SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Left Atrial Appendage Closure System

Device Trade Name: WATCHMAN Left Atrial Appendage Closure Device with Delivery System

WATCHMAN FLX Left Atrial Appendage Closure Device with Delivery System

Device Procode: NGV

Applicant's Name and Address: Boston Scientific Corporation
Three Scimed Place
Maple Grove, MN 55311

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P130013/S035

Date of FDA Notice of Approval: July 21, 2020

The original PMA (P130013) for the WATCHMAN Left Atrial Appendage (LAA) Closure Device with Delivery System was approved on March 13, 2015. The device was initially indicated to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin therapy; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin therapy, taking into account the safety and effectiveness of the device compared to warfarin therapy.

The SSED to support the indication is available on the CDRH website and is incorporated by reference here. https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130013b.pdf
The current supplement was submitted to include a modified version of the WATCHMAN Left Atrial Appendage Closure Device with Delivery System referred to as the WATCHMAN FLX Left Atrial Appendage Closure Device with Delivery System and to expand the indication to include patients who are recommended and suitable for anticoagulation therapy other than warfarin.

II. INDICATIONS FOR USE

The WATCHMAN Device and WATCHMAN FLX Device are indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for anticoagulation therapy; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to anticoagulation therapy, taking into account the safety and effectiveness of the device compared to anticoagulation therapy.

III. CONTRAINDICATIONS

Do not use the WATCHMAN Device or the WATCHMAN FLX Device if:

- Intracardiac thrombus is present.
- An atrial septal defect repair or closure device or a patent foramen ovale repair or closure device is present.
- The LAA anatomy will not accommodate a Closure Device.
- The patient has a known hypersensitivity to any portion of the device material or the individual components (see Device Description section) such that the use of the WATCHMAN Device or WATCHMAN FLX Device is contraindicated.
- Any of the customary contraindications for other percutaneous catheterization procedure (e.g., patient size too small to accommodate TEE probe or required catheters) or conditions (e.g., active infection, bleeding disorder) are present.
- There are contraindications to the use of anticoagulation therapy, aspirin, or P2Y12 inhibitor.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the WATCHMAN LAA Closure Device with Delivery System and WATCHMAN FLX LAA Closure Device with Delivery System labeling.

V. DEVICE DESCRIPTION

There are two versions of the WATCHMAN devices: The WATCHMAN LAA Closure Device with Delivery System and the The WATCHMAN FLX LAA Closure Device with Delivery System. Both versions are described below.

A. WATCHMAN Closure Device with Delivery System

The WATCHMAN LAA Closure Device with Delivery System consists of:

- WATCHMAN LAA Closure Device (also referred to as “WATCHMAN Device”, “WATCHMAN Closure Device”, “Device”, and “Implant”)

- WATCHMAN Delivery System (consisting of Delivery Catheter and loaded Implant)

The WATCHMAN Closure Device (implant) is a self-expanding nitinol (nickel-titanium alloy) structure with a polyethylene terephthalate (PET) porous membrane on the proximal face (see **Figure 1**). Fixation anchors are located on the outer edge of the frame struts to provide stabilization in situ (see **Figure 2**). The device is designed to be permanently implantable in the LAA for a non-surgical closure of the LAA to reduce the risk of thromboembolism from the LAA.

Figure 1: WATCHMAN Closure Device

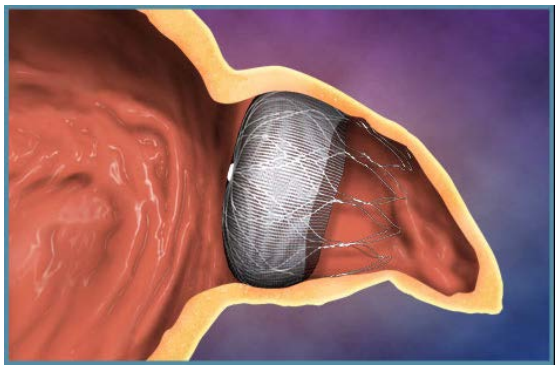

Figure 2: WATCHMAN® Closure Device In Situ at the Ostium of the LAA

The WATCHMAN Closure Device is pre-loaded in a Delivery System which permits Closure Device placement in the left atrial appendage (LAA) via femoral venous access and interatrial septum crossing into the left atrium. The Delivery Catheter is a 12 Fr reinforced catheter with a distal radiopaque marker band for in situ visualization. Within the Delivery System is a threaded core wire which provides the mechanism for deployment and release or recapture of the Closure Device.

The WATCHMAN LAA Closure Device with Delivery System is described in detail in the device description of the SSED available on the CDRH website and is incorporated by reference here. https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130013b.pdf

B. WATCHMAN FLX Closure Device with Delivery System

The WATCHMAN FLX LAA Closure Device with Delivery System consists of:

- WATCHMAN FLX LAA Closure Device (also referred to as "WATCHMAN FLX Device", "WATCHMAN FLX Closure Device", "Device", and "Implant")
- WATCHMAN FLX Delivery System (consisting of Delivery Catheter and loaded Implant)

Like the WATCHMAN Closure Device described above, the WATCHMAN FLX Closure Device (implant) is a self-expanding nitinol (nickel-titanium alloy) structure with a polyethylene terephthalate (PET) porous membrane on the proximal face (see **Figure 3)**.

Fixation anchors are located on the outer edge of the frame struts to provide stabilization in situ (see **Figure 4**). The shape of the WATCHMAN FLX Closure Device frame is different than the WATCHMAN Closure Device. The WATCHMAN FLX closure device frame is closed at both ends and has an extra row of anchors that are used to secure the WATCHMAN FLX Closure Device.

