SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Replacement Heart Valve, Aortic

Device Trade Name: Avalus™ Bioprosthesis, Model 400

Device Procode: LWR

Applicant's Name and Address: Medtronic, Inc.
1851 E. Deere Avenue
Santa Ana, CA 92705

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170006

Date of FDA Notice of Approval: July 31, 2017

II. INDICATIONS FOR USE

The Avalus™ bioprosthesis is indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Avalus bioprosthesis labeling.

V. DEVICE DESCRIPTION

The Avalus bioprosthesis (Figure 1) is a stented bovine pericardial tissue valve intended to replace diseased, damaged or malfunctioning native or prosthetic aortic valves via surgical implantation. The valve is manufactured by suturing valve leaflets, made from laser cut bovine pericardial tissue, into a trileaflet configuration within a polyetheretherketone (PEEK) base frame and trileaflet support frame. A polyester sewing ring is integrated into the inflow aspect of the base frame cover to allow for suturing and seating of the valve in the supra-annular position.

Figure 1: Avalus Bioprosthesis

The Avalus bioprosthesis is processed with alpha oleic acid (AOA™), which is an antimineralization treatment that has been shown to mitigate leaflet calcification in animal studies. A disposable valve holder (Figure 2) is attached to the outflow of the valve to facilitate implantation.

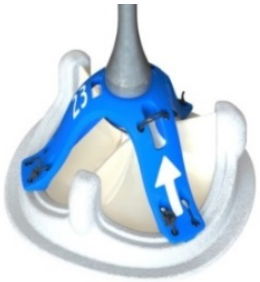

Figure 2: Avalus Valve Holder

The disposable holder is designed to fit the reusable Valve Handle, Model 7420 (Figure 3), and features a single cut point to remove the holder from the valve. Double ended sizers (Figure 4) are used to select the appropriate valve size. The barrel end represents the valve orifice while the replica end imitates the prosthesis geometry.

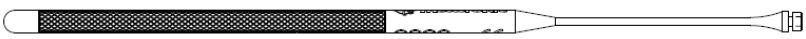

Figure 3: Avalus Valve Handle, Model 7420

Figure 4: Avalus Sizer, Model 7400S

The Avalus bioprosthesis (Model 400) is available in sizes 19, 21, 23, 25, and 27 mm. For further details, refer to the Avalus Bioprosthesis Instructions for Use.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of diseased, damaged, or malfunctioning aortic heart valves. Alternative treatments include palliative medical therapy, aortic balloon valvuloplasty (opening the narrowed aortic valve with a balloon catheter), aortic valve repair, transcatheter aortic valve replacement , treatment with homografts, and surgical replacement with another commercially available mechanical or bioprosthetic valve. 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

The Avalus bioprosthesis has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Angina
- Cardiac dysrhythmias
- Endocarditis
- Heart failure
- Hemolysis
- Hemolytic anemia
- Hemorrhage
- Infection other than endocarditis
- Leak, transvalvular or paravalvular
- Myocardial infarction
- Nonstructural valve dysfunction (leaflet entrapment/impingement, obstructive pannus ingrowth, suture dehiscence, inappropriate sizing or positioning, or other)
- Pericardial effusion or tamponade
- Prosthesis regurgitation
- Prosthesis stenosis
- Prosthesis thrombosis
- Stroke
- Structural valve deterioration (calcification, leaflet tear or perforation, or other)
- Thromboembolism
- Tissue dehiscence
- Transient ischemic attack

These complications could lead to:

- Reoperation
- Explant of the bioprosthesis
- Permanent disability
- Death

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

1. Biocompatibility

Biocompatibility evaluations were completed on the Avalus bioprosthesis in accordance with ISO 10993-1:2009/AC:2010, *Biological Evaluation of Medical Devices Part 1: Evaluation and testing within a risk management process*, and FDA's General Program Memorandum No. G95-1, *Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.*" The required testing for each component was determined based on the nature and duration of body contact in accordance with ISO 10993-1:2009/AC:2010. Test articles consisted of the patient-contacting device components after exposure to all manufacturing processes, including sterilization. The biocompatibility test results for the Avalus bioprosthesis are summarized in Table 1.

