SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Left Atrial Appendage Closure System

Device Trade Name: WATCHMAN FLX™ Left Atrial Appendage (LAA) Closure Technology

WATCHMAN FLX™ Left Atrial Appendage Closure Device with Delivery System

WATCHMAN FLX™ Pro Left Atrial Appendage Closure Device with Delivery System

Device Procode: NGV

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

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P130013/S074

Date of FDA Notice of Approval: July 16, 2025

The Original PMA (P130013) for the WATCHMAN® LAA Closure Technology 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 warfarin 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

A PMA Supplement (P130013/S035) 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.

The SSED to support the indication is available on CDRH website and is incorporated by reference here: https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130013S035B.pdf

The current PMA Supplement (S074) was submitted to expand the Indications for Use for the WATCHMAN FLX™ Left Atrial Appendage Closure Device with Delivery System and WATCHMAN FLX™ Pro Left Atrial Appendage Closure Device with Delivery System. The expanded Indications for Use are specific to patients who have undergone a catheter ablation for non-valvular atrial fibrillation and receive a WATCHMAN FLX™ or WATCHMAN FLX™ Pro Device (concomitantly or sequentially). Additionally, the PMA Supplement updates the post-implant drug regimen to allow physicians the option of prescribing non-vitamin K oral anticoagulant (NOAC) alone to patients who have received the device.

II. INDICATIONS FOR USE

The WATCHMAN FLX™ Device and the WATCHMAN FLX™ Pro 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 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.

Following catheter ablation for non-valvular atrial fibrillation (concomitantly or sequentially with WATCHMAN FLX™ or WATCHMAN FLX™ Pro implantation):

The WATCHMAN FLX™ Device and WATCHMAN FLX™ Pro 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 CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for anticoagulation therapy.

III. CONTRAINDICATIONS

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

- Intracardiac thrombus is present.
- An atrial septal defect repair or closure device is present.
- 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 FLX™ Device or WATCHMAN FLX™ Pro 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 $P2Y_{12}$ inhibitor.

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

The WATCHMAN FLX™ and WATCHMAN FLX™ Pro Devices are self-expanding nitinol (nickel-titanium alloy) structures with a polyethylene terephthalate (PET) porous membrane on the proximal face. Fixation anchors are located on the outer edge of the frame struts to provide stabilization in situ. Reference **Figure 1** for image representation of the WATCHMAN FLX™ and WATCHMAN FLX™ Pro Devices in situ.

The WATCHMAN FLX™ and WATCHMAN FLX™ Pro Devices are pre-loaded in a Delivery System (Delivery Catheter and Closure Device) 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 Closure Devices are 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. The WATCHMAN FLX™ LAA Closure Devices are available in 5 sizes, 20 mm, 24 mm, 27 mm, 31 mm, and 35 mm. The WATCHMAN FLX™ Pro LAA Closure Devices are available in the same 5 sizes but have an additional 40 mm size. Appropriate Closure Device sizing is determined by LAA measurements using fluoroscopy and echocardiographic guidance during the procedure or using cardiac CT or transesophageal echocardiography during pre-procedural planning. Reference **Table 1** for Device Sizing information.

Table 1: Device Sizing

WATCHMAN FLX™			WATCHMAN FLX™ Pro	
Device Size (mm)	**Max LAA Ostium (mm)**		**Device Size (mm)**	**Max LAA Ostium (mm)**
20	14.0 – 18.0		20	14.0 – 18.0
24	16.8 – 21.6		24	16.8 – 21.6
27	18.9 – 24.3		27	18.9 – 24.3
31	21.7 – 27.9		31	21.7 – 27.9
35	24.5 – 31.5		35	24.5 – 31.5
N/A	N/A		40	28.0 – 36.0

The WATCHMAN FLX™ Pro Device is based on the WATCHMAN FLX™ Device with the addition of a HEMOCOAT™ Technology coating on the PET fabric and three tantalum radiopaque (RO) markers at the plane of maximum diameter of the implant to aid in fluoroscopic assessment.

Figure 1a: WATCHMAN FLX™ Device

Figure 1b: WATCHMAN FLX™ Pro Device

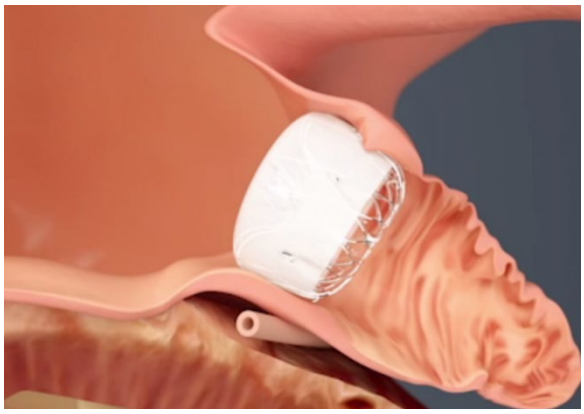

Figure 1c: WATCHMAN FLX™ Device In Situ at the Ostium of the LAA

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.

Other treatment options include occlusion of the left atrial appendage via commercially available transcatheter occluders, surgical clips, or surgical suturing.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

As of October 4, 2024, the WATCHMAN FLX™ LAA Closure Device with Delivery System is commercially available in the following countries as listed within **Table 2**.