Figure 3: WATCHMAN FLX Closure Device

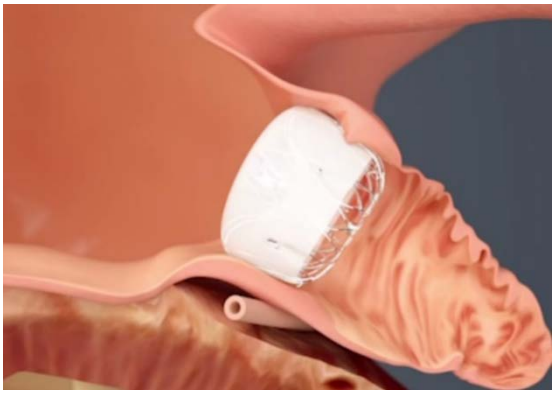

Figure 4: WATCHMAN FLX™ Device In Situ at the Ostium of the LAA

The WATCHMAN FLX Closure Device is pre-loaded into the WATCHMAN FLX Delivery System which permits Closure Device placement in the left atrial appendage (LAA) via femoral venous access and interatrial septum crossing into the left atrium. The WATCHMAN FLX Delivery Catheter is a 12 Fr reinforced catheter with a distal radiopaque marker band for in situ visualization. Within the WATCHMAN FLX Delivery System is a threaded core wire which provides the mechanism for deployment and release or recapture of the WATCHMAN FLX Closure Device.

The WATCHMAN FLX Delivery System is based on the design of the WATCHMAN Delivery System. The WATCHMAN FLX Closure Device is fully recapturable and repositionble. This means even after the WATCHMAN FLX Closure Device is deployed from the WATCHMAN FLX Delivery System, the WATCHMAN FLX Closure Device can be completely pulled back (retracted) into the Delivery System during the procedure until the physician can place the WATCHMAN FLX Closure Device in the right location in the left atrial appendage.

C. WATCHMAN and WATCHMAN FLX Device Sizing

The WATCHMAN FLX Closure Device is also designed to occlude a wider size range of left atrial appendages than the WATCHMAN Closure Device as described in **Table 1** below. Appropriate WATCHMAN FLX Closure Device and WATCHMAN Closure Device sizing is determined by LAA measurements using fluoroscopy (fluoro) and echocardiographic guidance.

Table 1: Device Sizing

WATCHMAN Device Size (mm)	Max LAA Ostium (mm)		WATCHMAN FLX Device Size (mm)	Max LAA Ostium (mm)
21	17 - 19		20	14.0 - 18.0
24	20 - 22		24	16.8 - 21.6
27	23 - 25		27	18.9 - 24.3
30	26 - 28		31	21.7 - 27.9
33	29 - 31		35	24.5 - 31.5

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for reducing the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation.

Oral anticoagulants effectively reduce the risk of cardioembolic stroke and are the most commonly used treatments in at-risk patients with non-valvular atrial fibrillation.

Certain surgical clips are indicated for the occlusion of the LAA under direct visualization, in conjunction with other open cardiac surgical procedures.

An alternative to using a device for LAA closure is direct closure during open-heart surgery (nearly always as an adjunct procedure to treat another primary cardiac condition). LAA closure is commonly performed following or in tandem with an open MAZE procedure for atrial fibrillation or other open heart procedures such as mitral valve repair or replacement.

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 WATCHMAN Closure Device with Delivery System is commercially-available in the following countries listed below:

Albania	Algeria	Antigua / Barbuda	Argentina
Armenia	Aruba	Australia	Austria
Azerbaijan	Bahamas	Bahrain	Barbados
Belgium	Belize	Bermuda	Bolivia
Bonaire Saba	Brazil	Brunei Darussalam	Bulgaria
Canada	Cayman Islands	Chile	China
Colombia	Costa Rica	Croatia	Curacao
Cyprus	Czech Republic	Denmark	Dominican Republic
Dutch Antilles	Ecuador	El Salvador	Estonia

Finland	France	Georgia	Germany
Great Britain	Greece	Guam	Guatemala
Guyana	Haiti	Honduras	Hong Kong
Hungary	Iceland	India	Indonesia
Iran	Iraq	Ireland	Israel
Italy	Japan	Jamaica	Jordan
Kazakhstan	Kenya	Kuwait	Latvia
Lebanon	Libya	Liechtenstein	Lithuania
Luxembourg	Macau	Malaysia	Malta
Martinique	Mexico	Mongolia	Morocco
Myanmar	Nepal	Netherlands	New Zealand
Norway	Oman	Pakistan	Panama
Paraguay	Peru	Philippines	Poland
Portugal	Qatar	Romania	Russian Federation
Saudi Arabia	Serbia	Singapore	Slovakia
Slovenia	South Africa	South Korea	Spain
State of Palestine	Suriname	Sweden	Switzerland
Taiwan	Tajikistan	Thailand	Trinidad, Tobago
Tunisia	Turkey	United Arab Emirates	United States
			Venezuela
			Yemen

The WATCHMAN FLX Closure Device with Delivery System is commercially-available in the following countries listed below:

Albania	Dutch Antilles	Israel	Netherlands
Andorra	Estonia	Italy	Norway
Austria	Finland	Kosovo	Poland
Belgium	France	Kuwait	Portugal
Bulgaria	Germany	Latvia	Romania
Canada	Great Britain	Liechtenstein	Singapore
Costa Rica	Greece	Lithuania	Slovakia
Croatia	Hong Kong	Luxembourg	Slovenia
Cyprus	Hungary	Macau	Spain
Czech Republic	Iceland	Malta	Switzerland
Denmark	Ireland	Malaysia	Sweden

Neither WATCHMAN® nor WATCHMAN FLX™ have been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Air embolism
- Airway trauma
- Allergic reaction to the contrast media, anesthetic, WATCHMAN implant material, or medications
- Altered mental status
- Anemia requiring transfusion
- Anesthesia risks
- Angina
- Anoxic encephalopathy
- Arrhythmias
- Atrial septal defect
- Bruising, hematoma, or seroma near the catheter insertion site
- Cardiac perforation
- Chest pain/discomfort
- Confusion post procedure
- Congestive heart failure
- Contrast related nephropathy
- Cranial bleed
- Death
- Decreased hemoglobin
- Deep vein thrombosis
- Device embolism
- Device fracture
- Device thrombosis
- Edema
- Embolism
- Excessive bleeding
- Fever
- Fistula
- Groin pain
- Groin puncture bleed
- Hematuria
- Hemoptysis
- Hypotension
- Hypoxia
- Improper wound healing
- Inability to reposition, recapture, or retrieve the device

- Infection/pneumonia
- Interatrial septum thrombus
- Intratracheal bleeding
- Major bleeding requiring transfusion
- Misplacement of the device/improper seal of the appendage/movement of device from appendage wall
- Myocardial erosion
- Nausea
- Oral bleeding
- Pericardial effusion/tamponade
- Pleural effusion
- Prolonged bleeding from a laceration
- Pseudoaneurysm
- Pulmonary edema
- Renal failure
- Respiratory insufficiency/failure
- Stroke - Hemorrhagic
- Stroke - Ischemic
- Surgical removal of the device
- TEE complications (e.g., throat pain, bleeding, esophageal trauma)
- Thrombocytopenia
- Thrombosis
- Transient ischemic attack (TIA)
- Valvular or vascular damage
- Vasovagal reactions

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Nonclinical studies were not required to support the change in indication for the WATCHMAN LAA Closure Device with Delivery System.