Table 1. Summary of Avalus Bioprosthesis Biocompatibility Testing

Biological Effect per ISO 10993-1	Test Method	Results
Cytotoxicity	Colony Assay	Pass
Sensitization	ISO Guinea Pig Maximization Sensitization	Pass
Irritation or Intracutaneous Reactivity	Intracutaneous Irritation in Rabbits	Pass
Systemic Toxicity	Acute Systemic Toxicity in Mice	Pass
	USP Material Mediated Pyrogen	Pass
Genotoxicity	Ames Bacterial Reverse Mutation	Pass
	Chromosomal Aberration in Chinese Hamster Ovary (CHO) Cells	Pass
	Mouse Peripheral Blood Micronucleus Study	Pass
Implantation	4 weeks - ISO Muscle Implantation Study in Rabbit	Pass
	13 Weeks - Systemic Toxicity in Rats Following Subcutaneous Implantation	Pass
Hemocompatibility	*In vitro* Hemolysis (Indirect)	Pass
	In vitro Hemolysis (Direct Method)	Pass
	Partial Thromboplastin Time	Pass
	Complement Activation (C3a/SC5b-9)	Pass

2. Hydrodynamic Performance

A comprehensive *in vitro* testing program was completed in accordance with EN ISO 5840:2009, *Cardiovascular implants – Cardiac valve prostheses.* Hydrodynamic performance testing results are provided in Table 2.

Table 2: Summary of Avalus Hydrodynamic Performance Testing

Test	Test Description	Test/Reference Articles	Results
Pulsatile Forward Flow	This test evaluated the pressure gradients and effective orifice area of the Avalus bioprosthesis under pulsatile flow conditions.	Test: Avalus, all sizes Reference: Edwards Perimount Magna Ease sizes 19, 23, 29 mm	The Avalus bioprosthesis demonstrated hydrodynamic results comparable to the reference valve and met the minimum effective orifice area required by ISO 5840:2009.
Pulsatile Back Pressure	This test provided information about the regurgitant volumes of the Avalus bioprosthesis under pulsatile flow conditions.	Test: Avalus, all sizes Reference: Edwards Perimount Magna Ease sizes 19, 23, 29 mm	The Avalus bioprosthesis showed acceptable hydrodynamic results, comparable to those of the reference valve, and did not exceed the regurgitant fractions specified in ISO 5840:2009.
Dynamic Regurgitation	This test characterized the regurgitant volume of the Avalus bioprosthesis under pulsatile flow conditions at various beats per minute.	Test: Avalus, all sizes Reference: Edwards Perimount Magna Ease sizes 19, 23, 29 mm	The total regurgitant volumes for all sizes showed a decrease with increase in beat rate. Varying back pressure had minimal to no impact on the regurtitant volumes for all sizes.
Leaflet Kinematic Characterization	This test was performed to provide qualitative information about the Avalus bioprosthesis leaflet function during valve opening and closing under pulsatile flow conditions.	Test: Avalus, all sizes Reference: Edwards Perimount Magna Ease sizes 19, 23, 29 mm	All valves exhibited synchronicity in leaflet closure, with full opening and closing.
Flow Visualization Characterization	This test provided information about the flow characteristics of the Avalus bioprosthesis under pulsatile conditions.	Test: Avalus, smallest size Reference: N/A	The Avalus bioprosthesis demonstrated acceptable flow characteristics. The flow profile was symmetric and centered and flow exited the valve in

Test	Test Description	Test/Reference Articles	Results
			parallel streamlines. There is flow in the sinus region behind the valve leaflets and there is no particle stagnation. The peak velocity and peak major RSS data were acceptable.
Bernoulli Relationship	This test verified the use of the Bernoulli relationship in calculating transvalvular pressure gradients with Doppler ultrasound.	Test: Avalus, smallest, medium, and largest sizes Reference: N/A	The results of pressure drop testing indicate that standard Doppler measurement techniques can be used to assess the pressure gradient across the Avalus bioprosthesis.

3. Structural Performance, Material Property, and Device Specific Testing

Structural performance, material property, and device specific testing was performed on the Avalus bioprosthesis in accordance with EN ISO 5840:2009 and is summarized in Table 3.

Table 3. Summary of Avalus Bioprosthesis Structural Performance

Test	Test Description	Test/Reference Articles	Results
Structural Performance Testing			
Accelerated Wear Testing	This test assessed the structural longevity of the Avalus bioprosthesis over simulated conditions out to 200M cycles (equates to five-year lifetime).	Test: Avalus, smallest, medium, and largest sizes Reference: Edwards Perimount Magna Ease sizes 19, 23, 29 mm	All valves survived durability testing to 200 million cycles in accelerated wear testers without functional impairment. At the completion of 200 million cycles, all valves met the effective orifice area and regurgitation fraction requirements of ISO 5840:2009.
Dynamic Failure Mode	This test applied increasing pressure loading to determine the ultimate failure	Test: Avalus, largest size	All test valve failures occurred

