SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

DEVICE GENERIC NAME:	Replacement Heart Valve
DEVICE TRADE NAME:	Freedom SOLO Stentless Heart Valve SOLO Smart Stentless Heart Valve (Aortic sizes: 21 mm, 23 mm, 25 mm, and 27 mm)
DEVICE PRODUCT CODE:	LWR
APPLICANT'S NAME AND ADDRESS:	Sorin Group Canada Inc. 5005 North Fraser Way Burnaby, British Columbia V5J 5M1 Canada
DATE OF PANEL RECOMMENDATION:	None
Premarket Approval Application (PMA) NUMBER:	P130011
DATE OF FDA NOTICE OF APPROVAL:	June 24, 2014

II. INDICATIONS FOR USE

The Freedom SOLO and the SOLO Smart Stentless Heart Valves are indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves.

III. CONTRAINDICATIONS

None known.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Freedom Solo and Solo Smart labeling.

V. DEVICE DESCRIPTION

The Freedom SOLO and the SOLO Smart valves are stentless bioprosthetic heart valves made of bovine pericardium stabilized in buffered glutaraldehyde solutions and indicated for the replacement of damaged or malfunctioning aortic heart valves or prostheses in humans (see **Figure 1** for a representation of the SOLO valve without holders).

The SOLO Smart heart valve represents a modification of the Freedom SOLO Stentless heart valve, where the same valve prosthesis is attached to a flexible holder that acts as a temporary stent. The flexible holder is made of shape- memory alloy (Nitinol) and is designed to provide support to the valve while suturing and to enhance the ergonomics of implantation. Once the valve is sutured to the aortic root, the holder is removed leaving the stentless valve in place.

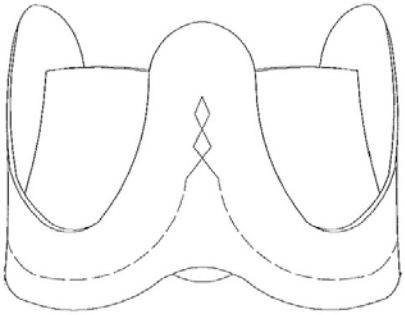
The prosthesis is designed for implantation in a supraannular position, with a single suture line.

The Freedom SOLO and the SOLO Smart valves consist of two pericardial sheets shaped according to a patented process. The pericardial tissue is selected and fixed in a glutaraldehyde based process in which the stabilizing agent reacts under dynamic conditions. The first sheet has the form of three valvular cusps arranged to allow the blood to flow in only one direction. The second sheet has an outflow edge that allows suturing to the aortic wall.

The two pericardium sheets are connected with a suture made of a thread coated with Carbofilm^{TM}, a thin film of turbostratic carbon with a high density.

The prosthesis is treated for the elimination of aldehyde residues and stored in a buffered solution without aldehydes.

Figure 1 – SOLO Heart Valve



The Freedom SOLO valve is packaged with a rigid valve holder. The SOLO Smart valve is identical to the Freedom SOLO valve, but is packaged with a flexible valve holder that is attached to the valve by means of a polypropylene suture thread.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The alternative treatments to the Freedom SOLO and SOLO Smart valves include drug therapy or surgical treatments such as annuloplasty or valvuloplasty (with or without the use of implantable materials). If patients require replacement of his or her native or previously implanted prosthetic valve, the alternatives include other commercially available mechanical valves or bioprosthetic valves, or a homograft. The choice of replacement valve depends on an assessment of patient factors which include age, preoperative condition, anatomy, and the patient's ability to tolerate long-term anticoagulant therapy. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his or her physician to select the method that best meets expectations and lifestyles.