The following sections detail the nonclinical studies performed to support the modifications to the WATCHMAN Closure Device nitinol structure and modifications to the WATCHMAN Delivery System (referred to as the WATCHMAN FLX™ LAA Closure Device with Delivery System). Testing was referenced from PMA submission P130013 for those evaluations that could be leveraged from previous testing. A summary of previously reported non-clinical studies can be found in the Summary of Safety and Effectiveness Data (SSED) for the original PMA (https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130013B.pdf).

i. Biocompatibility

Biocompatibility testing of the WATCHMAN FLX LAA Closure Device with Delivery System was conducted according to Good Laboratory Practices Regulations (21 CFR § 58) and ISO 10993-1: *Biological Evaluation of Medical Devices: Evaluation and Testing within a Risk Management Process (2016)*. According to ISO 10993, the WATCHMAN FLX Delivery System is classified as a limited exposure (< 24 hours) externally communicating, circulating blood contact device. The WATCHMAN FLX Closure Device is classified as a long-term implantable device contacting blood for >30 days.

The required testing for each component was determined based on the nature and duration of body contact in accordance with ISO 10993-1:2018. All tests performed met the requirements of ISO 10993-1: 2018. Summaries of the test results for the Closure Device and Delivery System are provided in **Table 2.**

Table 2: List of Biocompatibility Tests

Biologic Effect	Test Name/ Description	Implant	Delivery System	Results
Cytotoxicity	ISO 10993-5 MEM Elution Assay with L-929 Mouse Fibroblast Cells	X	X	Pass – non-cytotoxic
Sensitization	ISO 10993-10 Guinea Pig Maximization Sensitization Test	X	X	Pass – non-sensitizer
Irritation	ISO 10993-10 Intracutaneous Reactivity Test	X	X	Pass – non-irritant
Systemic Toxicity (Acute)	ISO 10993-11 Acute Systemic Injection Test	X	X	Pass - No evidence of systemic toxicity
Systemic Toxicity (Chronic)	ISO 10993-11 Systemic Toxicity Study Following Subcutaneous Implantation 4 week and 13 week	X	N/A	Pass - No evidence of systemic toxicity
Materials Mediated Pyrogenicity	ISO 10993-11 Material Medicated/Rabbit Pyrogen	X	X	Pass – non-pyrogeic
Genotoxicity	Ames and Mouse Lymphoma	X	N/A	Pass - Non-mutagenic
Hemocompatibility	ISO 10993-4 Hemolysis / Direct and Extract, Complement Activation, PTT, In Vitro Hemocompatibility	X	X	Pass – non-hemolytic
Chemical Characterization	Testing compared extractable/leachable profile between WATCHMAN and WATCHMAN FLX Implants	X	N/A	Pass
Carcinogencity	Leveraged from WATCHMAN	X	N/A	Pass
Chronic Toxicicty	Leveraged from WATCHMAN	X	N/A	Pass
Nickel Elution Study	Evaluated nickel leach from nitinol implant frame	X	N/A	Pass

ii. Bench Testing

In vitro engineering studies conducted on the WATCHMAN FLX LAA Closure Device with Delivery System are listed in **Table 3**. All testing was conducted in accordance with national and international standards and FDA guidance documents, as applicable.

Table 3: Summary of WATCHMAN FLX Bench Testing

Test	Test Description	Results
WATCHMAN FLX LAA Closure Device Testing		
Implant Dimensions	These tests quantitatively evaluate the expansion of the frame to its final diameter and length required to oppose and seal the LAA ostium.	Pass
Implant Radial Expansion Force	This test quantitatively assessed the radial force of a properly constrained WATCHMAN FLX implant.	Pass
Implant Filtration	This test quantitatively assessed the flow rate and particle exclusion properties of the LAA implant filter.	Pass
Implant Dislodgement Force	This test quantitatively assessed the force required to dislodge a properly sized and positioned WATCHMAN FLX implant.	Pass
Implant Deployment and Recapture Force	This test quantitatively assessed the forces required to deploy and recapture the LAA implant via the delivery system and access system.	Pass
Implant and delivery system/access system connection strength	This test quantitatively assessed the forces required to deploy and recapture the LAA implant via the delivery system and access system.	Pass
Finite Element Analysis (for characterization)	This test assessed the stress/strain levels in key areas of the implant	Pass
Implant Durability	Implant Durability/Fatigue (Test articles were cycled up to the equivalent of 10 years of use or 400,000,000 cycles) These tests quantitatively evaluate resistance to in-vivo fatigue-related damage.	Pass
Corrosion Resistance	These tests quantitatively evaluate the corrosion resistance of the implant.	Pass
MRI compatibility testing	This test assessed the conditions under which the device may be scanned safely. Additional MRI information is provided below this table.	Pass

Test	Test Description	Results
WATCHMAN FLX Delivery System Testing		
Delivery System Working Length	This test quantitatively evaluated the length of the catheter and compatibility with required accessories.	Pass
Kink Resistance – Delivery System	This test quantitatively evaluated the kink resistance of the WATCHMAN FLX Delivery System shaft.	Pass
System Visualization	This test evaluated the visualization factors of the implant and delivery system.	Pass
Delivery System Forces	These tests quantitatively evaluated the force required by the Delivery System.	Pass
Bond Tensile	These tests quantitatively evaluated the tensile forces for each bond within the Delivery System.	Pass
Leak Free Fluid Conduit	These tests quantitatively evaluated the Delivery System to ensure it remains leak free during clinical use and allows a flow rate at constant pressure.	Pass
Delivery System Corrosion Resistance	This test qualitatively evaluated the corrosion resistance of the Delivery System components.	Pass
Particulate Testing	Evaluated the particulate levels generated from the product with its accessories in a simulated use model	Pass
Delivery System Fatigue Resistance	The test qualitatively evaluated for Delivery System durability.	Pass