Test	Test Description	Test/Reference Articles	Results
	mode(s) of the Avalus bioprosthesis.	Reference: N/A	at pressures well above those expected *in vivo*.
Sewing Ring Integrity	This test evaluated the structural integrity and attachment strength of the sewing ring to the covered stent under static loading conditions.	Test: Avalus, smallest, medium, and largest sizes Reference: N/A	All test samples met the device specification for ultimate attachment strength.
Finite Element Analysis	This test characterized the maximum principal stress of the trileaflet support frame and base models using a finite element analysis model.	Test: All Avalus sizes were included in the analysis Reference: N/A	The findings of the stress analysis provide confidence that the structural components of the Avalus bioprosthesis are durable for their intended use.
Stent Post Deflection	This test provided information about the *in vitro* deflections for each commissure post of the Avalus bioprosthesis as a function of applied backpressure.	Test: Avalus, all sizes Reference: N/A	The test results showed that commissure post deflection increases directly with the valve size and differential pressure.
Stent Fatigue Testing	This test evaluated commissure post fatigue of the PEEK stent.	Test: Avalus, largest size Reference: N/A	No loss of structural integrity was observed in any of the frames at the completion of 600 million cycles.
Material Property Testing			
Stent Mechanical and Creep Characterization	This test characterized the mechanical properties of the PEEK material used in the trileaflet support frame and base component.	Test: PEEK specimens Reference: N/A	The PEEK material properties were within expectations.
Tissue Mechanical Properties	This test characterized the uniaxial tensile properties of bovine pericardium with respect to tissue orientation.	Test: Fixed bovine pericardium samples Reference: N/A	Testing indicated that bovine pericardial tissue is anisotropic in nature.
Absorption Study	This test characterized PEEK water absorption rate in an aqueous solution.	Test: PEEK specimens	The PEEK material

Test	Test Description	Test/Reference Articles	Results
		Reference: N/A	properties were within expectations.
Device Specific Testing			
Magnetic Resonance Imaging (MRI)	The purpose of this test is to evaluate the safety and compatibility of the device in conjunction with the use of MRI.	Test: N/A Reference: N/A	Because the Avalus bioprosthesis does not contain metal and poses no known hazards in an MR environment, it was determined to be MR safe on the basis of scientific rationale.
Dimensional Verification	This test verified the final dimensional specifications of the Avalus bioprosthesis.	Test: Avalus, all sizes Reference: N/A	All valve sizes met the dimensional specifications.
Human Factors Validation	This test validated that the usability of the Avalus bioprosthesis and its accessories was acceptable to qualified, trained, and experienced physicians.	Test: Avalus, all sizes Reference:N/A	The Avalus bioprosthesis showed generally very good performance and there were no surgical errors observed that would result in issues with patient safety.

B. Animal Studies

Two preclinical *in vivo* studies (90-day and 150-day) were performed to support the safety of the Avalus bioprosthesis. The studies evaluated the Avalus bioprosthesis compared to a Carpentier-Edwards PERIMOUNT Magna Ease control valve. A total of 10 test articles and four (4) control articles were implanted for 90 days, and a total of 11 test articles and four (4) control articles were implanted for 150 days. In both studies, the valves were implanted in the aortic position in an adult sheep model to most accurately simulate the human anatomy and physiology. The hemodynamic performance and valve related pathology characteristics observed in the test group (Avalus valve) were assessed in a chronic setting and compared with the same characteristics in the control group (Carpentier-Edwards PERIMOUNT Magna Ease

valve). As demonstrated through the results, the test articles met all the following acceptance criteria:

- Survival at 90 days and at 150 days with mortality rates consistent with literature and historic experience with the sheep model.
- Blood chemistry within normal ranges.
- Pathological findings were comparable to the control device within the normal variation seen in the sheep model.
- Hemodynamic changes over time were comparable to the control device, consistent with the variation in pathologic findings.

C. Additional Studies

1. Sterilization

The Avalus bioprosthesis is sterilized by liquid chemical sterilization in a glutaraldehyde solution. The sterilization process involves incubation of the valve in sterilant solution at an elevated temperature for a defined period of time. This process has been validated to a Sterility Assurance Level (SAL) of 10^{-6}.

2. Packaging and Shelf Life

The Avalus bioprosthesis is packaged in a glass jar filled with glutaraldehyde solution. The glass jar is placed in a shelf carton with a temperature indicator to identify products exposed to transient temperature extremes. The accessory components are packaged and marketed separately from the Avalus bioprosthesis.