Table 2: Countries Where WATCHMAN FLX™ LAA Closure Device with Delivery System is Commercially Available

Albania	Algeria	Andorra	Argentina
Australia	Austria	Belarus	Belgium
Brazil	Brunei Darussalam	Bulgaria	Canada
Chile	China	Colombia	Costa Rica
Croatia	Cyprus	Czech Republic	Denmark
Dominican Republic	Ecuador	Egypt	Estonia
Finland	France	Georgia	Germany
Great Britain	Greece	Guam	Hong Kong
Hungary	Iceland	India	Indonesia
Ireland	Israel	Italy	Japan
Jamaica	Jordan	Kazakhstan	Kenya
Kuwait	Latvia	Lebanon	Kosovo
Liechtenstein	Lithuania	Luxembourg	Macau
Malaysia	Malta	Mauritius	Mexico
Morocco	Nicaragua	Netherlands	New Zealand
Norway	Oman	Pakistan	Panama
Paraguay	Peru	Poland	Portugal
Qatar	Romania	Russian Federation	Saudi Arabia
Serbia	Singapore	Slovakia	Slovenia
South Africa	South Korea	Spain	Sweden
Switzerland	Taiwan	Thailand	Trinidad, Tobago
Tunisia	Turkey	United Arab Emirates	United States
Venezuela	Uruguay		

As of October 4, 2024, the WATCHMAN FLX™ Pro LAA Closure Device with Delivery System is commercially available in the following countries as listed within **Table 3**.

Table 3: Countries Where WATCHMAN FLX™ Pro is Commercially Available

Canada	Guam	Japan
Hong Kong	Kuwait	Macau
Taiwan	United States	

Neither WATCHMAN FLX™ nor WATCHMAN FLX™ Pro 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) which may be associated with the use of a left atrial appendage closure device or the implantation procedure.

- Air embolism
- Airway trauma
- Allergic reaction to contrast media, anesthetic, WATCHMAN implant material, or medication
- 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
- Myocardial infarction
- Nausea
- Oral bleeding
- Pericardial effusion/tamponade
- Pleural effusion
- Prolonged bleeding from a laceration
- Pseudoaneurysm
- Pulmonary edema
- Radiation injury
- 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 NON-CLINICAL STUDIES

No new nonclinical (laboratory or animal) studies were submitted or required for the approval of the expanded indication or alternative post-implant drug regimen proposed within this PMA Supplement for the WATCHMAN FLX™ LAA Closure Device with Delivery System or the WATCHMAN FLX™ Pro LAA Closure Device with Delivery System. Reference the previous SSEDs cited in Section I details regarding tests previously performed.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of left atrial appendage closure with the WATCHMAN FLX™ Left Atrial Appendage Closure Devices with Delivery System for reducing the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation following catheter ablation for non-valvular atrial fibrillation (concomitantly or sequentially with WATCHMAN FLX™ implantation) and**:**

- Are at increased risk for stroke and systemic embolism based on CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for anticoagulation therapy

This clinical study was conducted in the US, Australia, Belgium, Denmark, France, Germany, Italy, Netherlands, Poland, Spain under IDE # G180270. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

Since the WATCHMAN FLX™ Pro Closure Device with Delivery System and its predecessor (WATCHMAN FLX™) share similar designs and the same principle of operation, the clinical data of the WATCHMAN FLX™ Closure Device with Delivery System can be leveraged to support the performance of the WATCHMAN FLX™ Pro Closure Device with Delivery System for the proposed indication.

A. OPTION

A. Study Design

Patients were treated between June 11, 2019 and July 16, 2021. The database for this Panel Track Supplement reflected data collected through July 24, 2024 and included 1600 randomized patients. There were 114 investigational sites. The study was a prospective, randomized, multicenter, randomized clinical study. The control group was catheter ablation for non-valvular atrial fibrillation followed by indefinite oral anticoagulation (OAC) therapy.

Patients with non-valvular atrial fibrillation who were deemed by their physicians to be suitable for oral anticoagulation (OAC) therapy to reduce the risk of ischemic stroke and systemic embolism were included in this study. All subjects underwent catheter ablation either 90-180 days prior to randomization (sequential) or within 10

days following randomization (concomitant). The planned ablation type, concomitant or sequential, must have been specified prior to randomizing the subject. Subjects were randomized (1:1) to receive either a WATCHMAN FLX™ LAAC device or oral anticoagulation (control group) following ablation, and both groups were followed through 36 months. Randomization was stratified by sequential vs. concomitant ablation timing to help ensure balance of treatment assignments within these subgroups. However, subjects were not randomized to concomitant versus sequential groups within the same treatment arm. The study was not powered nor designed for a direct comparison between concomitant and sequential cohorts for patients undergoing WATCHMAN FLX™ LAAC.

This study utilized an independent data and safety monitoring committee to oversee trial safety and conduct, a clinical events committee to adjudicate all outcome events, and an independent core laboratory to assess all imaging.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the OPTION study was limited to patients who met the following inclusion criteria:

   1. The subject is of legal age to participate in the study per the laws of their respective geography.
   2. Underwent a prior catheter ablation procedure for non-valvular atrial fibrillation (AF) between 90 and 180 days prior to randomization (sequential) or is planning to have clinically indicated catheter ablation within 10 days of randomization (concomitant).
   3. The subject has a calculated CHA_2DS_2-VASc score of 2 or greater for males or 3 or greater for females.
   4. The subject is deemed by the treating physician to be suitable for the protocol defined pharmacologic regimens.
   5. The subject is able to undergo transesophageal echocardiography (TEE) examinations.
   6. The subject or legal representative is able to understand and is willing to provide written informed consent to participate in the trial.
   7. The subject is able and willing to return for required follow-up visits and examinations.

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

   1. The subject is currently enrolled in another investigational study that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments. Each instance must be brought to the attention of the sponsor to determine eligibility, regardless of type of co-enrollment being proposed.

