnicity

Outcomes by race and ethnicity in the LFII study are presented in Table 25. Of the 1203 patients, 902 were white (75.0%) and 45 were Black or African American (3.7%), while 19 (1.6%) were Hispanic or Latino. The available race and ethnicity information is too limited to comment on any potential associations.

Table 25. Primary and Secondary Endpoints By Race and Ethnicity

Endpoint	White (N=902)	American Indian or Alaska Native (N=3)	Asian (N=8)	Black or African American (N=45)	Hispanic or Latino (N=19)
Cardiac Death / All MI	75 (8.5%)	0 (0%)	0 (0%)	5 (11.17%)	2 (10.53%)
All death	63 (7.08%)	0 (0%)	0 (0%)	4 (8.89%)	2 (10.53%)
Cardiovascular Death	26 (2.97%)	0 (0%)	0 (0%)	2 (4.44%)	1 (5.26%)
Non-cardiac Death	37 (4.24%)	0 (0%)	0 (0%)	2 (4.65%)	1 (5.88%)
All MI	50 (5.73%)	0 (0%)	0 (0%)	5 (11.17%)	1 (5.26%)
Target-Vessel MI	32 (3.65%)	0 (0%)	0 (0%)	4 (9.15%)	1 (5.88%)
Major Bleeding (BARC 3-5)	63 (7.12%)	0 (0%)	0 (0%)	6 (13.78%)	3 (17.11%)
Definite or Probable Stent Thrombosis	15 (1.7%)	0 (0%)	0 (0%)	1 (2.27%)	0 (0%)
Clinically-indicated Target Lesion Revascularization	60 (7.01%)	0 (0%)	1 (12.5%)	4 (9.09%)	2 (10.53%)
Clinically-indicated Target Vessel Revascularization	64 (7.46%)	0 (0%)	1 (12.5%)	4 (9.09%)	2 (10.53%)
Target Lesion Failure	96 (10.94%)	0 (0%)	1 (12.5%)	6 (13.33%)	3 (15.79%)

Endpoint	White (N=902)	American Indian or Alaska Native (N=3)	Asian (N=8)	Black or African American (N=45)	Hispanic or Latino (N=19)
Target Vessel Failure	100 (11.38%)	0 (0%)	1 (12.5%)	6 (13.33%)	3 (15.79%)

4. Poolability Analyses

As LF II combined subjects from the US, Canada, and Europe, the study SAP specified that the primary endpoints would be presented by region and by site, and that heterogeneity of treatment effects with respect to sites would be explored. Table 256 presents primary endpoint results by region. Effectiveness results did appear to vary by region, with US patients experiencing fewer CD-TLR events than OUS patients at 6 months. However, this does not raise a concern for the performance of the BioFreedom DCS in US patients. For the multiple center effect analysis, a logistic regression model including an intercept term and fixed effect for sites showed no issues of poolability between investigational sites for the primary safety or primary effectiveness endpoints.

Table 25. Geographic Poolability Evaluation

	KM Estimated Rate of Death or MI at 6 Months (N=1203)	KM Estimated Rate of CD-TLR at 6 Months (N=1203)
US	3.1% (18/594)	4.4% (26/594)
OUS	4.3% (25/609)	8.6% (52/609)

5. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

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 LFII clinical study included 413 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 regarding the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

LFII was the pivotal trial used to support this PMA. Several additional clinical studies have been conducted on the BioFreedom DCS as chronologically outlined in Table 267.