The shelf life of the Avalus bioprosthesis is 1.5 years as demonstrated by functional product integrity testing on real-time aged samples and package integrity testing on accelerated-aged samples.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of aortic heart valve replacement with the Avalus bioprosthesis in the US, Canada, and Europe under IDE # G140056. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between May 12, 2014 and September 7, 2016. The database for this PMA reflected data collected through October 31, 2016 and included 962 patients. There were 36 investigational sites.

The Pericardial Surgical Aortic Valve Replacement (PERIGON) Trial was a prospective, non-randomized, multi-center, global trial for the Avalus bioprosthesis

implanted in patients requiring native or prosthetic aortic valve replacement. The design and analysis of this study was based on adverse event rates as compared to a set of established Objective Performance Criteria (OPC) and to literature-based control data. New York Heart Association (NYHA) functional classification status and hemodynamic performance of the valve by echocardiography were evaluated using a comparison to literature-based control data. The study utilized an independent Data Safety Monitoring Board (DSMB), a Clinical Events Committee (CEC) that was responsible for adjudicating adverse events, and an echocardiography core laboratory.

1. Clinical Inclusion and Exclusion Criteria

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

   - Patient has moderate or greater aortic stenosis or regurgitation, and there is clinical indication for replacement of their native or prosthetic aortic valve with a bioprosthesis, with or without concomitant procedures, which are limited to any of the following:
     - LAA ligation
     - CABG
     - PFO closure
     - Ascending aortic aneurysm or dissection repair not requiring circulatory arrest
     - Resection of a sub-aortic membrane not requiring myectomy
   - Patient is geographically stable and willing to return to the implanting site for all follow-up visits
   - Patient is of legal age to provide informed consent in the country where they enroll in the trial
   - Patient has been adequately informed of risks and requirements of the trial and is willing and able to provide informed consent for participation in the clinical trial

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

   - Patient has a pre-exisitng prosthetic valve or annuloplasty device in another position or requires replacement or repair of the mitral, pulmonary, or tricuspid valve
   - Patient has had previous implant and then explant of the Avalus Model 400 aortic valve bioprosthesis
   - Patient presents with active endocarditis, active myocarditis, or other systemic infection
   - Patient has an anatomical abnormality which would increase surgical risk of mobidity or mortality, including:
     - Ascending aortic aneurysm or dissection repair requiring circulatory arrest

  - Acute Type A aortic dissection
  - Ventricular aneurysm
  - Porcelain aorta
  - Hostile mediastinum
  - Hypertrophic obstructive cardiomyopathy (HOCM)
  - Documented pulmonary hypertension (systolic > 60 mmHg)
- Patient has a non-cardiac major or progressive disease, with a life expectancy of less than 2 years. These conditions include, but are not limited to:
  - Child-Pugh Class C liver disease
  - Terminal cancer
  - End-stage lung disease
- Patient has renal failure, defined as dialysis therapy or GFR < 30 mL/min/1.73 m^2
- Patient has hyperparathyroidism
- Patient is participating in another investigational device or drug trial or observational competitive study
- Patient is pregnant, lactating, or planning to become pregnant during the trial period
- Patient has a documented history of substance (drug or alcohol) abuse
- Patient has greater than mild mitral valve regurgitation or greater than mild tricuspid valve regurgitation as assessed by echocardiography
- Patient has systolic EF < 20% as assessed by echocardiography
- Patient has Grade IV Diastolic Dysfunction
- Patient has documented bleeding diatheses
- Patient has had an acute preoperative neurological deficit or myocardial infarction and has not returned to baseline or stabilized ≥ 30 days prior to enrollment
- Patient requires emergency surgery

2. Follow-up Schedule

   All patients were scheduled to return for follow-up examinations at baseline, index procedure, discharge, 3-6 months, 1 year, and annually thereafter up to 5 years.

   Preoperatively, demographic and baseline data were collected. Postoperatively, the objective parameters measured during the study included echocardiographic data and NYHA functional classification. Adverse events and complications were recorded at all visits.