Non-clinical testing has demonstrated the WATCHMAN FLX Closure Device is MR Conditional. A patient with the WATCHMAN FLX Closure Device can be scanned safely, immediately after placement of this implant, under the following conditions:

- Static magnetic field of 3.0 Tesla or 1.5 Tesla
- Maximum spatial gradient field of 2500 Gauss/cm
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of <2.0 W/kg (normal operating mode only)

Under the scan conditions defined above, the WATCHMAN FLX Closure Device is expected to produce a maximum temperature rise of less than 3.0° C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the device extends approximately 8.4 mm from the WATCHMAN FLX Closure Device when imaged with a gradient echo pulse sequence and a 3-Tesla MRI system.

iii. Sterilization

The WATCHMAN FLX Closure Device constrained in its Delivery System is sterilized using a 100% gaseous ethylene oxide sterilization. The sterilization process has been validated per ISO 11135:2014, "*Sterilization of health care products -- Ethylene Oxide -- Requirements for the development, validation, and routine control of a sterilization process for medical devices.*" Results from the sterilization studies demonstrate the validated EO sterilization process provides a sterility assurance level (SAL) of at least 10^{-6}. The amount of bacterial endotoxin was verified to be within the ANSI/AAMI ST72 specification limit.

iv. Packaging and Shelf Life

The WATCHMAN FLX Closure Device constrained in its Delivery System is placed into a protective carrier tube, which is then placed into a thermoformed tray. The thermoformed tray is then placed into a labeled Tyvek barrier bag, which is subsequently heat-sealed. This bag, known as the pouch, serves as the sterile barrier for the Delivery System to ensure sterility of the Delivery System is maintained. The sealed pouch is placed in a labeled shelf carton.

Shelf life studies were conducted to establish a shelf life/expiration date for the WATCHMAN FLX Closure Device with Delivery System. In addition, testing to establish package integrity and functional testing of the WATCHMAN FLX Closure Device with Delivery System was conducted on aged product to ensure that the device continues to meet specifications throughout its shelf life. The data generated support a 3-year shelf life for the WATCHMAN FLX Closure Device with Delivery System and the product is labeled accordingly.

B. Animal Studies

Because detailed arterial histopathology and histomorphometry data cannot be obtained through human clinical studies, a series of animal studies were conducted to evaluate safety, vascular compatibility, and acute product performance.

One chronic GLP study was conducted to assess the safety and vascular compatibility of the WATCHMAN FLX Closure Device with Delivery System, and is summarized in **Table 4**. The safety, vascular compatibility, and acute performance of WATCHMAN FLX Closure Device were evaluated in the non-injured canine left atrial appendage model. The chronic study was conducted in accordance with §21 CFR 58 (Good Laboratory Practices (GLP)). A non-GLP acute usability study was also conducted to evaluate the ease of device use and directions for use.

Table 4: Summary of Animal Evaluations

Study	Animals and Follow up; Species/Strain	Objectives	Results
SR17-047G, A Chronic GLP Study to Evaluate Device Performance and Chronic Biologic Response Following WATCHMAN FLX 2.0 in the Canine Left Atrial Appendage Model	6 animals; Follow up: implant, 7 days, 14 days, 45 days, 70 days and 90 days; Canine/ Mongrel Adult Male	To evaluate the overall safety, functionality, and biologic response of the final version of the WATCHMAN FLX Device in a canine LAA model at Implant and at 45- and 90-days post-Implant. Safety; ease of implantation; demonstrate that device does not promote organized thrombus 72 hrs post implant on atrial filter surface; assess level of endothelialization at 45 days; assess implant integrity and tissue response at 90 days post implant	The WATCHMAN FLX Closure Device met the requirements for establishing pre-clinical safety and functionality with regard to safe implantation, not promoting thrombus formation, endothelialization, implant integrity and tissue response.
Report 92211711, WATCHMAN FLX 2.0 Usability Summative Evaluation Report, non-GLP	Canine; Acute study; 5 physician users	To assess the usability and directions for use in an LAA model	No use errors occurred and all users were able to successfully implant the device

The results of the study indicate an acceptable tissue healing response to the implanted WATCHMAN FLX Closure Device with Delivery System. Animal studies performed on the WATCHMAN Closure Device with Delivery Systemare relevant to the performance of the WATCHMAN FLX Closure Device with Delivery System due to the use of identical materials and substantially similar device designs. The WATCHMAN and WATCHMAN FLX Closure Devices promote endocardial overgrowth and seal the LAA from the left atrium within 45 days. There were no visible strut fractures, and the devices caused no significant effects on adjacent tissues. Device implantation procedural methods were reproducible and safe.

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of transcatheter left atrial appendage closure with the WATCHMAN FLX Closure Device with Delivery System for reducing the risk of thromboembolism from the LAA in subjects with non-valvular atrial fibrillation who are eligible for direct oral anticoagulation therapy but have a rationale to seek a non-pharmacologic alternative in the US under IDE # G150200. Due to the similarities in the WATCHMAN Closure Device with Delivery System and WATCHMAN FLX Closure Device with Delivery System designs, the results of the PINNACLE FLX study are applicable to the WATCHMAN Closure Device with Delivery System. 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 07 May 2018 and 09 November 2018. The database for this Panel Track Supplement reflected data collected through 22 January 2020 and included 458 patients. There were 29 investigational sites in the United States.

The study is a prospective, non-randomzied, single-arm, open-label, mulit-center investigation to establish the safety and effectiveness of the WATCHMAN FLX Closure Device. The study enrolled subjects with non-valvular AF who are eligible for long-term non-vitamin K antagonist anticoagulation therapy (NOAC) to reduce the risk of stroke but have a rationale to seek a non-pharmacologic alternative. The study success is based on meeting the predetermined performance goal for the primary safety event rate at 7 days and effective LAA closure rate at one year. All treated patients are followed for two years.

The study is also powered to investigate the occurrence of ischemic stroke or systemic embolism at 24 months from the time of implant. The secondary endpoint will be evaluated after all patients complete 2 years of follow-up.