Table 26. Summary of Additional Clinical Studies

Study	# of Patients	Type	DAPT	Endpoints	Duration
BioFreedom First in Human (2008-2014)	60 BioFreedom DCS 60 Taxus Liberté	Prospective, randomized, 4 German sites	6 mo	Late lumen loss at 12 months	5 years
Summary of Results	This first-in-human study demonstrated non-inferiority to Taxus Liberté for the primary endpoint and demonstrated comparable MACE rates through 5 years of follow up.				
LEADERS FREE (LFI) (2012-2016)	1,239 BioFreedom DCS 1,227 Gazelle BMS	Prospective, randomized, double blind, 68 sites in 20 OUS countries	1 mo	1. MACE 2. Clinically driven TLR	2 years
Summary of Results	The BioFreedom DCS was shown to be superior to the Gazelle BMS with respect to the primary safety endpoint and demonstrated a significantly lower incidence of the primary efficacy endpoint when used with one month DAPT in patients with high bleeding risk following PCI.				
EGO BioFreedom (2012-2015)	100	Single arm, single center, serial OCT analysis	9 mo	% strut coverage from 1 to 9 months	1 year
Summary of Results	The study illustrated the early healing profile of the BioFreedom stent. At 1 month, median strut coverage was 85.77% [min. 48.16, max. 97.38]. At 9 months, median strut coverage reached 99.55% [min. 85.41, max. 100].				
BioFreedom Japan (2014-2017)	140	Single arm vs. LFI DCS	1 mo	1. MACE 2. Clinically indicated TLR	2 years
Summary of Results	At 1 year follow-up, in a population of 140 Japanese patients at high bleeding risk, there were 3 non-cardiac deaths (2.1%), one case of myocardial infarction (0.7%), and 2 clinically indicated TLR events. No cases of stent thrombosis were observed. The rate of BARC 3-5 bleeding was 5.0%.				
BioFreedom USA IDE Feasibility (G130034) (2014-2018)	72	Single arm vs. historical Taxus Express	3 mo	1. MACE 2. Late lumen loss	3 years
Summary of Results	The BioFreedom DCS demonstrated a mean in-stent late lumen loss of 0.32 mm ± 0.53 mm at 9 months. By comparison, the Taxus Express late loss at 9 months was 0.41 mm ± 0.56 mm (Escolar et al. 2007). The per protocol superiority test comparing both outcomes was not significant suggesting that				

Study	# of Patients	Type	DAPT	Endpoints	Duration
	the BioFreedom DCS stent is not superior to the Taxus Express stent in preventing late lumen loss.				
Pharmacokinetics (PK) Study (2017-2018)	15	Single arm, single Spanish site	N/A	To characterize Cmax and Tmax of BA9 and its metabolites sirolimus and everolimus	72 hours
Summary of Results	Biolimus A9 was quantifiable in systemic human blood at 15 minutes after stent implantation. The median maximum blood concentration (Cmax) of 6.60 ng/mL was reached after a median time of 1.0 hour. The highest Biolimus A9 blood concentration measured in any of the study participants at any sample collection time point was 12.90 ng/mL. Systemic exposure to everolimus (Biolimus A9 metabolite) was 19.7-fold lower than exposure to Biolimus A9. The pharmacokinetics of sirolimus was not analyzed as all concentrations were below the limit of quantification (< 0.1 ng/mL).				
ONYX ONE Study (2017-2019)	969 BioFreedom DCS 988 Resolute Onyx	Prospective, randomized, single blind, 84 sites in 20 OUS countries	1 mo	1. Cardiac death/MI/ST 2. TLF	1 year
Summary of Results	The BioFreedom DCS showed comparable performance in both safety and effectiveness to a contemporary DES in patients with high bleeding risk treated with one month of DAPT after PCI.				

More in-depth information regarding LFI, the BioFreedom USA IDE Feasibility study, and the ONYX ONE Global study is presented below.

A. LEADERS FREE (LFI)

Primary Objective:

Safety:

To demonstrate in coronary artery disease (CAD) patients who are at high risk of bleeding and/or medically unsuitable for >1-month treatment with DAPT that the BioFreedom DCS followed by 1-month DAPT is non-inferior to the Gazelle BMS followed by 1-month DAPT as measured by the composite primary endpoint of cardiac death, myocardial infarction, and definite/probable stent thrombosis at one year.

Effectiveness:

To demonstrate in CAD patients who are at high risk for bleeding and/or medically unsuitable for >1-month treatment with DAPT that the BioFreedom DCS followed by 1-month DAPT is superior to the Gazelle BMS followed by 1-month DAPT as measured by the incidence of clinically driven target lesion revascularization (TLR) at one year.

Design: LFI was a prospective, multicenter, double-blind, randomized trial. Patients were randomized at a 1:1 ratio, BioFreedom: Gazelle BMS, followed by one-month DAPT. All patients were followed for two years.

Inclusion and exclusion criteria were identical to LFII and the control group was used as the historical control for LFII, as described in Section X.

A total of 2466 patients from 68 centers in 20 countries in Europe, Australia, Asia and Canada were randomized, and 2432 patients had an index procedure. A total of 4401 stents were implanted, of which 2214 BioFreedom DCS stents were implanted in 1204 patients.

Demographics: Patient demographics were very similar to LFII. Average age was 75.7±9.4 years in the DCS group and 75.7±9.3 years in the BMS group. Approximately 70% of patients were male and approximately one-third had diabetes. Patients were well-matched in baseline demographics, including major coexisting conditions indicative of increased bleeding risk.