VII. MARKETING HISTORY

The Freedom SOLO valve received CE Mark in 2004, whereas the SOLO Smart valve received CE Mark in 2013. Both devices were first made available to the European market The Freedom SOLO and the SOLO Smart valves are currently distributed in the following countries: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iran, Israel, Italy, The Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland, Turkey, Ukraine, and the United Kingdom. This Freedom Solo and SOLO Smart valves have never been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events potentially associated with the use of bioprosthetic heart valves (in alphabetical order) include, but may not be limited to:

- angina
- cardiac arrhythmia
- cardiac tamponade
- endocarditis
- heart failure (acute cardiac failure)
- hemolysis
- hemolytic anemia
- hemorrhage (bleeding)
- infection other than endocarditis
- myocardial infarction
- nonstructural valve dysfunction (e.g., entrapment by pannus or suture, inappropriate sizing or positioning, etc.)
- pericardial effusion
- paravalvular (perivalvular) leak
- prosthesis regurgitation
- prosthesis stenosis
- prosthesis thrombosis
- stroke or any related neurologic disorders
- structural valve deterioration (SVD) (e.g., calcification, leaflet tear or perforation, etc.)

- thromboembolism
- tissue dehiscence
- stenosis

It is possible that these adverse events could lead to:

- reoperation
- explantation
- permanent disability
- death

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

In Vitro Preclinical (Bench) Testing

In vitro testing was performed for the Freedom SOLO Stentless Heart Valve in accordance with ISO 5840: Cardiovascular Implants - Cardiac Valve Prostheses (2005).

The development of the SOLO Smart Heart Valve included the following additional laboratory tests: biocompatibility testing (including leaching analysis), distribution testing, and flexible holder usability and safety testing.

Hydrodynamic Performance

Hydrodynamic performance studies were completed on Freedom SOLO valve in accordance with the ISO 5840, Cardiovascular Implants – Cardiac Valve Prosthesis (2005). Testing included steady flow pressure drop, steady backflow leakage, pulsatile flow pressure drop, pulsatile flow regurgitation, flow visualization and the verification of the Bernoulli relationship. Commercially available bioprosthetic heart valves were used as controls. The characterization was conducted using both low compliant and high compliant chambers. Test results are summarized in **Table 1**.

Table 1 – Hydrodynamic Performance Summary

Test	Sample Size	Control Size	Results
Steady Flow Pressure Drop in low compliant chamber	3 valves of each size	1 valve, size 19*, 23, and 27 mm	Freedom SOLO valve shows lower pressure drop and higher EOA compared to the reference valve
Steady Flow Pressure Drop in high compliant chamber	3 valves, size 19, 23, and 27 mm	1 valve, size 19, 23, and 27 mm	Freedom SOLO valve shows lower pressure drop and larger EOA compared to the reference valve
Steady Backflow Leakage in low compliant chamber	3 valves of each size	1 valve, size 19, 23, and 27 mm	Freedom SOLO valve closes completely and maintains complete coaptation under all back pressure conditions
Steady Backflow Leakage in high compliant chamber	3 valves, size 19, 23, and 27 mm	1 valve, size 19, 23, and 27 mm	Freedom SOLO valve closes completely and maintains complete coaptation under all back pressure conditions
Pulsatile Flow Pressure Drop in low complaint chamber	3 valves of each size	1 valve, size 19, 23, and 27 mm	Freedom SOLO valve shows larger EOA than those required by the ISO5840:2005 acceptance criteria for aortic valves
Pulsatile Flow Pressure Drop in high complaint chamber	3 valves, size 19, 23, and 27 mm	1 valve, size 19, 23, and 27 mm	Freedom SOLO valve shows larger EOA than those required by the ISO5840:2005 acceptance criteria for aortic valves
Pulsatile Flow Regurgitation in low compliant chamber	3 valves of each size	1 valve, size 19, 23, and 27 mm	Freedom SOLO valve shows lower RF than those required by the ISO5840:2005 acceptance criteria for aortic valves
Pulsatile Flow Regurgitation in high compliant chamber	3 valves, size 19, 23, and 27 mm	1 valve, size 19, 23, and 27 mm	Freedom SOLO valve shows lower RF than those required by the ISO5840:2005 acceptance criteria for aortic valves
Flow Visualization in low compliant chamber	1 valve, size 19 mm	NA	A large vena contracta width is observed, indicating a large flow orifice area. No area of stasis or valvular incompetence, no jets due to regurgitant flow are observed.
Flow Visualization in high compliant chamber	1 valve, size 19 and 27 mm	NA	A large vena contracta width is observed, indicating a large flow orifice area. No area of stasis or valvular incompetence, no jets due to regurgitant flow are observed.
Bernoulli Relationship in low compliant chamber	1 valve, size 19, 23, and 27 mm	NA	Pressure drop results for Freedom SOLO demonstrate correlation with the Bernoulli relationship
Bernoulli Relationship in high compliant chamber	1 valve, size 19, 23, and 27 mm	NA	Pressure drop results for Freedom SOLO demonstrate correlation with the Bernoulli relationship