The study utilized an independent Data Safety Monitoring Board (DSMB) to oversee study progress and review clinical data and safety, an independent Clinical Events Committee (CEC), and an independent Echocardiography Core Lab for the interpretation of all echocardiographic data.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the PINNACLE FLX study was limited to patients who met the following inclusion criteria

   1. The subject is 18 years of age or older.
   2. The subject has documented paroxysmal, persistent, permanent or long-term/longstanding persistent non-valvular atrial fibrillation (i.e., the subject has not been diagnosed with rheumatic mitral valvular heart disease).

3. The subject is eligible for the defined protocol pharmacologic regimen of anticoagulation and antiplatelet therapy following WATCH WATCHMAN FLX Closure Device implant.
4. The subject is eligible to come off of anticoagulation therapy if the LAA is sealed (i.e. the subject has no other conditions that would require long-term anticoagulation therapy suggested by current standard medical practice).
5. The subject has a calculated CHA_2DS_2-VASc score of 2 or greater for males or 3 or greater for females.

Patients were <u>not</u> permitted to enroll in the PINNACLE FLX study if they met any of the following exclusion criteria:

1. The subject requires long-term anticoagulation therapy for reasons other than AF-related stroke risk reduction.
2. The subject is contraindicated for short-term anticoagulant therapy with DOAC post-implant.
3. The subject is contraindicated to aspirin and/or clopidogrel.
4. The subject is indicated for long-term clopidogrel therapy or has taken clopidogrel within 7 days prior to the WATCHMAN FLX Closure Device implant.
5. The subject had a prior stroke (of any cause, whether ischemic or hemorrhagic) or transient ischemic attack (TIA) within the 90 days prior to enrollment.
6. The subject has a history of atrial septal repair or has an ASD/PFO device.
7. The subject has implanted mechanical valve prosthesis in any position.
8. The subject has New York Heart Association Class IV Congestive Heart Failure at the time of enrollment.

Echo Exclusion Criteria

1. The subject has LVEF < 30%.
2. The subject has intracardiac thrombus, LAA sludge (gelatinous, non-adherent, intracavitary echo-density more layered than dense spontaneous echo contrast (SEC) seen continuously throughout cardiac cycle) or dense SEC visualized by TEE within 3 calendar days prior to implant.
3. The subject has an existing pericardial effusion with a circumferential echo-free space > 5mm, and/or the subject has signs/symptoms of acute or chronic pericarditis, and/or there is evidence (clinically or echocardiographically) of tamponade physiology.
4. The subject has a high- risk patent foramen ovale (PFO) defined as an atrial septal aneurysm (excursion > 15mm or length > 15mm) or a large shunt (early, within 3 beats and/or substantial passage of bubbles).
5. The subject has significant mitral valve stenosis (i.e., MV <1.5 cm2).
6. The subject has complex atheroma with mobile plaque of the descending aorta and/or aortic arch.
7. The subject has a cardiac tumor

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 45 days, 6 months, 12 months, 18 months, and 24 months postoperatively. The key timepoints and evaluations conducted at all time points are shown in **Table 5**.

Adverse events and complications were recorded at all visits. The key timepoints are shown below in the tables summarizing safety and effectiveness.

Table 5: Data Collection Schedule

Procedure/Assessment	Enrollment	Implant	Follow-up Visits				
			45-Day Office or Phone Visit	6-Month Office Visit	12 months Office Visit	18 months Office Visit	24 Month Office Visit
Informed consent form, including informed consent signature date	X						
Demographics, including age, gender, and race and ethnicity	X						
Physical exam including vital signs	X		X	X	X	X	X
Medical history	X						
Transthoracic echocardiogram (TTE)[a]	X						
Transesophageal echocardiogram (TEE)	X[b]	X	X	X[e]	X		
Brain Imaging (MRI/CT)	X[c]		As required[d]	As required[d]	As required[d]	As required[d]	As required[d]
Anticoagulant and antiplatelet medications	X		X	X	X	X	X
Modified Rankin Scale	X		X	X	X	X	X
NIH Stroke Scale	X		X		X		X
Device and implant details		X					
Adverse event/ Device Deficiency monitoring	X	X	X	X	X	X	X

[a] An LVEF value obtained from a TTE performed within 90 days prior to enrollment may be used. If a significant cardiac event occurs after the TTE which causes a change in cardiac status [i.e., major Congestive Heart Failure (CHF) decompensation] the enrollment TTE must be repeated at enrollment

[b] Within 3 calendar days prior to implant

[c] Obtain MRI/CT required at baseline if subject had prior stroke or TIA. A MRI or CT performed within in 90 days prior to enrollment may be used.

[d] Brain MRI or CT required if subject suffers stroke or TIA

[e] Only required for subjects that did not have a seal at the 45-day visit

3. Clinical Endpoints

With regards to safety, the primary safety endpoint was the occurrence of one of the following events between the time of implant and within 7 days following the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair.

With regards to effectiveness, the primary effectiveness endpoint was the rate of effective closure defined as any peri-device leak ≤ 5mm demonstrated by TEE at 12 months as assessed by the core lab.

Implant procedure success was defined as the successful delivery and release of a WATCHMAN FLX device into the LAA. With regard to success/failure criteria, each primary endpoint will be assessed compared to a performance goal. The study is considered a success when both of the following criteria are met:

- The primary safety endpoint event rate meets the prespecified performance goal of 4.21%.

  Hypotheses:

  H_0: Ps ≥ 4.21%

  H_a: Ps < 4.21%

  where Ps is the rate of subjects experiencing a safety endpoint event within 7 days or hospital discharge, whichever is later.
  The null hypothesis will be rejected if the resulting p-value is less than 0.05.

  and

- The proportion of subjects with effective LAA closure at 12 months (the primary effectiveness endpoint rate) meets the prespecified performance goal of 97%

  Hypotheses:

  H_0: P_{e1} ≤ 97.0%

  H_a: P_{e1} > 97.0%

  where P_{e1} is the Primary Effectiveness Endpoint rate.
  The null hypothesis will be rejected if the resulting p-value is less than 0.05.

- The secondary effectiveness endpoint (the occurrence of ischemic stroke or systemic embolism at 24 months from the time of implant) meets the prespecified performance goal of 8.7%.

  Hypotheses:
  H_0: $P_{e2} \geq 8.7\%$

  H_0: $P_{e2} < 8.7\%$

  where P_{e2} is the 2-year Kaplan-Meier rate of the Secondary Effectiveness Endpoint.