Baseline lesion characteristics: Baseline lesion characteristics were also very similar to LFII. Mean reference vessel diameter was 2.99±0.49 mm in the DCS group and 3.00±0.49 mm in the BMS group. Percent diameter stenosis was 81.6±12.3% in the DCS group and 81.7±12.2% in the BMS group.

Results:
Safety Endpoints
At one year, the BioFreedom DCS demonstrated non-inferiority and superiority to the Gazelle BMS in the primary safety endpoint of cardiac death, MI (3rd Universal Definition), and definite/probable stent thrombosis. The endpoint occurred in 110 patients (9.2%) in the BioFreedom DCS group and in 151 patients (12.7%) in the BMS group (estimated risk difference: −3.45%; two-sided 95% CI: −5.9% to −0.9%; $p<0.0001$ for non-inferiority, $p=0.006$ for superiority). Note that unlike LFII, endpoint rates were not KM estimates.

At two years, the primary safety endpoint occurred in 147 patients (12.6%) in the DCS group and in 180 patients (15.3%) in the BMS group.

Other secondary safety endpoints are summarized in Table 308 below. LFII BioFreedom DCS safety outcomes at one year were very similar.

Table 27. Summary of LFI Secondary Safety Endpoints

Endpoints	Study Device			
		1 Month	1 Year	2 Years
All Death	DCS	1.2% (14)	7.5% (91)	13.1% (156)
	BMS	1.0% (12)	8.7% (105)	13.8% (164)
Cardiac Death	DCS	1.0% (12)	4.1% (49)	6.6% (76)
	BMS	0.8% (10)	5.1% (61)	6.9% (80)

Endpoints	Study Device			
		1 Month	1 Year	2 Years
All MI (3rd Universal)	DCS	2.0% (25)	5.9% (70)	7.7% (90)
	BMS	2.6% (31)	8.8% (103)	10.1% (117)
All Bleeding	DCS	10.7% (129)	17.9% (213)	22.0% (258)
	BMS	10.5% (126)	19.1% (225)	22.2% (258)
Major Bleeding (BARC 3-5)	DCS	3.5% (42)	7.2% (85)	9.0% (105)
	BMS	3.0% (36)	7.3% (85)	9.2% (105)
Stent Thrombosis (ARC Definite/Probable)	DCS	1.0% (12)	2.0% (24)	2.1% (25)
	BMS	1.1% (13)	2.2% (26)	2.3% (27)

Effectiveness Endpoints
At one year, the BioFreedom DCS demonstrated superiority to the Gazelle BMS in the primary effectiveness endpoint of clinically driven TLR. The endpoint occurred in 57 patients (4.9%) in the BioFreedom DCS group and in 107 patients (9.3%) in the BMS group (estimated risk difference, −4.4 %; two-sided 95% CI, −6.5% to −2.3%; p<0.0001 for superiority).

At two years, the primary effectiveness end point occurred in 77 patients (6.8%) in the DCS group and in 136 patients (12%) in the BMS group.

Other secondary effectiveness endpoints are summarized in Table 289 below. LFII BioFreedom DCS effectiveness outcomes at one year were very similar.

Table 28. Summary of LFI Secondary Effectiveness Endpoints

Endpoints	Study Device			
		1 Month	1 Year	2 Years
Urgent TLR	DCS	0.7% (8)	3.2% (38)	3.7% (43)
	BMS	0.5% (6)	5.6% (65)	6.1% (70)
Clinically Driven TVR	DCS	0.7% (8)	5.5% (64)	8.0% (90)
	BMS	0.5% (6)	10.0% (115)	13.0% (147)

B. BioFreedom US IDE Feasibility

Primary Objective:
Safety:
The primary safety endpoint was the occurrence of major adverse cardiac events (MACE, defined as the composite of cardiac death, MI (3rd Universal Definition), TLR, and ARC definite stent thrombosis) within 9 months following implantation.
Effectiveness:
The primary effectiveness endpoint was in-stent late lumen loss (LLL) at 9 months as compared to historical control.

Design: The BioFreedom US IDE Feasibility study was a prospective, multicenter, non-randomized, open label trial. Patients were treated with the BioFreedom DCS followed by 3 months of DAPT. All patients were followed for three years.

Patients enrolled had clinical evidence of ischemic heart disease, stable or unstable angina, silent ischemia, or a positive functional study. Unlike in LFI and LFII, there were no inclusion criteria related to bleeding risk. Outcomes were compared to a historical control, the Taxus Express stent as studied in the TAXUS IV, V, and VI trials (REF, Escolar).