*size 19 is currently not approved in the USA

Structural Performance

Structural performance studies were conducted on Freedom SOLO valve through Accelerated Wear testing in accordance with the ISO 5840, Cardiovascular Implants – Cardiac Valve Prosthesis (2005). Commercially available bioprosthetic heart valves were used as controls. The characterization was conducted using low compliant chamber. All the valves passed the test. Test results are summarized in **Table 2**.

Table 2 – Structural Performance Summary

Test	Sample Size	Control Size	Results
Accelerated Wear	4 valves, 19, 23, and 27 mm	2 valves, size 19, 23, and 27 mm	Freedom SOLO valve maintains its performance and does not demonstrate significant wear out to 200 million cycles

Biocompatibility Studies

Biocompatibility testing for the Freedom SOLO valve was conducted in accordance with the requirements of ISO 10993, Biological Evaluations of Medical Devices. All biocompatibility testing was successful and the results are provided in **Table 3**.

Table 3 – Biocompatibility Studies for the Freedom SOLO valve

Test	Objectives	Results
Cytotoxicity	Assessment of test device toxicity on specific in vitro cell culture	Non-cytotoxic
Irritation (ISO Rabbit Intracutaneous Reactivity)	Evaluation of local irritation or toxic effects of leachable chemicals extracted from the test article following intra-cutaneous injection in rabbits	Non-irritant
Sensitization (ISO Guinea Pig Maximization Test)	Determination of the potential for contact sensitization by extracts of test device	No evidence of sensitization
Acute Systemic Toxicity (ISO Mouse Systemic Injection)	Evaluation of acute systemic toxicity of leachable chemicals extracted from the test article following a single intravenous injection in mice	Non-toxic
Pyrogen Test (USP Rabbit Pyrogen)	Assessment of the potential febrile response from material mediated reaction occurring after intravenous injection of test article extracts in rabbits	Non-pyrogenic
LAL test	Determination of the presence of bacterial endotoxins	Bacterial endotoxin-free

Test	Objectives	Results
Haemocompatibility	Assessment of the in vitro effects of the test article or its extract on blood properties, including hemolytic potential and alterations of the coagulation response	No alterations in blood
Genotoxicity (Ames test)	Evaluation of the potential of the test article to induce DNA reverse mutations in five strains of Salmonella typhimurium in the presence and absence of metabolic activation system	Non-mutagenic
Mouse Lymphoma Test	Detections of mutations at the thymidine kinase DNA locus caused by base pair changes, frameshift and small deletions.	Non-mutagenic
Implantation test (ISO Rabbit Subcutaneous and Intramuscular)	Evaluation of the test article local and systemic effects on living tissue throughout chronic implantation in rabbit	No signs of toxicity

In order to confirm the biological safety of the SOLO Smart valve, which is different from the Freedom SOLO only for the presence of the flexible holder, additional biocompatibility testing was carried out to account for the presence of the holder. The biocompatibility testing of the flexible holder was performed according to Good Laboratory Practices (**Table 4**).

Table 4 – Biocompatibility Studies on the SOLO Smart flexible holder

Test	Objectives	Results
Cytotoxicity by elution test	Assessment of test device toxicity on specific in vitro cell culture	Non-cytotoxic
Irritation (ISO Rabbit Intracutaneous Reactivity)	Evaluation of local irritation or toxic effects of leachable chemicals extracted from the test article following intra-cutaneous injection in rabbits	Non-irritant
Sensitization (ISO Guinea Pig Maximization Test)	Determination of the potential for contact sensitization by extracts of test device	Non sensitizing
Acute Systemic Toxicity (ISO Mouse Systemic Injection)	Evaluation of acute systemic toxicity of leachable chemicals extracted from the test article following a single intravenous injection in mice	No signs of acute toxicity
Pyrogenicity	Assessment of the potential febrile response from material mediated reaction occurring after intravenous injection of the test article in rabbits	Non-pyrogenic
Haemocompatibility	Assessment of the in vitro effects of the test article or its extract on blood properties, including hemolytic potential and alterations of the coagulation response	No alterations in blood