B. Accountability of PMA Cohort

At the time of database lock, 508 patients enrolled in the PMA study. Of these, 29 subjects failed the screening and 21 subjects met the clinical eligibility criteria but did not undergo an implant. Of the remaining 458 subjects, there were 58 Roll-In subjects and 400 Main Cohort subjects. The WATCHMAN FLX Closure Device was successfully implanted in 395/400 (98.8%) subjects who underwent the implant procedure.

At the time of database lock, of 400 Main Cohort patients enrolled in the PMA study, 88.8% (N=355) patients completed the 12-month follow-up visits and are available for analysis. **Table 6** shows an accounting of follow-up visit attendance. Subjects who exited the study due to death or withdrawal were not counted as having expected visists after the date of study exit.

Table 6: Visit Compliance

Visit	All Enrolled Subjects (N=400)
45-day	100.0% (400/400)
6-month	96.1% (370/385)
12-month	95.4% (355/372)
18-month	91.5% (86/94)
24-month	N/A
Values presented are % (# visits observed/ # visits expected)	

The analysis set for the primary safety analysis is the intent-to-treat analysis set, including all 400 implanted or attempted subjects. The analysis set for the primary effectiveness analysis includes 342 implanted subjects with a completed 12-month TEE, and who have not had any LAA closure procedures other than the initial

WATCHMAN FLX Closure Device implant attempt. Roll-in subjects are excluded from all primary analyses.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a nonvalvular atrial fibrillation study performed in the US. Patient demographics, AF-related stroke risk factors, and bleeding risk factors are summarized in **Table 7**, **Table 8**, and **Table 9**, respectively.

Table 7: PINNACLE FLX Baseline Demographics

Measure	Main Cohort (N=400)
Age	73.8 ± 8.6 (400) [44.0, 98.0]
Female Sex	35.5% (142/400)
Race/Ethnicity	
American Indian or Alaska native	0.3% (1/382)
Asian	0.5% (2/382)
Black or African heritage	4.7% (18/382)
Caucasian	93.7% (358/382)
Hispanic or Latino	2.6% (10/382)
Native Hawaiian or other Pacific Islander	0.0% (0/382)
Other race	0.0% (0/382)
AF Pattern	
Paroxysmal AF	51.8% (207/400)
Persistent AF	36.5% (146/400)
Permanent AF	10.5% (42/400)
Paced Rhythm	1.3% (5/400)

Table 8: PINNACLE FLX Baseline AF-related Stroke Risk Factors

Risk Factor and Risk Score	Main Cohort (N=400)
CHADS2 Score (Continuous)	2.3 ± 1.2 (400) [0, 6.0]
CHA2DS2-VASc score	4.2±1.5 (400) [2.0, 9.0]

1	0.0% (0/400)
2	13.8% (55/400)
3	21.3% (85/400)
4	25.3% (101/400)
5	21.3% (85/400)
6	10.5% (42/400)
7	6.5% (26/400)
8	0.8% (3/400)
9	0.8% (3/400)
History of CHF, LV Dysfunction, or Cardiomyopathy	31.8% (127/400)
Hypertension	85.8% (343/400)
Age 65-74	35.8% (143/400)
Age ≥75	50.5% (202/400)
Diabetes	30.5% (122/400)
Previous stroke, TIA, or TE	22.3% (89/400)
Vascular disease	55.0% (220/400)
Female Sex	35.5% (142/400)

Table 9: PINNACLE FLX Baseline HAS-BLED Score and Components

Bleeding Risk Factor and Score	**Main Cohort (N=400)**
HAS-BLED score	2.0±1.0 (400) [0.0, 5.0]
0	4.8% (19/400)
1	27.5% (110/400)
2	37.5% (150/400)
3	22.0% (88/400)
4	8.0% (32/400)
5	0.3% (1/400)
Uncontrolled hypertension, >160 mmHg systolic	1.5% (6/400)
Abnormal renal function	11.3% (45/400)
Abnormal liver function	1.3% (5/400)
Previous stroke	15.5% (62/400)

Prior major bleeding or predisposition to bleeding	33.0% (132/400)
Age ≥65	86.3% (345/400)
Medication usage predisposing to bleeding	47.3% (189/400)
Alcohol use >8 drinks per week	5.8% (23/400)

D. Safety and Effectiveness Results

1. Safety Results

Primary Safety Endpoint

The primary safety endpoint is the occurrence of one of the following events between the time of implant and within 7 days following the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. The primary analysis of safety was based on the intention to treat cohort of 400 Main Cohort subjects who underwent device implantation. The key safety outcomes for this study are presented in **Table 10**. Two subjects experienced post-implant ischemic stroke between the time of implant and within 7 days of the procedure. The primary safety endpoint rate was 0.5%. The one-sided 95% confidence interval upper bound was 1.6%, which met the performance goal of 4.21% ($p<0.0001$).

Table 10: Primary Safety Endpoint

Event	Event Rate (n/N)	Upper 1-sided 95% Confidence Interval	P Value
Primary safety endpoint	0.5% (2/400)	1.6%	<0.0001

Major Clinical Events

In the PINNACLE FLX trial, CEC adjudicates all major clinical events, including: all-cause stroke and TIA, systemic embolism, all-cause death, major bleeding events (BARC 3 or 5), device embolization, device thrombus, and pericardial effusion resulting in an invasive intervention. A summary of CEC adjudicated Major Clinical Events reported through the time of data cutoff is presented in **Table 11**.

Table 11: CEC Adjudicated Major Clinical Events

Event	Number of Events	Number of Subjects with an Event
All-cause death	27	27
Cardiovascular/Unknown Death	16	16
All stroke	12	12
Ischemic stroke	11	11
Hemorrhagic stroke	1	1
Transient Ischemic Attack (TIA)	1	1
Systemic Embolism	1	1
Device Embolization	0	0
Device Thrombus	7	7
Pericardial Effusion (PE) resulting in invasive intervention	5	5
PE requiring open cardiac surgery	0	0
PE requiring pericardiocentesis or pericardial puncture	4	4
Major Bleeding (BARC 3 or 5)	36	32
BARC 3 bleeding	34	30
BARC 5 bleeding	2	2

Mortality

There were 27 deaths in the main study cohort as of the data cutoff date. Of these, 16 deaths were adjudicated as cardiovascular or unexplained. The Kaplan-Meier estimates for the 12-month total and CV/unexplained mortality rates are 6.6% (N=25; 95% Cl: 4.4, 9.8) and 4.2% (N=14, 95% Cl: 2.4, 7.1), respectively.