A total of 83 lesions in 72 patients from 10 centers in the US were treated with BioFreedom DCS.

Demographics: Average age was 63.5±9.0 years. Approximately 80% of patients were male and approximately one-third had diabetes. Unstable angina was present in 38% of patients.

Baseline lesion characteristics: Mean reference vessel diameter was 2.67±0.59 mm. Percent diameter stenosis was 66.0±13.5%.

Results:
Safety Endpoints
At 9 months, the occurrence of MACE was 8.4% (6 events), which was the primary safety endpoint of the study. At 1 year, MACE was reported in 14.1% of patients, and at 2 years in 16.2% of patients. No statistical analyses were prespecified for this endpoint.

Other safety outcomes collected during the course of the trial and adjudicated by the CEC are summarized in Table 2930.

Table 29. Feasibility Trial Safety Outcomes

***N*=72**	**1M**	**9M**	**1Y**	**2Y**	**3Y**
MACE (%)	4 (5.6%)	6 (8.4%)	10 (14.1%)	11 (16.2%)	15 (22.1%)
Death (%)	1 (1.4%)	3 (4.2%)	4 (5.6%)	8 (11.8%)	8 (11.8%)
Cardiac Death (%)	0 (0%)	1 (1.4%)	1 (1.4%)	1 (1.5%)	1 (1.5%)
MI (%)	4 (5.7%)	4 (5.6%)	4 (6.0%)	5 (7.7%)	7 (10.3%)
Def/Prob ST (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
All Bleeding	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

There was a total of 16 device-related (possible, probable, or definite) adverse events. These events are summarized in Table 3031.

Table 30. Feasibility Trial Device-related Adverse Events

Preferred Term	**# of Events**
Acute myocardial infarction	4
Coronary artery dissection	1

Preferred Term	# of Events
Cardiac arrest	1
Angina pectoris	1
Chest discomfort	2
Thrombosis in device	1
Coronary artery restenosis	5
Dyspnoea	1

Effectiveness Endpoints
At 9 months, the BioFreedom DCS did not demonstrate superiority to the historical control (Taxus Express) in the primary effectiveness endpoint of in-stent late lumen loss measured by quantitative coronary angiography (QCA). Sixty-six lesions from 59 patients were available for 9-month QCA analysis.

The BioFreedom DCS demonstrated a mean in-stent late lumen loss of 0.32 mm ± 0.53 mm at 9 months (Table 23). By comparison, the Taxus Express late loss at 9 months was 0.41 mm ± 0.56 mm. The per protocol superiority test comparing both outcomes was not significant (one-sample t-test, t = -1.34, df = 65, p = 0.19).

Target lesion revascularization rates were 7.5% (5 events) at 1 year, 7.7% at 2 years, and 11.8% at 3 years.

C. ONYX ONE Study

The ONYX ONE study (Windecker et al. 2020) was not conducted by the applicant; however, the BioFreedom DCS was used as the comparator device in a global trial of another manufacturer's DES (Medtronic's Resolute Onyx) in patients at high risk for bleeding. FDA reviewed only summary level data of this study, but it was a large, randomized, controlled trial that compared the clinical performance of the BioFreedom DCS with a contemporary DES approved for use in patients at high risk for bleeding.

Primary Objective:
Safety:
The primary endpoint was the composite of cardiac death, MI (3rd Universal Definition), or definite or probable stent thrombosis one year after implantation.

Effectiveness:
The effectiveness endpoint was TLF at one year.

Design: The ONYX ONE study was a prospective, multicenter, single-blind, randomized trial. Patients were randomized and implanted with the Resolute Onyx DES or BioFreedom DCS at a 1:1 ratio, followed by one-month DAPT.

Patients enrolled were acceptable candidates for treatment with a DES, met pre-defined criteria for being at high risk for bleeding, and were candidates for treatment with one month of DAPT. The criteria defining high bleeding risk were the same as

LFII and LFI, apart from a 12-month instead of 6-month window for planned surgery that would require interruption of DAPT. Exclusion criteria were also very similar to LFII and LFI.

A total of 1996 patients from 84 centers in 20 countries in Europe, Oceania, and Asia were randomized, with 1003 patients assigned to the DES and 993 to the DCS.

Demographics: Average age was 74±10 years. Two thirds of patients were male and 39% had diabetes. Patients were well-matched in baseline demographics, including major coexisting conditions indicative of increased bleeding risk.