2. The subject requires long-term anticoagulation therapy for reasons other than AF-related stroke risk reduction, for example due to an underlying hypercoagulable state (i.e., even if the device is implanted, the subjects would not be eligible to discontinue oral anticoagulation (OAC) due to other medical conditions requiring chronic OAC therapy).
3. The subject is deemed by the treating physician to be unsuitable for chronic anticoagulation and/or aspirin therapy due to bleeding risk, allergy, or other reasons.
4. The subject had or is planning to have any cardiac or major non-cardiac interventional or surgical procedure (excluding non-valvular AF ablation and cardioversion) within 30 days prior to or 60 days after randomization [including, but not limited to: percutaneous coronary intervention, other cardiac ablation (ventricular tachycardia (VT) ablation, etc.), etc.].
5. The subject had a stroke or transient ischemic attack (TIA) within the 60 days prior to randomization.
6. The subject had a prior major bleeding event per International Society on Thrombosis and Haemostasis (ISTH) definition within the 14 days prior to randomization. Lack of resolution of related clinical sequelae or planned and pending interventions to resolve bleeding/bleeding source, are a further exclusion regardless of timing of the bleeding event.
7. The subject has had a myocardial infarction documented in the clinical record as either a non-ST elevation myocardial infarction (MI) or as an ST-elevation MI, with or without intervention, within 90 days prior to randomization.
8. The subject has a history of atrial septal repair or has an atrial septal defect (ASD)/patent foramen ovale (PFO) device.
9. The subject has an implanted mechanical valve prosthesis in any position.
10. The subject is of childbearing potential and is, or plans to become pregnant during the time of the study (method of assessment upon study physician's discretion)
11. The subject has a documented life expectancy of less than two years.
12. The subject has a cardiac tumor.
13. The subject has signs/symptoms of acute or chronic pericarditis.
14. There is evidence of tamponade physiology.
15. The subject has contraindications (anatomical or medical) to percutaneous catheterization procedures.
16. The subject has documented New York Heart Association (NYHA) Class IV heart failure.
17. The subject has documented surgical closure of the left atrial appendage.
18. The subject has an active infection.

After signature of the informed consent and prior to randomization, all enrolled subjects underwent a transthoracic echocardiographic (TTE) evaluation to confirm eligibility. Subjects who met any one of the following echocardiographic exclusion criteria were excluded and were not randomized:

1. The subject has left ventricular ejection fraction (LVEF) < 30%

2. The subject has an existing pericardial effusion with a circumferential echo-free space >5mm.
3. The subject has a high- risk patent foramen ovale (PFO) with an atrial septal aneurysm excursion > 15mm or length > 15mm.
4. The subject has a high-risk PFO with a large shunt defined as early, within 3 beats and/or substantial passage of bubbles.
5. The subject has significant mitral valve stenosis (i.e., area <1.5 cm^2).

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 3 months, 12 months, 24 months, and 36 months following randomization.

Pre-procedurally, the following procedures/assessments were performed or collected for patients: informed consent process, including consent signature date, demographics, physical assessment, medical history, ablation information, transthoracic echocardiography, optional brain imaging, serum creatinine or Glomerular Filtration Rate (GFR)/Estimated Glomerular Filtration Rate (eGFR), platelet count and hemoglobin level, National Institutes of Health (NIH) Stroke Scale, Quality of Life (QoL) (EuroQol five-dimensional(EQ-5D)/SF12), medication regimen review, and adverse event assessment. Post-procedurally, the objective parameters measured during the study included the following in **Table 5.**

Table 4: Study Event Schedule Procedures and Assessments

Procedure/Assessment	Baseline Assessment (Prior to Randomization	Index Procedure (Ablation Procedure ± WATCHMAN FLX)	Follow-up Schedule[f]			
			3-Month Follow-up	12-Month Follow- up	24-Month Follow- up	36-Month Follow- up
Informed consent process, including consent signature date	X	--	--	--	--	--
Demographics	X	--	--	--	--	--
Physical assessment	X	DG and CC	X	X	X	X
Medical history	X	--	--	--	--	--
Ablation Information	X	CC	O	O	O	O
Device Information	--	DG	--	--	--	--
Procedure information and discharge assessment		DG and CC				
TTE	X[c]	--	--	--	--	--
Pre-procedure LAA imaging (TEE or CT)	--	DG[d]	--	--	--	--
Implant procedure TEE/ICE	--	DG				
Follow-up LAA imaging (TEE or CT)	--	--	DG[a]	DG[a]	O	O
Brain Imaging (CT or MRI)	O[b]	O[b]	O[b]	O[b]	O[b]	O[b]
Serum Creatinine or GFR/eGFR	X	--	--	--	--	--
Platelet count and Hemoglobin level	X	--	--	--	--	--
NIH Stroke Scale	X	--	X	X	X	X
Modified Rankin Scale[e]	X	--	X	X	X	X
QoL (EQ-5D/SF12)	X	--	--	X	--	X
Medication Regimen Review	X	X	X	X	X	X
AE assessment / device deficiency monitoring (as applicable)	X	X	X	X	X	X

X = All subjects; DG = Device Group; CC = Concomitant; O = Optional, data is collected if available

a: Implant subjects only (does not include Intent or Attempt subjects)
b: For subjects with prior stroke or TIA, prior MRI/CT scans may have been requested by BSC. For subjects who had a neurologic event during the trial, a copy of prior MRI/CT scans and MRI/CT scans from the event may have been requested.
c: The baseline TTE was done to evaluate all exclusion criteria to confirm subject eligibility. Other recent cardiac imaging may have been used to evaluate exclusion criteria if available in the subject's medical record.
d: Pre-procedure LAA imaging (TEE or CT) was required for ICE-guided WATCHMAN FLX™ implants and optional for TEE-guided WATCHMAN FLX™ implants
e: Modified Rankin Scale may have been completed via telehealth or phone at the discretion of certified , trained study personnel.
f: Physical exam and NIH stroke scale may not have bene completed remotely if the follow-up visit was conducted via phone. QoL may have been completed remotely if phone interview script was utilized.
Abbreviations: AE: Adverse Event; CT: computed tomography; MRI: magnetic resonance imaging; TEE: Transesophageal echocardiogram; TTE: transthoracic echocardiogram

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

The primary analysis population was the intent-to-treat population with each patient analyzed as being part of their randomized group regardless of the actual treatment received.