Test	Objectives	Results
Analysis of Nitinol leachables	Determination and toxicological evaluation of the levels of Nickel and Titanium potentially leaking from the SOLO flexible holder	No relevant Nitinol leaching substance released

B. Animal Studies

None. There was sufficient OUS clinical data on the Freedom SOLO valve to obviate the need for additional pre-clinical in vivo testing.

C. Additional Studies

Sterilization

The Freedom SOLO valve is provided sterile. The sterilization process consists of exposure to a liquid glutaraldehyde sterilant solution. The sterilization process has been validated to assure a sterility assurance level (SAL) of 10^{-6}.

Package Integrity

Package integrity studies were conducted after simulated shipping process (manual handling, vehicle stacking, vibration, low pressure hazard), to ensure integrity of packaging. The results demonstrate that the package integrity is maintained.

Product Integrity

Integrity of the finished device was evaluated after 4 years of real-time aging. This evaluation included testing on: pericardial tissue (shrinkage temperature, biomechanical properties, collagen content, tissue microstructure); storage solution (pH value, residuals), valve (hydrodynamic performance and accelerated wear testing) and jar (microbiological barrier and leaching analysis). Testing results demonstrated that the device integrity is maintained.

Distribution Testing

Both the Freedom SOLO valve and the SOLO Smart valve are provided sterile in a polycarbonate jar filled with a sterile phosphate buffer solution with Paraben. Distribution testing was conducted to verify the safety and effectiveness of the packaging during shipping.

Testing was first subjected to environmental conditioning according to ASTM D4169-09 standards. After the completion of the environmental conditioning,

distribution simulation testing was performed according to ISO 11607-1:06 and ASTM standards. Testing results demonstrated that the package integrity was maintained.

Testing of the SOLO Smart (i.e., the SOLO valve with flexible holder) proved the safety and effectiveness of the flexible holder design through the full battery of distribution testing.

Flexible Holder Usability and Safety

The design of the flexible holder was validated in terms of:

- adequate connection between holder and support disk (push-off test);
- adequate connection between holder and surgical instrument;
- resistance to fatigue of holder and spring protection.

According to the test results, the usability of the flexible holder was considered validated in terms of its mechanical characteristics.

X. SUMMARY OF PRIMARY CLINICAL STUDY

A. Study design

The PMA clinical study for the Freedom SOLO valve was a prospective, multicenter, non-randomized, observational study without concurrent or matched controls. The study was conducted at 18 centers in Europe, 9 centers in the United States, and 6 centers in Canada. A total of 804 patients were implanted in the study, all of whom underwent isolated implantation of the Freedom SOLO valve in the aortic position. The implant period for the study was from March 17, 2009 to January 8, 2013. All sites in the study followed a common protocol including inclusion/exclusion criteria (listed below) and obtained an informed consent. Any differences in the inclusion/exclusion criteria between the European and North American sites are indicated in the sections below in italic fonts (the italic font applies to the North American sites).

The evaluation of safety involved a comparison of postoperative linearized late adverse event rates to the FDA Objective Performance Criteria (OPCs) and a comparison of postoperative early, linearized late, and Kaplan-Meier adverse event rates to literature-based control data. The evaluation of effectiveness involved a comparison of postoperative New York Heart Association (NYHA) functional classification data to baseline and literature-based control data and a comparison of postoperative echocardiographic hemodynamic data to literature-based control data.

1. Clinical Inclusion and Exclusion Criteria

Study Inclusion Criteria

Candidates for enrollment were those patients who met the following inclusion criteria:

a. The patient is male or female 18 years old or older.

b. The patient is willing to sign the informed consent. (*The subject or the subject's legal representative is willing to sign the informed consent.*)

c. The patient had a preoperative evaluation which indicated the need for native or prosthetic aortic valve replacement.

d. Any patient amenable to aortic valve replacement with biological prosthesis should be enrolled in the study, even in conjunction with valve repair, coronary artery bypass grafting, and other procedures.

e. The patient is located in a geographic location that will enable the subject to return to the study site for all follow-up examinations (i.e., geographically stable).

f. Patient will be available to the investigator(s) for postoperative follow- up beyond one year.