Baseline lesion characteristics: Mean reference vessel diameter was 2.84±0.46 mm in the DES group and 2.83±0.44 mm in the DCS group. Percent diameter stenosis was 68.6±13.4% in the DES group and 68.2±13.2% in the BMS group.

Results:
Safety Endpoints
At one year, the primary safety endpoint of cardiac death, MI (3rd Universal Definition), and definite/probable stent thrombosis had occurred in 169 patients (17.1%) in the DES group and in 164 patients (16.9%) in the BioFreedom DCS group. The endpoint was influenced by higher-than-expected rates of peri-procedural MI in both groups (9.4% of DES patients and 7.9% of BioFreedom DCS patients). While the MI definition was the same one used in LFI and LFII, the higher rates are hypothesized by the study authors to be due to differences in "ascertainment and adjudication of events between the trials" (Windecker et al. 2020). Cardiac death and stent thrombosis rates in the BioFreedom DCS group were very similar to those seen in LFI and LFII and comparable to the DES group.

Other secondary safety endpoints are summarized in Table 3132 below.

Table 31. Summary of ONYX ONE Secondary Safety Endpoints at One Year

Endpoints	BioFreedom DCS (N=969)	Contemporary DES (N=988)
All Death	7.4% (72)	8.8% (87)
Cardiac Death	3.7% (36)	4.5% (44)
All MI (3rd Universal)	14.7% (142)	13.4% (132)
All Bleeding	16.3% (158)	17.7% (175)
Major Bleeding (BARC 3-5)	13.7% (133)	15.1% (149)
Stent Thrombosis (Definite/Probable)	2.1% (20)	1.3% (13)

Effectiveness Endpoints
The effectiveness endpoint of TLF at one year was very similar in both groups, with the endpoint occurring in 174 patients (17.6%) in the DES group and in 169 patients (17.4%) in the BioFreedom DCS group.

Other secondary effectiveness endpoints are summarized in Table 323 below.

Table 32. Summary of ONYX ONE Secondary Effectiveness Endpoints at One Year

Endpoints	BioFreedom DCS (N=969)	Contemporary DES (N=988)
Revascularization (any)	6.8% (66)	5.8% (57)
Clinically indicated TLR	4.0% (39)	2.8% (28)
Clinically indicated TVR	5.3% (51)	3.6% (36)

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

The principal safety and effectiveness information for the BioFreedom Drug Coated Coronary Stent System is derived from preclinical studies and from the LEADERS FREE II clinical trial.

Preclinical testing performed during the design and development of the BioFreedom DCS confirmed the product design characteristics, specifications, and intended use.

The in vitro engineering testing conducted on the stent and delivery system demonstrated that the performance characteristics met the product specifications. The biocompatibility evaluation and in vivo animal studies demonstrated that the acute and chronic in vivo performance characteristics of the BioFreedom DCS are safe and acceptable for clinical use. The sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The shelf-life testing has established acceptable performance for the labeled shelf life of nine months.

A. Effectiveness Conclusions

The results from the LEADERS FREE II trial demonstrated that, in high bleeding risk patients, the rate of clinically driven target lesion revascularization in the BioFreedom DCS group was superior to the historical control Gazelle BMS group at 6 months post PCI. TLR rates remained lower in BioFreedom DCS patients at 1 year (7.2% vs 9.2%). Other revascularization endpoints (urgent TLR, clinically driven TLR, and clinically driven TVR) all favored the BioFreedom DCS over the BMS historical control at 6 months and 1 year.

In LEADERS FREE I, the rate of clinically driven TLF in BioFreedom DCS patients was 4.9% at 1 year, similar to the rate in the published results of the more recent ONYX ONE trial conducted in a similar OUS high bleeding risk population.

These endpoints are clinically meaningful and commonly used in coronary stent trials. Taken together, these results demonstrate superior effectiveness to a BMS and reproducibility of effectiveness across trials.

B. Safety Conclusions

The risks of the BioFreedom DCS are based on nonclinical laboratory and animal studies, as well as data collected in clinical studies conducted to support PMA approval as described above.

No safety signals of concern were identified from a review of serious adverse events and CEC-adjudicated events. Device or procedure-related serious adverse events included myocardial infarction (3.4%), angina/chest pain (1.1%), repeat coronary revascularization (2.7%), and thrombosis (1.9%). These adverse events have been seen at similar rates in other coronary stent trials.

The LEADERS FREE II trial demonstrated that, in high bleeding risk patients, the rate of cardiac death or MI in the BioFreedom DCS group was superior to the historical control Gazelle BMS group at 6 months post PCI. Rates remained lower in BioFreedom DCS patients at 1 year (9.3% vs 12.4%). Therefore, the independent LFII BioFreedom DCS cohort reproduced the finding of superior safety to the Gazelle BMS in high bleeding risk patients treated with one month of DAPT reported in the LFI study.