Primary Safety

With regards to safety, the primary safety endpoint was the occurrence of non-procedural bleeding which includes International Society on Thrombosis and Haemostasis (ISTH) major bleeding and clinically relevant non-major bleeding through 36 months.

The objective of the primary safety endpoint analysis was to test the null hypothesis that time-to-event distributions do not differ between the Device and Control groups. The null hypothesis was to be tested vs. the 2-sided alternative hypothesis that the time-to-event curves are different. The hypothesis for the primary safety endpoint was as follows:

H_0: $S1(t) = S0(t)$
H_a: $S1(t) \neq S0(t)$,

where S1(t) and S0(t) are the time-to-event curves for ISTH major bleeding and clinically relevant non-major bleeding of the Device and Control groups, respectively.

A sample of 1280 patients was estimated to provide the trial with 86% power to show superiority of LAAC versus oral anticoagulation with regard to the primary safety end point assuming a rate of 14% in the LAAC group and 20% in the OAC group. A sample size of 1600 patients was chosen to allow for withdrawals and loss to follow-up. Testing for superiority at a two-sided alpha level of 0.05 was

performed with a log rank P value based on the Kaplan-Meier estimation. All subjects in the randomized cohort were included in the analysis.

Primary Effectiveness

With regards to effectiveness, the primary effectiveness endpoint was the occurrence of stroke (including ischemic and/or hemorrhagic), all-cause death, and systemic embolism at 36 months.

The objective of the primary effectiveness endpoint analysis was to test the null hypothesis that the difference in cumulative incidence between the Device and Control groups is greater than a prespecified noninferiority margin δ. The null hypothesis was to be tested vs. the one-sided alternative hypothesis that the difference in cumulative incidence is less than a noninferiority margin δ. The hypothesis for the primary effectiveness endpoint was as follows:

H_0: $S1(t) \geq S0(t) + \delta$
H_a: $S1(t) < S0(t) + \delta$,

where S1(t) and S0(t) are the Kaplan Meier estimates for the cumulative incidence of stroke (including ischemic and/or hemorrhagic), all-cause death, and systemic embolism at 36 months for the Device and Control groups, respectively, and δ is a noninferiority margin of 5%.

The 97.5% one-sided upper bound of confidence limit of the difference between WATCHMAN FLX™ and Control rates was to be calculated using Greenwood formula for the variance of the Kaplan Meier estimates. The objective was to be met if this confidence limit is less than the predefined noninferiority margin.

If the non-inferiority hypothesis objective is met and the observed event rate favors the Device arm, i.e., $S1(t) < S0(t)$, a superiority test was to be subsequently performed.

The trial was also powered to detect noninferiority with respect to the primary effectiveness end point. It was assumed that 10% of the patients in each group would have a primary effectiveness endpoint event. A noninferiority margin of 5% was chosen, which represents a relative risk of 1.5. With 1600 patients, the trial provides more than 85% power to show noninferiority on the basis of the Farrington–Manning test at a one-sided type I error of 0.025. The study was considered successful if superiority testing of the primary safety end point and noninferiority testing of the primary effectiveness end point were met.

Secondary Endpoint

The secondary endpoint was the occurrence of ISTH major bleeding (including procedural bleeding) at 36 months.

This endpoint was defined as the Kaplan Meier estimates of time to first occurrence of major bleeding at 36 months and was to be tested for non-inferiority of WATCHMAN to Control.

If study success was met, this endpoint would be tested for noninferiority. With an assumed 11% rate in each cohort of patients and noninferiority margin of 5.25%, 1600 patients provided 84% power to show noninferiority on the basis of the Farrington–Manning test at a one-sided type I error of 0.025. If the non-inferiority hypothesis objective was met, a superiority test would subsequently be performed as part of hierarchical testing and a one-sided p-value of 0.025 will be considered significant.

The objective of the secondary endpoint analysis was to test the null hypothesis that the difference in cumulative incidence between the Device and Control groups is greater than a prespecified noninferiority margin δ. The null hypothesis was to be tested vs. the one-sided alternative hypothesis that the difference in cumulative incidence is less than a noninferiority margin δ. The hypothesis for the secondary endpoint is as follows:

H_0: $S1(t) \geq S0(t) + \delta$
H_a: $S1(t) < S0(t) + \delta$,

where S1(t) and S0(t) are the Kaplan Meier estimates for cumulative incidence of all ISTH major bleeding at 36 months for the Device and Control groups, respectively, and δ is a noninferiority margin of 5.25%

Study Success
To avoid multiplicity issues for additional statistical tests, a hierarchical order for the hypothesis tests and a testing significance level of a one-sided alpha of 0.025 for all hypotheses was used. Testing was performed in the following steps with each step needing to reject the null hypothesis in order to proceed to the next step:

1. Superiority testing of the primary safety endpoint and non-inferiority testing of the primary efficacy endpoint,
2. Non-inferiority testing of the secondary endpoint,
3. Superiority testing of the secondary endpoint and
4. Superiority testing of the primary efficacy endpoint.