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

3. Clinical Endpoints

With regards to safety, the study evaluated the time-related incidence of valve-related adverse events and death, including:

- Thromboembolism
- Thrombosis
- Hemorrhage (all and major)
- Paravalvular leak (all and major)
- Endocarditis
- Hemolysis
- Stuctural valve deterioration
- Non-structural dysfunction
- Reintervention
- Explant
- Death

With regards to effectiveness, the following criteria were evaluated:

- NYHA functional classification status
- Hemodynamic performance evaluated by echocardiography, including peak gradient, mean gradient, effective orifice area (EOA), effective orifice area index (EOAI), performance index, cardiac output, cardiac index, and valvular regurgitation (transvalvular, paravalvular, and total)

With regard to success/failure criteria, success was defined by comparing event rates with 2x the OPC values listed in ISO 5840:2009 as well as a comparison of literature controls from commercially available devices.

B. Accountability of PMA Cohort

At the time of database lock, of 962 patients enrolled in the PMA study, 89.8% (864) patients were implanted with the Avalus bioprosthesis and are available for analysis, and 904.1 total patient-years were collected (834.2 late patient-years). Twenty five (25) subjects were classified as attempted but not implanted and were not included in the main analysis. Subject follow-up compliance is detailed in Table 4.

Table 4. Subject Follow-up Compliance

Visit interval	Number expected	Number evaluated % (n)	Censored[a]
Baseline	962	99.3% (955)	0
Procedure	864	100.0% (864)	98
Discharge	859	100.0% (859)	5
3–6 Months	821	99.0% (813)	38
1 Year	581	99.3% (577)	240
2 Year	101	99.0% (100)	480

[a]Censored includes visits due but not yet occurred, visits not yet due, death, explant, lost to follow-up (LTF), or withdrawn (by self or physician).

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a surgical aortic valve replacement study performed in the US. Baseline demographics and characteristics are shown in Table 5.

Table 5. Baseline demographics and characteristics

Age at implant	**N: Mean ± SD (min – max)**
Age (years)	864: 70.4 ± 8.9 (21.1 – 90.9)
Gender	**% (n / N)**
Female	25.5% (220/864)
Male	74.5% (644/864)
Body surface area	**N: Mean ± SD (min – max)**
BSA (m^2)	864: 2.0 ± 0.2 (1.4 – 2.9)
NYHA classification	**% (n / N)**
Class I	11.3% (98/864)
Class II	47.5% (410/864)
Class III	39.6% (342/864)
Class IV	1.6% (14/864)
STS risk scores	**N: Mean ± SD (min – max)**
STS risk of mortality	864: 2.0 ± 1.4 (0.4 – 10.1)
STS risk of morbidity or mortality	864: 14.8 ± 6.0 (5.6 – 48.7)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the 864 patients that received the Avalus bioprosthesis over the course of 904.1 total patient-years. The key safety outcomes and adverse events for this study are presented below in Tables 6 and 7. Simple proportions are used to describe early event rates, linearized rates (%/patient-year) are presented for late events, and "freedom from event" at 1-year based on Kaplan-Meier analysis are provided based on all reported events both "early" and "late".

Table 6. Summary of observed adverse event rates

Adverse events	**Early events[a]**			**Late events[b]**			**Freedom from event[c] at 1 Year (95% CI[d]) n = 577**
	Number of events	**Number of sub-jects**	**Early event rate**	**Number of events**	**Number of sub-jects**	**Linearized late event rate[e]**	
All-cause mortality	10	10	1.2%	28	28	3.4%	96.4 (94.8,97.5)
Valve-related mortality	0	0	0.0%	4	4	0.5%	99.7 (98.6,99.9)
Thromboembolism	12	11	1.4%	14	14	1.7%	97.2 (95.7,98.1)

Stroke	8	8	0.9%	8	8	1.0%	98.0 (96.7,98.8)
Transient ischemic attack	4	4	0.5%	6	6	0.7%	98.8 (97.7,99.4)
Valve thrombosis	0	0	0.0%	0	0	0.0%	100.0 (NA)
All hemorrhage[f]	14	13	1.6%	30	28	3.6%	95.1 (93.2, 96.4)
Major hemorrhage[f]	8	8	0.9%	21	19	2.5%	96.9 (95.4, 97.9)
All paravalvular leak	2	2	0.2%	5	5	0.6%	99.3 (98.3, 99.7)
Major paravalvular leak	1	1	0.1%	0	0	0.0%	99.9 (99.2, 100.0)
Endocarditis	2	2	0.2%	11	11	1.3%	98.7 (97.4, 99.3)
Clinically significant hemolysis	0	0	0.0%	0	0	0.0%	100.0 (NA)
Structural valve deterioration	0	0	0.0%	0	0	0.0%	100.0 (NA)
Nonstructural valve dysfunction[g] (NSVD)	2	2	0.2%	5	5	0.6%	99.3 (98.3, 99.7)
Explant[h]	4	4	0.5%	6	6	0.7%	98.9 (97.8, 99.5)
Reintervention[h]	4	4	0.5%	6	6	0.7%	98.9 (97.8, 99.5)