Study Exclusion Criteria

Patients were not enrolled in the study if any of the exclusion criteria listed below was met:

a. The patient has preexisting valve prosthesis in the mitral, pulmonary, or tricuspid position.

b. The patient requires a double or triple valve replacement (a valve repair is not considered an exclusion criterion).

c. The patient has a previously implanted SOLO valve, within the clinical study, that requires replacement.

d. The patient has active endocarditis. (*The patient has active endocarditis or myocarditis*.)

e. The patient is or will be participating in a concomitant research study of an investigational product.

f. The patient is a minor, intravenous drug user, alcohol abuser, prisoner, institutionalized, or is unable to give informed consent.

g. The patient has a major or progressive non-cardiac disease that, in the investigator's experience, results in a life expectancy of less than 1 year, or the implant of the device produces an unacceptable increased risk to the patient.

h. The patient is pregnant or lactating. (*The patient is pregnant, planning to become pregnant, or lactating*.)

i. Patients with congenital bicuspid aortic valve.

j. Patients are known to be noncompliant or are unlikely to complete the study.

k. (*The subject is undergoing renal dialysis for chronic renal failure or has been diagnosed with hyperparathyroidism*.)

l. (*The subject has had an acute preoperative neurological deficit, myocardial infarction, or cardiac event that has not returned to baseline or stabilized ≥ 30 days prior to the planned valve implant surgery*.)

m. (*The subject has an extensive calcification of the aortic root where removal of the calcified tissue cannot be achieved*.)

n. (*The subject has a significantly dilated aortic root that is not surgically corrected*.)

o. (*The subject requires replacement of the aortic root / full root procedure*.)

2. Follow-up Schedule

Patients were evaluated at each of the following time intervals:

- preoperatively,
- at implant,
- in the early postoperative period (at hospital discharge or within 30 days postoperatively),
- in the late postoperative period (between 3 and 6 months postoperatively),
- at 1 year (between 11 and 13 months postoperatively), and
- annually until study completion.

Preoperative demographic and baseline data including NHYA functional classification were collected before surgery. Postoperative data, including blood value, NYHA functional class, and echocardiography data were collected at each follow-up. All echos were sent to the Echocardiography Core Laboratory for interpretation. Adverse event data were collected at the time of occurrence or site notification using the definitions from Edmunds et al.[1]

3. Clinical Endpoints

The objectives of the clinical investigation were:

- to demonstrate that the complication and survival rates for the Freedom SOLO valve are comparable to appropriate historical controls manifested as Objective Performance Criteria (OPCs), and to that reported in the literature for other stentless bioprostheses and stented pericardial valves;
- to demonstrate that the hemodynamic performance of the Freedom SOLO valve is comparable to that reported in the literature for other stentless bioprostheses and stented pericardial valves; and
- to demonstrate clinically significant improvement in overall patient condition by comparison of preoperative and postoperative NYHA functional classifications, and to demonstrate that the postoperative NYHA functional classification is comparable to that reported in the literature for other stentless bioprostheses and stented pericardial valves.

B. Accountability of PMA Cohort

As noted above, the Freedom SOLO valve cohort consisted of 804 patients who underwent isolated aortic valve replacement from March 17, 2009 to January 8, 2013. The cut-off date for data included in the PMA application was February 19, 2013.

Total follow-up through last protocol evaluation for all 804 patients was 1101.5 patient-years with a mean follow-up of 16.5 ± 10.8 months (1.4 ± 0.9 years) and range of follow-up of 0 to 40.5 months (0 to 3.4 years).

Table 5 summarizes patient compliance in the study.