At one year, 7.6% of patients treated with the BioFreedom DCS had died of any cause, compared to 8.7% of patients treated with the historical control BMS. Deaths adjudicated as having cardiac causes occurred in 3.5% of DCS patients and 5.1% of BMS historical control patients at one year. MI rates, including target vessel MI, favored the BioFreedom DCS over the BMS historical control at 6 months and 1 year.

Bleeding rates were high (approximately 20% of all patients experienced a bleeding event by 1 year, and 7% experienced serious bleeding) and similar in both groups, as expected in the high bleeding risk trial population. Approximately half of bleeding events occurred in the first month after PCI, before the cessation of DAPT. There is no information available related to bleeding rates with longer durations of DAPT.

At one year, ARC definite/probable stent thrombosis rates were low and similar in both groups (1.8% in BioFreedom DCS vs. 2.2% in the historical control BMS group). BioFreedom DCS stent thrombosis rates were also consistent across trials, with a 2.0% rate in LFI at one year, and the ONYX ONE investigators reporting 2.1% at one year.

The safety endpoints studied in LFII are clinically meaningful and commonly used in coronary stent trials. Taken together, these results demonstrate superior safety to a BMS, reproducibility of safety findings across trials, and comparable safety to a contemporary DES.

C. Benefit-Risk Determination

The probable benefits of the BioFreedom DCS when used to treat patients at high risk for bleeding with symptomatic ischemic heart disease are based on data collected in the LEADERS FREE II clinical study conducted to support PMA approval as described above. Historically, patients at high risk for bleeding treated for symptomatic ischemic heart disease have been treated with bare metal stents. This was intended to decrease the risk of bleeding associated with prolonged treatment with dual antiplatelet therapy, which was believed to be necessary when implanting drug eluting stents to prevent life-threatening stent thrombosis events. The polymer coatings used on early generation drug eluting stents were hypothesized to increase the risk of stent thrombosis. The BioFreedom DCS was developed without a polymer specifically to decrease this risk and allow treatment of high bleeding risk patients with a drug coated stent and shorter durations of DAPT, desirable because of the known increase in effectiveness (reduced need for future revascularizations) of drug eluting stents compared to bare metal stents. LEADERS FREE I was the first clinical study to demonstrate that both safety and effectiveness outcomes were improved when treating patients at high risk of bleeding with a drug coated stent compared to a bare metal stent. LEADERS FREE II was developed to demonstrate that these results could be replicated in a patient population that included US patients.

Probable benefits for high bleeding risk patients include a decreased need for target lesion revascularization when compared to treatment with a bare metal stent. LEADERS FREE II showed this benefit to persist for one year after PCI with a hazard ratio of 0.72, and the earlier OUS study LEADERS FREE I reported increased improvement (hazard ratio of 0.54) in clinically driven target lesion revascularization compared to a bare metal stent through two years of follow up.

Other probable benefits for high bleeding risk patients compared to treatment with a bare metal stent include decreased rates of cardiac death or myocardial infarction. This benefit persisted for one year after PCI with a hazard ratio of 0.72. LEADERS FREE I reported a similar benefit through two years of follow up in OUS patients, with a hazard ratio of 0.795.

The probable risks of the BioFreedom DCS are also based on data collected in the LEADERS FREE II clinical study conducted to support PMA approval as described above. Major bleeding occurred in 3.5% of BioFreedom DCS patients by one month post PCI, before DAPT discontinuation. Probable or definite stent thrombosis was seen in approximately 2% of BioFreedom DCS patients in LFI,

LFII, and ONYX ONE after one year. While low, these rates are higher than those seen in most contemporary DES studies. This may be due to both the high bleeding risk population also being at higher risk for clotting than lower risk PCI populations, and to the relatively thicker strut design of the BioFreedom DCS compared to contemporary DES devices.

LEADERS FREE II did not find any procedure-related risks associated with the use of the BioFreedom DCS that would not be expected with any other coronary stent system. Please refer to Section VIII: Potential Adverse Effects of the Device on Health.