The study was to be considered successful if superiority testing of the primary safety endpoint and non-inferiority testing of the primary effectiveness endpoint were both met.

B. Accountability of PMA Cohort

At the time of database lock, 1600 patients were enrolled in the PMA study.

All results described here pertain to the main cohort, intention-to-treat analysis set. **Table 6** shows the accountability of participants during the study.

Table 5: Study Visit Compliance

Visit	Control (n=797)	WATCHMAN FLX™ (n=803)
3-month	94.8% (754/795)	96.1% (772/803)
12-month	90.5% (714/789)	94.3% (751/796)
24-month	89.9% (698/776)	93.6% (737/787)
36-month	89.0% (679/763)	92.2% (714/774)

Values presented are % (# visits observed / # visits expected).

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. Subject demographics and risk factors are summarized in **Table 7**, **Table 8**, and **Table 9**.

Table 6: OPTION Baseline Subject Demographics

Demographic	OPTION					
	Primary Analysis **Intent-to-Treat** (Combined Concomitant and Sequential Arms) (N=1600)		**Concomitant Arm Subgroup (N=654)***		**Sequential Arm Subgroup (N=946)†**	
	WATCHMAN FLX™ (N=803)	**Control** (N=797)	**WATCHMAN FLX™ (N=328)**	**Control (N=326)**	**WATCHMAN FLX™ (N=475)**	**Control (N=471)**
Age, years	69.7±7.4 (803) (39.0, 86.0)	69.4±7.9 (797) (32.0, 87.0)	70.1±7.6 (328) (43.0, 86.0)	70.0±7.3 (326) (38.0, 87.0)	69.3±7.2 (475) (39.0, 86.0)	69.1±8.3 (471) (32.0, 87.0)
Sex						
Female	35.2% (283/803)	33.0% (263/797)	36.9% (121/328)	31.9% (104/326)	34.1% (162/475)	33.8% (159/471)
Male	64.8% (520/803)	66.9% (533/797)	63.1% (207/328)	67.8% (221/326)	65.9% (313/475)	66.2% (312/471)
Intersex	0.0% (0/803)	0.1% (1/797)	0.0% (0/328)	0.3% (1/326)	0.0% (0/475)	0.0% (0/471)
Race / Ethnicity						
American Indian or Alaskan	0.2% (2/803)	0.1% (1/797)	0.0% (0/328)	0.3% (1/326)	0.4% (2/475)	0.0% (0/471)
Asian	0.5% (4/803)	0.1% (1/797)	0.3% (1/328)	0.0% (0/326)	0.6% (3/475)	0.2% (1/471)
Black / African American	1.7% (14/803)	1.4% (11/797)	2.4% (8/328)	0.3% (1/326)	1.3% (6/475)	2.1% (10/471)
Caucasian	83.8% (673/803)	86.1% (686/797)	77.7% (255/328)	80.4% (262/326)	88.0% (418/475)	90.0% (424/471)
Hispanic / Latino	1.6% (13/803)	1.5% (12/797)	1.2% (4/328)	0.9% (3/326)	1.9% (9/475)	1.9% (9/471)
Hawaiian / Pacific Islander	0.0% (0/803)	0.0% (0/797)	0.0% (0/328)	0.0% (0/326)	0.0% (0/475)	0.0% (0/471)
Other	0.4% (3/803)	0.4% (3/797)	0.0% (0/328)	0.3% (1/326)	0.6% (3/475)	0.4% (2/471)
AF Pattern						
Paroxysmal AF	59.4% (477/803)	62.9% (501/797)	48.8% (160/328)	43.3% (141/326)	65.1% (309/475)	67.1% (316/471)

Persistent AF	40.6% (326/803)	37.1% (296/797)	51.2% (168/328)	56.7% (185/326)	34.9% (166/475)	32.9% (155/471)
Permanent AF	N/A	N/A	N/A	N/A	N/A	N/A
Paced AF	N/A	N/A	N/A	N/A	N/A	N/A
Unknown	N/A	N/A	N/A	N/A	N/A	N/A

*defined as concomitant ablation and LAAC within 10 days of randomization in the WATCHMAN FLX™ arm and as ablation within 10 days of randomization in the control arm

†defined as ablation 90 to 180 days before LAAC in WATCHMAN FLX™ patients and as ablation occurring 90 to 180 days before randomization in control patients

Table 7: OPTION CHA_2DS_2-VASc Score and Components

Measure	Control (n=797)	WATCHMAN FLX™ (n=803)
CHA_2DS_2-VASc score	3.5±1.3 (797) (1.0, 8.0)	3.5±1.3 (803) (1.0, 8.0)
1	0.9% (7/797)	0.6% (5/803)
2	21.0% (167/797)	21.5% (173/803)
3	32.0% (255/797)	31.8% (255/803)
4	24.2% (193/797)	25.3% (203/803)
5	14.3% (114/797)	13.3% (107/803)
6	6.0% (48/797)	5.7% (46/803)
7	1.5% (12/797)	1.4% (11/803)
8	0.1% (1/797)	0.4% (3/803)
9	0.0% (0/797)	0.0% (0/803)
CHF	26.5% (211/797)	26.9% (216/803)
Hypertension	88.0% (701/797)	89.8% (721/803)
Age 65-74	54.5% (434/797)	54.5% (438/803)
Age ≥75	26.2% (209/797)	27.4% (220/803)
Diabetes	27.7% (221/797)	27.6% (222/803)
Previous stroke, TIA, or TE	12.5% (100/797)	10.3% (83/803)
Vascular disease	47.7% (380/797)	44.1% (354/803)
Female sex	33.0% (263/797)	35.2% (283/803)

Data are Mean ± SD (n) [min, max] or % (n'/n).