Table 5 – Patient Compliance

Visit interval	Eligible patients (n)	Completed n_1 (%[1])
Preoperative	804	804 (100%)
Early Post-op	787	787 (100%)
3-6 Months	697	661 (94.8%)
1 Year	584	572 (97.9%)
2 Years	366	363 (99.2%)
3 Years	70	70 (100%)

[1] Percent calculated as = n_1 /n

C. Study Population: Preoperative Patient Demographics and Characteristics

The study cohort consisted of 804 patients who received an isolated aortic valve implant with the Freedom SOLO valve at sites in Europe (EU), Canada, and the United States (NA). **Table 6** presents the patients' preoperative characteristics including the demographic profile of the study cohort. The mean age at implant was 74.9 years old (range 42.4 - 90.3 years). There were 45.1% females and 54.9% males. The majority of the patients were in NYHA Classes II and III.

Table 6 – Freedom SOLO Study Preoperative Patient Characteristics

Total patients in study cohort	804
Mean age ± SD (range)	74.9 ± 6.3 (42-90)
Age	
40-49	2 (0.2%)
50-59	10 (1.2%)
60-69	159 (19.8%)
70-79	484 (60.2%)
80-89	146 (18.2%)
90-99	3 (0.4%)
Sex	
F	363 (45.1%)
M	441 (54.9%)
Race	
White	796 (99.0%)
Black	2 (0.2%)
Asian	3 (0.4%)
Other[1]	3 (0.4%)

[1] One Native American, one Persian, one Filipino

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the treated cohort of 804 patients over the course of 1101.5 patient-years. The key safety outcomes and adverse event rates for aortic valve replacement for the study are presented in **Table 7**. The data are presented as percentages for early events, linearized rates (%/patient-year) for the late events, and "freedom from event" as actuarial analyses at years 1, 2, and 3 post-implant.

Table 7 – Observed Adverse Event Rates

(Total patients N = 804, Cumulative follow-up = 1101.5 patient-years and 1099.6 late patient-years)

Adverse event	Early events [1]		Late events [2]		Freedom From Event (%) [95% CI] [4]		
	n	%	n	%/pt-yr [3]	1 year	2 years	3 years
All mortality	14	1.7	50	4.55	94.0 [91.9 – 95.5]	90.5 [87.7 – 92.7]	82.6 [75.7 – 89.6]
Valve-related death	1	0.1	11	1.00	98.8 [97.6 – 99.4]	98.3 [96.8 – 99.1]	95.5 [89.2 – 98.2]
Explant	4	0.5	19	1.73	97.4 [95.8 – 98.3]	96.5 [94.6 – 97.8]	95.2 [91.3 – 97.4]
All bleeding	36	4.5	35	3.18	86.2 [83.6 – 88.5]	85.7 [83.0 – 88.1]	84.7 [81.3 – 87.6]
Major bleeding	23	2.9	25	2.27	88.4 [85.9 – 90.5]	87.9 [85.3 – 90.1]	87.9 [85.3 – 90.1]
Anticoagulation-related bleeding	3	0.4	9	0.82	98.6 [97.4 – 99.2]	98.1 [96.5 – 98.9]	97.0 [93.4 – 98.6]
Thromboembolic events	17	2.1	40	3.64	93.3 [91.1 – 94.9]	89.9 [87.1 – 92.2]	87.4 [82.7 – 91.1]
Major thromboembolic events	12	1.5	14	1.27	96.9 [95.3 – 97.9]	95.6 [93.6 – 97.0]	94.3 [90.5 – 96.7]
Endocarditis	2	0.2	17	1.55	97.6 [96.1 – 98.5]	97.0 [95.3 - 98.2]	97.0 [95.3 - 98.2]
Valve thrombosis	0	0	0	0.00	100 [100 - 100]	100 [100 - 100]	100 [100 - 100]
Structural valve deterioration	0	0	6	0.55	99.8 [98.6 - 100]	99.2 [97.4 – 99.7]	97.1 [91.8 – 99.0]
Nonstructural valve dysfunction[5]	13	1.6	9	0.82	97.2 [95.7 – 98.2]	97.2 [95.7 – 98.2]	94.6 [89.3 – 97.3]
Major Paravalvular leak	4	0.5	2	0.18	99.3 [98.4 – 99.7]	99.3 [98.4 – 99.7]	98.0 [92.6 – 99.5]
Hemolysis secondary to PVL	0	0	0	0.00	100 [100 - 100]	100 [100 - 100]	100 [100 - 100]

[1]- Early valve related events include postoperative events occurring 1-30 days post-implant. Early events rates calculated as the number of events divided by the total number of patients, times 100.