a Early events include events that occurred on or before 30 days post-procedure.
b Late events include events that occurred greater than 30 days post-procedure.
c Freedom from event rate is based on Kaplan-Meier analysis.
d CI= Confidence Interval. The 95% CI is calculated using the loglog transformed 95% CI based on Greenwood formula. The lower and upper bound are presented, respectively.
e Late linearized rates (percent per patient-year) were calculated by dividing the number of late events by the sum of the late patient-years of experience and expressed as a percentage.
f Anticoagulant-related and/or antiplatelet-related events only included.
g NSVD is inclusive of all paravalvular leak events. No NSVD of other etiology was observed.
h One outcome was due to a procedure-related event and not a valve-related event.

The results of the PERIGON study were compared to the OPC as described in Table R.1 in EN ISO 5840:2009, Annex R.1. Thromboembolism, valve thrombosis, all and major paravalvular leak, and endocarditis met the OPC. The OPC for all and major hemorrhage were not met; however, all of the hemorrhage events were anticoagulant- and/or antiplatelet-related and did not indicate a direct relation to the Avalus bioprosthesis.

Table 7. Late linearized event rates compared to objective performance criteria (OPC)

Adverse event	Late linearized event rate[a] (%) LPY[b] = 834.2	Number of events	Number of subjects	95% Upper confidence bound[c] of late linearized rate	2x OPC[d] (%/patient-year)
Thromboembolism	1.7%	14	14	2.55%	5.0%
Valve thrombosis	0.0%	0	0	0.00%	0.4%
All hemorrhage	3.6%	30	28	4.81%	2.8%
Major hemorrhage	2.5%	21	19	3.55%	1.8%
All paravalvular leak	0.6%	5	5	1.18%	2.4%

Major paravalvular leak	0.0%	0	0	0.00%	1.2%
Endocarditis	1.3%	11	11	2.11%	2.4%

[a] Late linearized event rate calculated by number of events/LPY, expressed as a percentage.
[b] LPY = Late patient-years. LPY are calculated from post-implant day 31 through last point of contact.
[c] Upper confidence bound calculated by Greenwood formula.
[d] OPC = Objective performance criteria for tissue valves, as described in Table R.1 of EN ISO 5840:2009, Annex R.1.

2. Effectiveness Results

The analysis of effectiveness was based on the 864 patients that received the Avalus bioprosthesis over the course of 904.1 total patient-years. Key effectiveness outcomes are presented in Tables 8 to 12.

Table 8. New York Heart Association (NYHA) classification

NYHA classification	Baseline (N = 864)	1 Year (N = 577)	2 Year (N = 100)
I	11.3% (98/864)	73.4% (423/576)	67.0% (67/100)
II	47.5% (410/864)	22.4% (129/576)	29.0% (29/100)
III	39.6% (342/864)	3.5% (20/576)	4.0% (4/100)
IV	1.6% (14/864)	0.2% (1/576)	0.0% (0/100)
Not done	0.0% (0/864)	0.5% (3/576)	0.0% (0/100)

Table 9. Change in NYHA classification from baseline

NYHA classification	1 Year (N = 577)	2 Year (N = 100)
Improved 3 class	1.4% (8/573)	0.0% (0/100)
Improved 2 class	24.8% (142/573)	26.0% (26/100)
Improved 1 class	48.9% (280/573)	48.0% (48/100)
No change	23.2% (133/573)	24.0% (24/100)
Worsened 1 class	1.7% (10/573)	2.0% (2/100)
Worsened 2 class	0.0% (0/573)	0.0% (0/100)
Worsened 3 class	0.0% (0/573)	0.0% (0/100)

Mean gradient and effective orifice area (EOA) at 1-year follow-up are presented in Table 10, and transvalvular and paravalvular regurgitation at 1-year are presented in Tables 11 and 12, respectively.

Table 10. Hemodynamic Results at 1-Year

Parameter	19 mm Mean ± SD (n[a])	21 mm Mean ± SD (n[a])	23 mm Mean ± SD (n[a])	25 mm Mean ± SD (n[a])	27 mm Mean ± SD (n[a])
Mean gradient (mmHg)	17.1 ± 5.0 (27)	14.5 ± 4.3 (106)	12.1 ± 3.8 (205)	11.7 ± 4.0 (170)	10.3 ± 4.2 (43)
EOA (cm^2)	1.11 ± 0.25 (25)	1.25 ± 0.25 (99)	1.47 ± 0.32 (201)	1.57 ± 0.31 (167)	1.77 ± 0.41 (41)

[a] n represents the number of subjects with evaluable data.