Abbreviations: CHF=congestive heart failure; LV=left ventricle; TIA=transient ischemic attack; TE=thromboembolism

Table 8: OPTION HAS-BLED Score and Components

Measure	Control (n=797)	WATCHMAN FLX™ (n=803)
HAS-BLED score	1.2±0.8 (797) (0.0, 5.0)	1.2±0.8 (803) (0.0, 4.0)
0	14.7% (117/797)	18.4% (148/803)
1	56.3% (449/797)	54.9% (441/803)
2	22.0% (175/797)	20.4% (164/803)
3	6.4% (51/797)	5.1% (41/803)
4	0.5% (4/797)	1.1% (9/803)
5	0.1% (1/797)	0.0% (0/803)
Uncontrolled hypertension, >160 mmHg systolic	3.3% (26/797)	3.1% (25/803)
Abnormal renal function	9.0% (72/797)	9.0% (72/803)
Abnormal liver function	1.3% (10/797)	0.9% (7/803)
Previous stroke	6.1% (49/797)	5.5% (44/803)
Prior major bleeding or predisposition to bleeding	6.6% (53/797)	6.0% (48/803)
Age ≥65	77.0% (614/797)	75.6% (607/803)
Medication usage predisposing to bleeding	9.7% (77/797)	8.7% (70/803)
Alcohol use >8 drinks per week	6.1% (49/797)	5.1% (41/803)

Data are Mean ± SD (n) [min, max] or % (n'/n).

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the intention-to-treat (ITT) cohort of 1600 patients (803 WATCHMAN FLX™ and 797 Control). A total of 758 WATCHMAN FLX™ subjects and 737 Control subjects either had an event or clinical follow-up after 3 years.

This study met the primary safety endpoint of the occurrence of non-procedural major bleeding or clinically relevant non-major bleeding at 36 months. As shown in **Table 10,** in the ITT analysis set, the rate for the WATCHMAN FLX™ group (8.5%) was superior to the rate for the Control group (18.1%). Superiority was concluded because the two-sided p-value from the log-rank test was $p<0.0001$.

Table 9: Primary Safety Endpoint

Primary Safety Endpoint	Control (n=797)	WATCHMAN FLX™ (n=803)	Hazard Ratio [95% CI]	P Value
Occurrence of non-procedural ISTH major bleeding and clinically relevant non-major bleeding	18.1%	8.5%	0.44 [0.33, 0.59]	<.0001

Numbers (%) are Kaplan-Meier rates through 36 months after randomization

Note: Non-procedural events are those occurring more than 3 days after the procedure

Figure 2 shows the Kaplan–Meier survival curves for the primary safety endpoint of non-procedural bleeding through 36 months after randomization based on the International Society on Thrombosis and Haemostasis (ISTH) major bleeding or clinically relevant non-major bleeding definitions. Shown are the two primary cohorts, device group (patients who underwent catheter ablation and implantation of a left atrial appendage closure device in blue) and control group (patients who underwent catheter ablation only in orange).

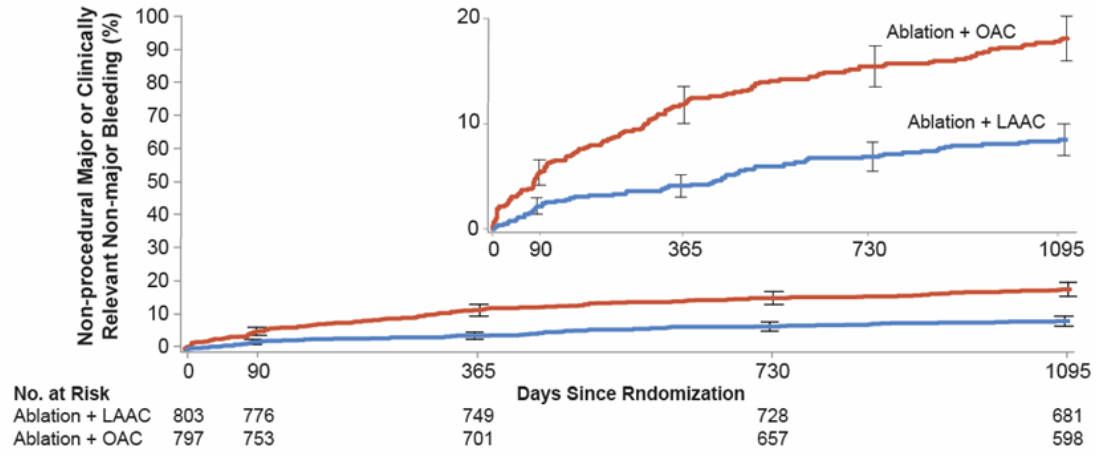

Figure 2: Kaplan Meier Incidence of Primary Safety Endpoint

The key safety outcomes for this study are presented below in **Table 11**. The hazard ratios and the 95% confidence intervals (C.I.) are exploratory in nature and cannot be used to make statistical inferences about these outcomes.