[2]-Late postoperative events (>30 days).

[3]-Late adverse event rate(%/pt-yr) is calculated as the number of late events divided by the total late patient-years, times 100.

[4]-Freedom from first event (early or late) rates were calculated using the Kaplan-Meier method.

[5]-Including paravalvular leak.

2. Effectiveness Results

The analysis of effectiveness was based on the evaluable patients at the annual endpoints. Key effectiveness outcomes are presented in **Table 8** and **Table 9**.

Reduction in mean gradients and increase in EOA were observed at one year follow up. An improvement at one year follow up was reported in NYHA class. This improvement remained stable over time. The percentages of AVR patients with postoperative aortic valvular regurgitation are similar to those in the literature-based control articles which have such data.

Table 8 – Effectiveness Outcome: NYHA Functional Classification

	Preoperative (n=804)	**1 year follow-up (n=572)**	**2 years follow-up (n= 354)**	**3 years follow-up (n=70)**
Class I	46 (5.7%)	374 (65.4%)	225 (63.6%)	43 (61.4%)
Class II	352 (43.8%)	176 (30.8%)	113 (31.9%)	21 (30.0%)
Class III	383 (47.6%)	15 (2.6%)	16 (4.5%)	6 (8.6%)
Class IV	22 (2.7%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
Unable to assess	1 (0.1%)	5 (0.9%)	-	-

Table 9 – Effectiveness Outcomes at 1 Year Follow-up Visit: Hemodynamic Results

Hemodynamic parameter	**19 mm**	**21 mm**	**23 mm**	**25 mm**	**27 mm**
1 Year Postoperative	N[1]=6	N=83	N=177	N=192	N=79
Mean Gradient [mmHg]	N[2]=4	n=74	n=153	n=176	n=69
Mean ±SD	10.6 ± 2.9	9.6 ± 4.4	7.7 ± 4.3	6.0 ± 2.9	5.6 ± 2.9
EOA [cm^2]	n=4	n=65	n=131	n=160	n=65
Mean ±SD	0.9 ± 0.2	1.2 ± 0.3	1.5 ± 0.4	1.7 ± 0.5	1.8 ± 0.5
Regurgitation	n=5	n=83	n=176	n=192	n=78
None	2 (40.0%)	32 (38.6%)	78 (44.3%)	93 (48.4%)	39 (50.0%)
Trace	1 (20.0%)	42 (50.6%)	76 (43.2%)	77 (40.1%)	24 (30.8%)
Mild	2 (40.0%)	7 (8.4%)	13 (7.4%)	20 (10.4%)	14 (17.9%)
Moderate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown[3]	0 (0%)	2 (2.4%)	9 (5.1%)	2 (1.0%)	1 (1.3%)

[1] N=number of patients with a complete echo per valve size.

[2] n=number of patients per valve size with available hemodynamic parameter.

[3] Unknown included echos that did not contain appropriate images to evaluate aortic regurgitation.

There were 441 males (54.9%) and 363 females (45.1%) in the Freedom SOLO valve study cohort. The ratio of male and female in the study is consistent with the distribution of male and female patients undergoing cardiac surgery.

The log-rank test was used to compare valve-related adverse events and outcomes by gender. There were no statistically significant differences between males and females for any safety endpoints (see **Table 10**). Therefore the results of the analysis of valve-related adverse events in the study are representative for both men and women.

Effectiveness endpoints were compared for both males and females. The two groups exhibited a significant improvement in NYHA functional classification at1 year follow-up. However, there was a significant difference in the 1 year NYHA functional class distribution between males and females (see **Table 11**).

Mean and peak pressure gradient, effective orifice area (EOA), and regurgitation severity were compared between males and females at 1 year follow-up. For all hemodynamic variables, p-values were based on the Wilcoxon signed-rank test. No differences were noted between the two groups.