There were no peri-procedural or procedure-related deaths. One death was adjudicated to be device-related. The 77-year-old man died of ischemic stroke on day 134 following device implant. Autopsy revealed premortem thrombus on the atrial facing surface of the left atrial appendage closure device.

Pericardial Effusion Requiring Intervention

There were 5 occurrences of pericardial effusion requiring pericardiocentesis (n=4) or transfusion (n=1). Of these, 3 occurred within 45 days (none within 7 days) and were device- or procedure-related.

Major Bleeding

A total of 36 major bleeding (BARC 3 or 5) events occurred in 32 subjects. The Kaplan-Meier estimate for major bleeding at 12 months is 7.9% (95% CI: 5.6%, 11.1%). In the PINNACLE FLX trial, most patients were prescribed apixaban (76.6%) or rivaroxaban (20.3%) post-implant and through 45 days following the procedure (refer to Table 12). During this period (0 – 45 days), there were 12 (3%) major bleeding events (procedure-related: 3, non-procedure related: 9).

Table 12: Oral Anticoagulant (OAC) Use (Post-Implant through 45 Days)

OAC	Percent of Total % (n/N)
Apixaban	76.7% (303/395)
Rivaroxaban	20.3% (80/395)
Dabigatran	2.0% (8/395)
Warfarin/VKA[a]	0.5% (2/395)
None[a]	0.3% (1/395)

[a]Documented as a protocol deviation

Device-Related Thrombus

The WATCHMAN FLX Closure Device was successfully implanted in 395/400 (98.8%) subjects. Implanted subjects in the study underwent mandatory TEE at 45 days (392/394, 99.5%) and one year (342/372, 91.9%). The incidence of device-related thrombus (DRT) was 1.8% (N = 7) at 12 months. All 7 subjects with DRT were taking aspirin or DAPT at the time of the event. Of these, 2 subjects experienced an ischemic stroke or systemic embolism at 12 months.

Adverse effects that occurred in the PMA clinical study:

Device and Procedure Related Serious Adverse Events

A summary of all device and procedure related serious adverse events for the main cohort subjects is presented in **Table 13**.

Table 13: Device- and Procedure-related Serious Adverse Events

	All Device or Procedure Related Events	
Sponsor Classification	**Events**	**% Subjects with Events**
Anemia requiring transfusion	1	0.3% (1/400)
Arrhythmias	2	0.3% (1/400)
Atrial Fibrillation (AF)	1	0.3% (1/400)
Death[a]	1	0.3% (1/400)
Device thrombus atrial facing – Post procedure	7	1.8% (7/400)
Fluid Overload	1	0.3% (1/400)
Gastrointestinal	1	0.3% (1/400)
Gastrointestinal bleeding	1	0.3% (1/400)
Peri-device leak[b]	10	2.5% (10/400)
Pericardial effusion	3	0.8% (3/400)
Prolonged bleeding from a laceration	1	0.3% (1/400)
Pulmonary	2	0.5% (2/400)
Respiratory insufficiency	1	0.3% (1/400)
Stroke (ischemic)	7	1.5% (6/400)
Systemic embolism	1	0.3% (1/400)
TEE/TTE related event	1	0.3% (1/400)
Thrombocytopenia	1	0.3% (1/400)
Total	**42**	**8.5% (34/400)**

[a] Cause of death (134 days following procedure): ischemic stroke. Autopsy revealed premortem thrombus on the surface of the left atrial appendage closure device.

[b] Core laboratory evaluation of TEEs assessed peri-device flow as ≤ 5 mm in all cases.

2. Effectiveness Results

Primary Effectiveness Endpoint

The Primary Effectiveness Endpoint is the rate of effective LAA closure at 12 months, defined as peri-device flow ≤ 5mm per core laboratory-assessed TEE.

The analysis of effectiveness was based on the 342 evaluable patients at the 12-month time point and who did not have any LAA closure procedures other than the initial WATCHMAN FLX Closure Device implant attempt. Key effectiveness outcomes are presented in **Tables 14** to **16**. The Primary Effectiveness Endpoint was achieved in 100% of evaluable subjects. The one-sided 95% confidence interval lower bound was 99.1%, which met the performance goal of 97%.

Table 14: Primary Effectiveness Endpoint

Event	Event Rate (n/N)	Performance Goal	Upper 1-sided 95% Confidence Interval	P Value
Primary effectiveness endpoint	100.0% (342/342)[a]	97.0%	99.1%	<0.0001

[a] In 2 subjects, an additional LAA closure procedure was performed prior to the 12-month TEE; thus, they were ineligible for the primary endpoint analysis.

A summary of the LAA closure rate for all WATCHMAN FLX Closure Device implant, 45-day and 12-month TEEs analyzed by the core laboratory at the time of database lock is presented in **Table 15.**

Table 15: Effective LAA Closure (Core Laboratory Assessment)

Peri-device flow	Implant	45 Days	12 Months
Jet size ≤ 5mm	100.0% (376/376) [99.0%, 100.0%]	100.0% (389/389) [99.1%, 100.0%]	100.0% (344/344[b]) [98.9%, 100.0%]
Jet size >0 and ≤ 5mm	7.4% (28/376) [5.0%, 10.6%]	17.2% (67/389) [13.6%, 21.4%]	10.5% (36/344 [b]) [7.4%, 14.2%]
Jet size > 5mm	0.0% (0/376) [0.0%, 1.0%]	0.0% (0/389) [0.0%, 0.9%]	0.0% (0/344 [b]) [0.0%, 1.1%]
TEE deemed not evaluable for leak by Core Laboratory[a]	2.3% (9/385) [1.1%, 4.4%]	0.8% (3/392) [0.2%, 2.2%]	0.9% (3/347) [0.2%, 2.5%]

[a] Site evaluation of TEEs assessed peri-device flow as ≤ 5 mm in all cases

[b] Two subjects had additional LAA intervention

Of 400 Main Cohort subjects, 56 subject did not have an evaluable 12-month TEE. The reasons for missing data are summarized in **Table 16**.