Table 10: Outcomes through 3 Years, Kaplan-Meier Event Rate Analysis

Outcomes Through 3 Year Post-Randomization	Control (n=797)	WATCHMAN FLX™ (n=803)	Hazard Ratio [95% C.I.]
CEC Adjudicated			
Stroke or all-cause mortality or systemic embolism	6.0% (45)	5.3% (41)	0.89 [0.58, 1.35]
All-cause mortality	4.5% (34)	3.8% (29)	0.83 [0.51, 1.36]
Cardiovascular	1.3% (10)	1.2% (9)	0.88 [0.36, 2.16]
Non-cardiovascular	2.6% (19)	1.9% (14)	0.72 [0.36, 1.43]
Unexplained death	0.7% (5)	0.8% (6)	1.17 [0.36, 3.82]
Stroke or systemic embolism	2.1% (16)	1.8% (14)	0.85 [0.42, 1.75]
Ischemic stroke or systemic embolism	1.5% (11)	1.5% (11)	0.97 [0.42, 2.25]
Stroke	2.0% (15)	1.6% (12)	0.78 [0.37, 1.67]
Ischemic	1.3% (10)	1.2% (9)	0.88 [0.36, 2.16]
Hemorrhagic	0.4% (3)	0.4% (3)	0.98 [0.20, 4.88]
Undetermined	0.3% (2)	0.0% (0)	0.00 [NA, NA]
Disabling (site-reported)	0.3% (2)	0.0% (0)	0.00 [NA, NA]
Non-disabling (site-reported)	1.1% (8)	0.8% (6)	0.73 [0.25, 2.11]
Systemic embolism	0.1% (1)	0.3% (2)	1.94 [0.18, 21.44]
TIA	1.5% (11)	1.6% (12)	1.07 [0.47, 2.42]
ISTH bleeding	18.1% (137)	9.5% (73)	0.50 [0.38, 0.66]
Major bleeding	5.0% (38)	3.9% (30)	0.77 [0.48, 1.24]
Non-major bleeding	14.6% (110)	6.0% (46)	0.39 [0.28, 0.55]
Pericardial effusion resulting in an intervention	0.7% (5)	0.3% (2)	0.39 [0.08, 2.01]
Non-procedural bleeding (after 3 days post procedure for device group)	NA	8.5% (65)	NA
ISTH non-major bleeding	NA	5.6% (43)	NA
ISTH major bleeding	NA	3.3% (25)	NA
Procedural bleeding (within 3 days post procedure for device group)	NA	1.0% (8)	NA
ISTH non-major bleeding	NA	0.4% (3)	NA
ISTH major bleeding	NA	0.6% (5)	NA
Pericardial Effusion resulting in an intervention	0.7% (5)	0.3% (2)	0.39 [0.08, 2.01]

Abbreviations: NA=not applicable; TIA=transient ischemic attack; ISTH=international society on thrombosis and hemostasis

Adverse effects that occurred in the PMA clinical study:

CEC-Adjudicated Clinical Events: Three-year Kaplan-Meier rates for CEC-adjudicated clinical events are shown in **Table 11** above. Device and procedure-related serious adverse events are reported in **Table 12** and **Table 13.** Events adjudicated by the CEC included the following: death (all cause, cardiovascular and non-cardiovascular), stroke (disabling, non-disabling, ischemic, and hemorrhagic), TIA, systemic embolism, bleeding (ISTH major and non-major, procedural and non-procedural), and pericardial effusion requiring intervention. Rates of mortality, stroke, or systemic embolism did not noticeably differ between the Control and Device groups. Control subjects experienced a higher rate of ISTH clinically relevant non-major bleeding compared to the WATCHMAN FLX™ Device group (Hazard Ratio = 0.39).

Table 11: Device and Procedure Serious Adverse Events

	All Device or Procedure Related Events		Device Related Events		Procedure Related Events	
Sponsor classification	**Events**	**% Subjects with Events**	**Events**	**% Subjects with Events**	**Events**	**% Subjects with Events**
Acute pulmonary oedema	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Air embolism	2	0.1% (2/1600)	2	0.1% (2/1600)	2	0.1% (2/1600)
Atrial fibrillation	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Atrial flutter	2	0.1% (2/1600)	0	0.0% (0/1600)	2	0.1% (2/1600)
Blood glucose increased	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Cardiac failure	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Catheter site hematoma	2	0.1% (2/1600)	1	0.1% (1/1600)	2	0.1% (2/1600)
Catheter site hemorrhage	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Cerebral hemorrhage	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Chronic kidney disease	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Death	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Device dislocation	3	0.2% (3/1600)	3	0.2% (3/1600)	2	0.1% (2/1600)
Device failure	1	0.1% (1/1600)	1	0.1% (1/1600)	1	0.1% (1/1600)
Device leakage	1	0.1% (1/1600)	1	0.1% (1/1600)	0	0.0% (0/1600)
Device related thrombosis	4	0.3% (4/1600)	4	0.3% (4/1600)	1	0.1% (1/1600)
Heart rate increased	1	0.1% (1/1600)	1	0.1% (1/1600)	0	0.0% (0/1600)
Nodal arrhythmia	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Odynophagia	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Pericardial effusion	3	0.2% (3/1600)	2	0.1% (2/1600)	3	0.2% (3/1600)
Pericarditis	3	0.2% (3/1600)	1	0.1% (1/1600)	3	0.2% (3/1600)
Pleuritic pain	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Pneumonia aspiration	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Post procedural complication	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Pulmonary embolism	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Pyrexia	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Retroperitoneal hemorrhage	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Sinus bradycardia	1	0.1% (1/1600)	0	0.0% (0/1600)	1	0.1% (1/1600)
Transient ischemic attack	2	0.1% (2/1600)	1	0.1% (1/1600)	1	0.1% (1/1600)
Vascular pseudoaneurysm	3	0.2% (3/1600)	0	0.0% (0/1600)	3	0.2% (3/1600)
Total	44	2.5% (40/1600)	17	1.1% (17/1600)	37	2.1% (33/1600)

Table 12: Imaging Endpoints through 1 Year for Subjects Randomized to WATCHMAN FLX™ (Core Laboratory)