Table 10 – Early Mortality and 1 Year Survival Comparisons by Gender

Parameter	**Female (N=363)**	**Male (N=441)**	**P-value[1]**
Early (≤ 30 days) mortality	1.4% (5/363)	2.0% (9/441)	0.521
Percent Survival at 1 Year (± SE[2])			
All mortality	95.3 ± 1.2	92.3 ± 1.4	0.210
Cardiovascular-related death	98.4 ± 0.7	97.4 ± 0.8	0.681
Valve-related death	98.7 ± 0.6	98.9 ± 0.6	0.775

[1] P-values are based on the results from Fisher's Exact test for operative mortality rate comparison between 2 groups and the Log-rank test for comparing survival distributions between males and females.

[2] SE = standard error.

Table 11 – Comparison of 1 Year NYHA Functional Classification by Gender

Postoperative NYHA Class (1 Year)	Female (n=261)	Male (n=311)	P-value[1]
Class I	146 (55.9%)	228 (73.3%)	**0.046**
Class II	99 (37.9%)	77 (24.8%)	
Class III	12 (4.6%)	3 (1.0%)	
Class IV	-	2 (0.6%)	
Unable to assess	4 (1.5%)	1 (0.3%)	

[1] P-value based on Fisher's exact test comparing NYHA Class I/II and Class III/IV by gender.

The statistical comparisons of safety and effectiveness data by gender support the conclusion that there is no gender bias in the Freedom SOLO valve cohort, and that therefore the results of the overall study regarding safety and effectiveness can be generalized for males and females.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 33 principal investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The clinical evaluation of effectiveness was based on the evaluation of NYHA functional classification data and echocardiographic hemodynamic data.

There was a statistically significant improvement in NYHA functional classification, (p-value <0.01) from the preoperative to one year visit. More than 85% of the clinical study patients had none or trace regurgitation at one year. A comparison of the Freedom SOLO valve hemodynamic data to literature-based hemodynamic data shows similar hemodynamic performance to other stentless and stented bioprosthetic aortic valves. The results of the clinical study therefore demonstrated the effectiveness of the Freedom SOLO Replacement Heart Valve.

B. Safety Conclusions

The results from the in vitro pre-clinical studies performed for biocompatibility, hydrodynamic performance, and structural performance demonstrate that the Freedom SOLO and the SOLO Smart valves are safe and effective and, therefore, suitable for long-term implant.

The results of the Freedom SOLO valve clinical investigation demonstrate that the adverse event rates for the major safety endpoints are significantly lower than the established standard of twice the FDA's Objective Performance Criteria for a bioprosthetic valve, with the exception of bleeding. Detailed analysis of the bleeding rates showed no clear indication that the bleeding events were directly related to the Freedom SOLO valve. Mortality, reoperation, and explant rates also support the safety of the valve.

C. Benefit-Risk Conclusions

The Freedom SOLO valve provides clinically significant improvement in NYHA functional classification and hemodynamic function compared to that which was present preoperatively. The postoperative NYHA functional classification and hemodynamic data are similar to those in the literature-based control articles which have such data.

There were elevated linearized late rates for all and major bleeding for the Freedom SOLO valve, however the data indicated that these bleeding events were related to factors such as anti-coagulation or occurred in areas other than the thoracic areas of patients. The elevated bleeding rates were therefore not directly related to the Freedom SOLO valve. The other potential risks associated with the Freedom SOLO valve are similar to those for other bioprosthetic heart valves on the market, and the safety profile of this device is within established objective performance criteria guidelines and similar to literature-based control data.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for the Freedom SOLO and SOLO Smart heart valves as indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves.

D . Overall Conclusion

The data in the PMA application demonstrate a reasonable assurance that the Freedom SOLO and the SOLO Smart valves are a safe and effective replacement for a malfunctioning native or prosthetic aortic heart valve when used in accordance with the Indications for Use.

XIV. CDRH DECISION

CDRH issued an approval order on June 24, 2014.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See 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

1. Edmunds LH, *et al.* Guidelines for reporting morbidity and mortality after cardiac valvular operations. *J Thorac Cardiovasc Surg* 1996;112:708-711.