Additional factors to be considered in determining probable risks and benefits for the BioFreedom DCS include:

Unlike most pivotal trials for coronary stents, the LEADERS FREE II study was not a randomized controlled trial, and the device chosen as the historical control (the Gazelle BMS) was not a device approved for use in the US. However, the study was well-conducted, used robust analyses of the study results, and demonstrated generalizability of the results seen in the LEADERS FREE I RCT in OUS patients. A randomized study against a US-approved bare metal stent was no longer feasible after the publication of the LEADERS FREE results; BMS use in the US declined rapidly. Selecting a DES as a control in high bleeding risk patients was also not feasible because there was very little data at the time on the safety of the use of approved DES with shorter durations of DAPT. The Gazelle BMS historical control allowed for the use of propensity matching and for a clear demonstration of the benefit of the biolimus coating as the stent backbone was the same as the BioFreedom DCS.

Another source of uncertainty is that high bleeding risk is not a binary risk; this patient population includes patients with a spectrum of bleeding and ischemic risk, depending on the nature and number of bleeding risk characteristics that are present. Therefore, the risk/benefit ratio of the BioFreedom DCS when used with one month of DAPT may not be the same for all patients meeting the high bleeding risk inclusion criteria used in the LEADERS FREE studies. It should not be assumed that discontinuing DAPT at one month is the right strategy for all high bleeding risk patients treated with the BioFreedom DCS. Not all patients enrolled in the LEADERS FREE studies discontinued DAPT at one month – 12% of BioFreedom DCS and 16% of historical control BMS patients received DAPT beyond 37 days post PCI. Other durations of DAPT were not studied, and whether extending the DAPT duration for the BioFreedom DCS could lower the rate of stent thrombosis without increasing the already substantial bleeding risk is unknown.

Another factor to be considered is the availability of alternative treatments. Coronary artery disease (CAD) can be accompanied by symptomatic chest pain or silent ischemia which affects patients' quality of life. CAD is treatable, but if left untreated, the condition can progress to further stenosis within the arteries, increased symptoms, and the need for revascularization. Available treatments for CAD include medical

therapy, percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) surgery. When treatment for coronary artery disease beyond medications and lifestyle changes is warranted, patients often choose stent deployment over surgical revascularization due to shorter recovery times and the less invasive nature of PCI. The risks associated with use of drug eluting stents are already well established, and in comparison to medical therapy, PCI has been shown to reduce the incidence of angina and increase quality of life.

At the time of PMA submission, no DES were indicated for the treatment of patients at high bleeding risk. The relative safety and effectiveness of the BioFreedom DCS with one month of DAPT compared with a current generation DES followed by a similar DAPT duration in the US HBR population is therefore not known. The ONYX ONE trial provides some preliminary insight in an OUS population, showing similar performance in the primary composite safety endpoint of cardiac death, MI, and definite/probable stent thrombosis at one year.

Patients not at high risk for bleeding were not studied in the pivotal trial and the benefit/risk profile of the BioFreedom DCS in the broader PCI patient population compared to other contemporary DES is therefore unknown.

1. Patient Perspectives
   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for improving coronary luminal diameter in patients at high risk for bleeding with symptomatic ischemic heart disease due to de novo lesions of length ≤ 32 mm in native coronary arteries with a reference diameter ranging between 2.25 mm and 4.0 mm, the probable benefits outweigh the probable risks.

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. Data from the LEADERS FREE II study support the safety and effectiveness of the BioFreedom Drug Coated Coronary Stent System for the treatment of patients at high risk of bleeding.

XIV. CDRH DECISION

CDRH issued an approval order on April 14, 2022. The final conditions of approval cited in the approval order are described below.

1. You will perform drug release testing of expired and variant samples using in vitro drug release (IVR) test conditions identified in your prior analysis (Step 1). To fulfill this condition of approval, you agree to use your smallest stent sizes (both diameter

and length) for the determination of medium volumes in the planned Step 2 testing, inclusion of additional sampling time points of 12, 18, and 48 hours, and to report percent IVR profile data considering both drug load/amount normalized (where applicable) and percent of target label claim.

2. Long-term drug stability studies will be completed on five finished product batches representing the commercial process each year, with product codes rotating in a 4 year cycle. All batches for these studies will be stored at Long Term Conditions of 25°C ± 2°C/60% RH ± 5%, per ICH Q1A(R2). Testing for all studies will occur at 0, 3, 6, 9, 12, 18, 24, and 36 months.

3. Final Reporting of the LEADERS FREE II (LFII) Clinical Study. The LFII Clinical Study (G130034) was a prospective, single arm, multi-center, multi-national, open label trial to evaluate the safety and effectiveness of the BioFreedom DCS in patients with coronary artery disease who were at high risk of bleeding. Patients received percutaneous coronary intervention (PCI) with the BioFreedom DCS followed by one month of dual antiplatelet therapy (DAPT) and followed through 36 months post-index procedure. To fulfill this condition of approval, you agree to provide the final clinical outcomes to FDA through 36 months post-procedure on patients enrolled in the LFII Clinical Study.