Table 11. Transvalvular Aortic Regurgitation

Visits	19mm % (n/N[a])	21mm % (n/N[a])	23mm % (n/N[a])	25mm % (n/N[a])	27mm % (n/N[a])	All Sizes % (n/N[a])
1 Year						
None	70.4% (19/27)	74.1% (80/108)	87.9% (181/206)	91.9% (158/172)	93.0% (40/43)	86.0% (478/556)
Trace	22.2% (6/27)	17.6% (19/108)	8.7% (18/206)	4.7% (8/172)	7.0% (3/43)	9.7% (54/556)
Mild	7.4% (2/27)	5.6% (6/108)	2.4% (5/206)	2.9% (5/172)	0.0% (0/43)	3.2% (18/556)
Moderate	0.0% (0/27)	0.0% (0/108)	0.0% (0/206)	0.0% (0/172)	0.0% (0/43)	0.0% (0/556)
Severe	0.0% (0/27)	0.0% (0/108)	0.0% (0/206)	0.6% (1/172)	0.0% (0/43)	0.2% (1/556)
Not evaluable	0.0% (0/27)	2.8% (3/108)	1.0% (2/206)	0.0% (0/172)	0.0% (0/43)	0.9% (5/556)

[a] n represents the number of subjects with evaluable data. N represents the number of subjects with data whose echo was performed.

Table 12. Paravalvular Aortic Regurgitation

Visits	19mm % (n/N[a])	21mm % (n/N[a])	23mm % (n/N[a])	25mm % (n/N[a])	27mm % (n/N[a])	All Sizes % (n/N[a])
1 Year						
None	96.3% (26/27)	89.8% (97/108)	92.7% (191/206)	93.0% (160/172)	93.0% (40/43)	92.4% (514/556)
Trace	3.7% (1/27)	6.5% (7/108)	4.4% (9/206)	1.2% (2/172)	2.3% (1/43)	3.6% (20/556)
Mild	0.0% (0/27)	0.9% (1/108)	1.9% (4/206)	4.7% (8/172)	2.3% (1/43)	2.5% (14/556)
Moderate	0.0% (0/27)	0.0% (0/108)	0.0% (0/206)	1.2% (2/172)	2.3% (1/43)	0.5% (3/556)
Severe	0.0% (0/27)	0.0% (0/108)	0.0% (0/206)	0.0% (0/172)	0.0% (0/43)	0.0% (0/556)
Not Evaluable	0.0% (0/27)	2.8% (3/108)	1.0% (2/206)	0.0% (0/172)	0.0% (0/43)	0.9% (5/556)

[a] n represents the number of subjects with evaluable data. N represents the number of subjects with data whose echo was performed.

3. Subgroup Analyses

Gender was evaluated for potential association with outcomes. Analysis was performed on the 864 subjects who were successfully implanted in order to assess potential differences between genders that may be relevant to the clinical evaluation of the Avalus bioprosthesis. Among the 864 subjects implanted, 74.5% were male and 25.5% were female. The PERIGON trial was not designed nor powered to study safety and effectiveness differences between genders, so this analysis is considered exploratory without definitive conclusions.

Safety endpoints stratified by gender are listed in Table 13.

Table 13. Death and Valve-Related Endpoints by Gender

	Male (N = 644)		Female (N = 220)	
Events	**# of events (# of subjects)**	**1 Year KM Event Rate (95% CI)**	**# of events (# of subjects)**	**1 Year KM Event Rate (95% CI)**
All Death	27 (27)	3.2% (1.9,4.9)	11 (11)	4.8% (2.3,8.5)
Valve-related Death	4 (4)	0.5% (0.1,1.6)	0 (0)	0.0% (NA)
Thromboembolism	22 (20)	3.1% (1.9,4.8)	4 (4)	2.0% (0.7,4.8)
Valve Thrombosis	0 (0)	0.0% (NA)	0 (0)	0.0% (NA)
All Hemorrhage	36 (32)	5.3% (3.6,7.5)	8 (8)	3.7% (1.6,7.2)
Major Hemorrhage	25 (22)	3.5% (2.2,5.3)	4 (4)	2.0% (0.7,4.8)
All Paravalvular Leak	6 (6)	0.8% (0.3,1.9)	1 (1)	0.5% (0.0,2.4)
Major Paravalvular Leak	1 (1)	0.2% (0.0,0.8)	0 (0)	0.0% (NA)
Endocarditis	11 (11)	1.4% (0.6,2.8)	2 (2)	1.1% (0.2,3.5)
Clinically Significant Hemolysis	0 (0)	0.0% (NA)	0 (0)	0.0% (NA)
Non-structural Valve Dysfunction	6 (6)	0.8% (0.3,1.9)	1 (1)	0.5% (0.0,2.4)
Structural Valve Deterioration	0 (0)	0.0% (NA)	0 (0)	0.0% (NA)
Reintervention	7 (7)	0.9% (0.4,2.1)	2 (2)	1.1% (0.2,3.6)
Explant	7 (7)	0.9% (0.4,2.1)	2 (2)	1.1% (0.2,3.6)