Table 16: Summary of Subjects without Primary Effectiveness Endpoint Data

		Prior Device Seal		
Rationale for Missing 12-month TEE	**No 12-Month TEE N=56**	**Complete seal at 45d N=41**	**Jet size ≤ 5mm at 45d N=7**	**Complete seal at implant N=3**
Implant Failure	5	--	--	--
Deceased Prior to 12-month visit	28	25	2	1
No 12-month TEE performed	13	8	4	1
Withdrawn prior to 12-month TEE	5	5	--	--
TEE images not evaluable by core lab	3	3	--	--
Subject unable to complete TEE	2	--	1	1

Secondary Effectiveness Endpoint

The Secondary Effectiveness Endpoint is the occurrence of ischemic stroke or systemic embolism at 24 months from the time of implant. The secondary endpoint will be evaluated after all patients complete 2 years of follow-up. At the time of data lock, 11 subjects and one subject experienced stroke and systemic embolism, respectively.

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 147 investigators of which none were full-time or part-time employees of the sponsor and 9 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: 9
- Proprietary interest in the product tested held by the investigator: none

- Significant equity interest held by investigator in sponsor of covered study: 1

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

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness outcomes of the PINNACLE FLX study demonstrate that the WATCHMAN FLX LAA Closure Device with Delivery System is effective for achieving adequate chronic LAA closure. Effective LAA closure at 12 months, defined as peri-device flow ≤ 5mm per core laboratory-assessed TEE, was achieved in all patients (100%), meeting the pre-specified performance goal of 97%. While the secondary effectiveness endpoint outcome is not available, the observed rate of ischemic stroke and systemic embolism at one-year follow-up is consistent with previous WATCHMAN trials. Since the WATCHMAN FLX Closure Device with Delivery Systemand its predecessor share similar designs and the same principle of operation, the clinical data of the WATCHMAN Closure Device with Delivery System can be leveraged to support the long-term performance of the WATCHMAN FLX Closure Device with Delivery System. The totality of clinical and pre-clinical evidence provides a reasonable assurance that the WATCHMAN FLX Closure Device with Delivery System is effective for reducing the risk of thrombolism from the left atrial appendage in nonvalvular atrial fibrillation patients who are eligible for anticoagulation therapy but have a rationale to seek a non-pharmacologic alternative.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and/or animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The results from the nonclinical laboratory and animal studies performed on the WATCHMAN FLX Closure Device with Delivery System demonstrate that this device is suitable for long-term implant. Since the WATCHMAN FLX Closure Device with Delivery System and its predecessor share similar designs and the same principle of operation, the clinical data of the

WATCHMAN Closure Device with Delivery System can be leveraged to support the long-term performance of the WATCHMAN FLX Closure Device with Delivery System. The potential risks associated with the device include procedure-related complications such as cardiac tamponade and procedure-related major bleeding complications.

The primary safety endpoint of the PINNACLE FLX study demonstrated a low rate of the major procedure-related complications (0.5%) and the primary safety event rate met the predetermined performance goal of 4.21%. With the post-device implant antithrombotic therapy recommended in the PINNACLE FLX study, the rates of peri-procedural major bleeding complications and device-related thrombus at one year are acceptable.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above and supplementary clinical experience from previous WATCHMAN trials. The probable benefits include a reduced risk of thromboembolism from the left atrial appendage and the ability for patients to discontinue anticoagulation (following successful closure of the left atrial appendage orifice) resulting in a reduced risk of long-term bleeding complications associated with chronic anticoagulation use. Based on the PINNACLE FLX study results, a significant portion of patients undergoing LAA closure with the WATCHMAN FLX device are expected to gain these probable benefits.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above and cumulative clinical experience with the WATCHMAN Closure Device with Delivery System. The probable risks of the WATCHMAN FLX Closure Device with Delivery System include procedure-related serious adverse events (such as cardiac tamponade and procedure related major bleeding complications) and ischemic stroke and/or systemic embolism due to device thrombosis. Past randomized controlled studies comparing LAA closure with the predecessor WATCHMAN Closure Device with Delivery System and chronic anticoagulation with warfarin also demonstrate an increased risk of ischemic stroke and systemic embolism with the non-pharmacologic approach.

In conclusion, given the available information above, the data show that for percutaneous, transcatheter closure of the left atrial appendage in patients meeting the criteria described in the indications for use statement, the probable benefits of the WATCHMAN Closure Device with Delivery System and WATCHMAN FLX Closure Device with Delivery System outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the WATCHMAN Closure Device with Delivery System and WATCHMAN FLX Closure Device with Delivery System to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for anticoagulation therapy; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to anticoagulation therapy, taking into account the safety and effectiveness of the device compared to anticoagulation therapy.

XIII. CDRH DECISION

CDRH issued an approval order on July 21, 2020. The final clinical conditions of approval cited in the approval order are described below.

PINNACLE FLX Continued Follow-up of IDE Cohorts: The study objective is to characterize the safety and effectiveness of the WATCHMAN FLX LAA Closure Device with Delivery System through 24 months post-procedure. This study should be conducted per version AF of the PINNACLE FLX protocol. The study will consist of all IDE patients who are currently enrolled and alive and will evaluate the secondary effectiveness endpoint. The secondary effectiveness endpoint is defined in the protocol as the occurrence of ischemic stroke or systemic embolism at 24 months from the time of implant. All available patients in PINNACLE FLX will be followed at post-enrollment intervals of 12 months, 18 months and 24 month follow up.

WATCHMAN FLX LAA Closure Device with Delivery System Real-World Use Surveillance: The applicant has agreed to work with the Society of American College of Cardiology (ACC) Left Atrial Appendage Occlusion (LAAO) Registry to ensure that FDA surveillance occurs for commercial uses of the WATCHMAN FLX LAA Closure Device with Delivery System. The surveillance will be carried out to characterize clinical outcomes and to assess the real-world use of the commercial WATCHMAN FLX LAA Closure Device with Delivery System.

Surveillance of the real-world use will involve all consecutive patients treated within the first 2 years that are entered into the LAAO Registry (enrollment period). The applicant has also agreed to link the data to the Centers for Medicare and Medicaid Services (CMS) claims database for long-term surveillance of these patients through 5 years post implantation (follow-up duration). This surveillance should monitor registry collected data (including: implant success rate, procedural safety, effective closure of the orifice of the left atrial appendage, and stroke [including ischemic or hemorrhagic] through one- year post-implant] and longer term identified occurrence of all stroke (including ischemic or hemorrhagic).

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.