The applicant's manufacturing facilities have been found to be in compliance with the device Quality System (QS) Regulation (21 CFR 820), via the supporting documentation provided in P190020, and through a risk-based assessment.

XV. APPROVAL SPECIFICATIONS

Directions for use: See device 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

Cutlip, Donald E., Stephan Windecker, Roxana Mehran, Ashley Boam, David J. Cohen, Gerrit-Anne van Es, P. Gabriel Steg, et al. 2007. "Clinical End Points in Coronary Stent Trials." *Circulation* 115 (17): 2344–51. https://doi.org/10.1161/CIRCULATIONAHA.106.685313.

Mehran, Roxana, Alexandra J Lansky, Bernhard Witzenbichler, Giulio Guagliumi, Jan Z Peruga, Bruce R Brodie, Dariusz Dudek, et al. 2009. "Bivalirudin in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction (HORIZONS-AMI): 1-Year Results of a Randomised Controlled Trial." *The Lancet* 374 (9696): 1149–59. https://doi.org/10.1016/S0140-6736(09)61484-7.

Räber, Lorenz, Henning Kelbæk, Miodrag Ostojic, Andreas Baumbach, Dik Heg, David Tüller, Clemens von Birgelen, et al. 2012. "Effect of Biolimus-Eluting Stents With Biodegradable Polymer vs Bare-Metal Stents on Cardiovascular Events Among Patients With Acute Myocardial Infarction: The COMFORTABLE AMI Randomized Trial." *JAMA* 308 (8): 777–87. https://doi.org/10.1001/jama.2012.10065.

Sabaté, Manel, Salvatore Brugaletta, Angel Cequier, Andrés Iñiguez, Antonio Serra, Rosana Hernádez-Antolín, Vicente Mainar, et al. 2014. "The EXAMINATION Trial (Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction): 2-Year Results From a Multicenter Randomized Controlled Trial." *JACC: Cardiovascular Interventions* 7 (1): 64–71. https://doi.org/10.1016/j.jcin.2013.09.006.

Spaulding, Christian, Emmanuel Teiger, Philippe Commeau, Olivier Varenne, Ezio Bramucci, Michel Slama, Keavin Beatt, et al. 2011. "Four-Year Follow-Up of TYPHOON (Trial to Assess the Use of the CYPHer Sirolimus-Eluting Coronary Stent in Acute Myocardial Infarction Treated With BallOON Angioplasty)." *JACC: Cardiovascular Interventions* 4 (1): 14–23. https://doi.org/10.1016/j.jcin.2010.10.007.

Steudel, Wolfgang, Colleen Dingmann, Yan-Ling Zhang, Jamie Bendrick-Peart, Claudia Clavijo, John Shulze, Ronald Betts, and Uwe Christians. 2011. "Randomized, Double-Blind, Placebo-Controlled, Single Intravenous Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of the Novel Coronary Smooth Muscle Cell Proliferation Inhibitor Biolimus A9 in Healthy Individuals." *The Journal of Clinical Pharmacology* 51 (1): 29–39. https://doi.org/10.1177/0091270010361255.

Thygesen, Kristian, Joseph S. Alpert, Allan S. Jaffe, Maarten L. Simoons, Bernard R. Chaitman, and Harvey D. White. 2012. "Third Universal Definition of Myocardial Infarction." *Circulation* 126 (16): 2020–35. https://doi.org/10.1161/CIR.0b013e31826e1058.

Valgimigli, Marco, Athanasios Patialiakas, Attila Thury, Eugene McFadden, Salvatore Colangelo, Gianluca Campo, Matteo Tebaldi, et al. 2015. "Zotarolimus-Eluting Versus Bare-Metal Stents in Uncertain Drug-Eluting Stent Candidates." *Journal of the American College of Cardiology* 65 (8): 805–15. https://doi.org/10.1016/j.jacc.2014.11.053.

Windecker, Stephan, Azeem Latib, Elvin Kedhi, Ajay J. Kirtane, David E. Kandzari, Roxana Mehran, Matthew J. Price, et al. 2020. "Polymer-Based or Polymer-Free Stents in Patients at High Bleeding Risk." *New England Journal of Medicine* 382 (13): 1208–18. https://doi.org/10.1056/NEJMoa1910021.