Effectiveness endpoints were compared for both males and females. The two (2) groups exhibited a clinically significant improvement in NYHA classification at all time points.

Table 14. NYHA Classification By Gender

NYHA Classification	**I / II**		**III / IV**	
Interval / Gender	**Male %(n/N[a])**	**Female %(n/N[a])**	**Male %(n/N[a])**	**Female %(n/N[a])**
Discharge up to 30 days	90.0% (439/488)	89.6% (155/173)	10.0% (49/488)	10.4% (18/173)
3-6 Months	97.5% (584/599)	96.0% (194/202)	2.5% (15/599)	4.0% (8/202)
1 Year	97.1% (408/420)	94.1% (144/153)	2.9% (12/420)	5.9% (9/153)
2 Year	97.3% (72/74)	92.3% (24/26)	2.7% (2/74)	7.7% (2/26)

[a] N is the number of subjects with available data at each visit.

The comparisons of safety and effectiveness data support the conclusion that the results of the overall study can be applied equally well to males and females.

4. 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 clinical study included 318 investigators of which none were full-time or part-time employees of the sponsor and 5 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none
- Significant payment of other sorts: 5
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: none

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. 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 Device panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the clinical study, the analysis of effectiveness is based on NYHA functional classification and echocardiographic hemodynamic data at 1-year. The PERIGON study results demonstrate an improvement in NYHA classification by at least one class for 75.1% of patients at 1-year from baseline.

Echocardiographic results from the Core Lab indicate that mean effective orifice areas and mean gradients are consistent with the corresponding data in the literature-based control articles for the study. Furthermore, 95.7% of patients had either no or trace transvalvular regurgitation at 1-year, and 96.1% of patients had either no or trace paravalvular regurgitation at 1-year. These results indicate acceptable hemodynamic performance of the Avalus valve. In all, the study results provide a reasonable assurance that the Avalus valve is effective for its intended use.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies, as well as data collected in a clinical study conducted to support PMA approval as described above. The results from the preclinical studies performed on the Avalus bioprosthesis for biocompatibility, hydrodynamic performance and structural integrity demonstrate that the device meets all specifications and is suitable for long-term implant. The animal studies performed in sheep further support the *in vivo* safety of the Avalus bioprosthesis.

The results of the PERIGON clinical study demonstrate that the adverse event rates for the major safety endpoints are lower than the established standard of twice the Objective Performance Criteria for a bioprosthetic valve, with the exception of all hemorrhage and major hemorrhage rates. In the PERIGON study, the upper 95% confidence limit for the late linearized rate for all hemorrhage was 4.81% and major hemorrhage was 3.55%, which exceed the criterion of twice the OPC (all hemorrhage: 2.8% and major hemorrhage: 1.8%). However, detailed analyses of the hemorrhage rates do not indicate a direct relation to the Avalus bioprosthesis. In all, the study results provide a reasonable assurance that the Avalus valve is safe in its intended use.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefits of the Avalus bioprosthesis include improved aortic valve hemodynamic performance and NYHA functional classification compared to baseline values. The risks associated with the Avalus bioprosthesis include complications such as valvular thrombosis, thromboembolism, paravalvular leak, endocarditis, structural valve deterioration, non-structural valve dysfunction, reoperation, explant, and death. However, these risks are similar to those observed with other surgical prosthetic aortic valves.

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 replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves 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. Preclinical and clinical studies provided in the PMA application demonstrate reasonable assurance that the Avalus bioprosthesis is safe and effective for replacement of diseased, damaged, or malfunctioning native or prosthetic aortic heart valves.

XIII. CDRH DECISION

CDRH issued an approval order on July 31, 2017.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See 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.