	Procedure	90 Days	1 Year
Device Marginal Residual Leak			
Residual Leak (mm)	0.1±0.9 (669) (0.0, 21.0)	0.4±1.0 (706) (0.0, 13.0)	0.4±0.9 (664) (0.0, 5.5)
Effective Device Closure (Residual Leak ≤5 mm)	99.9% (668/669)	99.7% (704/706)	99.8% (663/664)
Residual Leak=0 mm	97.2% (650/669)	81.0% (572/706)	79.7% (529/664)
0 mm <Residual Leak ≤5 mm	99.9% (668/669)	99.7% (704/706)	99.8% (663/664)
0 mm <Residual Leak ≤3 mm	2.7% (18/669)	17.6% (124/706)	18.1% (120/664)
3 mm <Residual Leak ≤5 mm	0.0% (0/669)	1.1% (8/706)	2.1% (14/664)
Residual Leak >5 mm	0.1% (1/669)	0.3% (2/706)	0.2% (1/664)
Approximate angle of jet (degrees)	78.6±46.6 (19) (0.0, 140.0)	68.2±49.2 (106) (0.0, 145.0)	77.3±50.4 (109) (0.0, 150.0)
Device-related Thrombus			
Thrombus on the atrial facing surface of device[a]	NA	1.1% (8/734)	1.9% (13/702)
Laminar	NA	0.4% (3/734)	1.3% (9/702)
Mobile	NA	0.0% (0/734)	0.3% (2/702)
Non-mobile	NA	0.4% (3/734)	0.9% (6/702)
Pedunculated	NA	0.5% (4/734)	0.4% (3/702)
Mobile	NA	0.4% (3/734)	0.4% (3/702)
Non-mobile	NA	0.0% (0/734)	0.0% (0/702)
Maximum area of WATCHMAN FLX™ device thrombus	NA	0.3±0.2 (7) (0.1, 0.6)	0.3±0.2 (13) (0.1, 0.9)
Thrombus in the left atrium	NA	0.0% (0/734)	0.0% (0/702)
Mobile	NA	0.0% (0/734)	0.0% (0/702)
Non-mobile	NA	0.0% (0/734)	0.0% (0/702)
Not Assessed	NA	0.0% (0/734)	0.0% (0/702)
Additional Imaging Endpoints			
Pericardial Effusion[b]	2.5% (18/714)	4.8% (35/734)	6.8% (48/702)
Effusion Size	12.0±15.7 (18) (1.0, 49.0)	11.9±14.5 (35) (1.0, 48.0)	18.8±17.8 (47) (1.0, 53.0)
Not Assessed	8.5% (61/714)	7.5% (55/734)	12.3% (86/702)
Residual atrial septal shunt	65.0% (464/714)	20.4% (150/734)	12.7% (89/702)
size of atrial septal shunt ≤3 mm	58.7% (419/714)	17.2% (126/734)	8.1% (57/702)
size of atrial septal shunt >3 mm	2.5% (18/714)	1.1% (8/734)	2.1% (15/702)
Not Assessed	3.8% (27/714)	2.2% (16/734)	2.4% (17/702)
Direction of atrial septal shunt	65.0% (464/714)	20.4% (150/734)	12.7% (89/702)
Left to right	64.3% (459/714)	18.9% (139/734)	12.1% (85/702)
Bidirectional	0.4% (3/714)	0.1% (1/734)	0.0% (0/702)
Right to left	0.1% (1/714)	0.0% (0/734)	0.0% (0/702)
Not Assessed	0.1% (1/714)	1.4% (10/734)	0.6% (4/702)
LVEF	NA	52.7±9.3 (530) (20.0, 70.0)	53.8±9.5 (400) (15.0, 85.0)

a: Thrombus mobility could not be assessed for one subject at both 90-day and 1-year follow up.
b: Includes pericardial effusions that did not require intervention
Abbreviations: NA=not applicable

In descriptively comparing adverse event occurrences through 3 years of follow-up, atrial tachycardia (serious and non-serious site-reported) occurred in 15 WATCHMAN FLX™ device subjects (ITT n=803) compared to 9 control subjects (ITT n=797), and serious and non-serious site-reported pericardial effusions occurred in 17 WATCHMAN FLX™ device subjects compared to 6 control subjects. Adverse events were not collected between ablation and LAAC in sequential patients, and procedure-related adverse events were not assessed for relatedness to the ablation procedure.

2. Effectiveness Results

The analysis of effectiveness was based on the intention-to-treat (ITT) cohort of 1600 patients (803 WATCHMAN FLX™ and 797 Control). A total of 758 WATCHMAN FLX™ subjects and 737 Control subjects either had an event or clinical follow-up after 3 years.

Primary effectiveness endpoint

The WATCHMAN FLX™ cohort was non-inferior to the Control cohort for the 3-year primary effectiveness endpoint (time to first occurrence of stroke, all cause death, and systemic embolism at 36 months). In the ITT analysis set, the rate for the WATCHMAN FLX™ group was 5.3% and the rate for the Control group was 5.8%. Non-inferiority was concluded because the one-sided upper 97.5% confidence bound on the difference between treatment groups (WATCHMAN FLX™ - Control; 1.8%) was less than the non-inferiority margin demonstrating clinical equivalence ($p < 0.001$). Superiority of WATCHMAN FLX™ to the Control cohort was not demonstrated as the two-sided p-value from the log-rank test exceeded the significance threshold.

Figure 3 shows the primary effectiveness endpoint of all-cause death, stroke, or systemic embolism 36 months post randomization. Shown are the two primary cohorts, device group (patients who underwent catheter ablation and implantation of a left atrial appendage closure device in blue) and control group (patients who underwent catheter ablation only in orange).

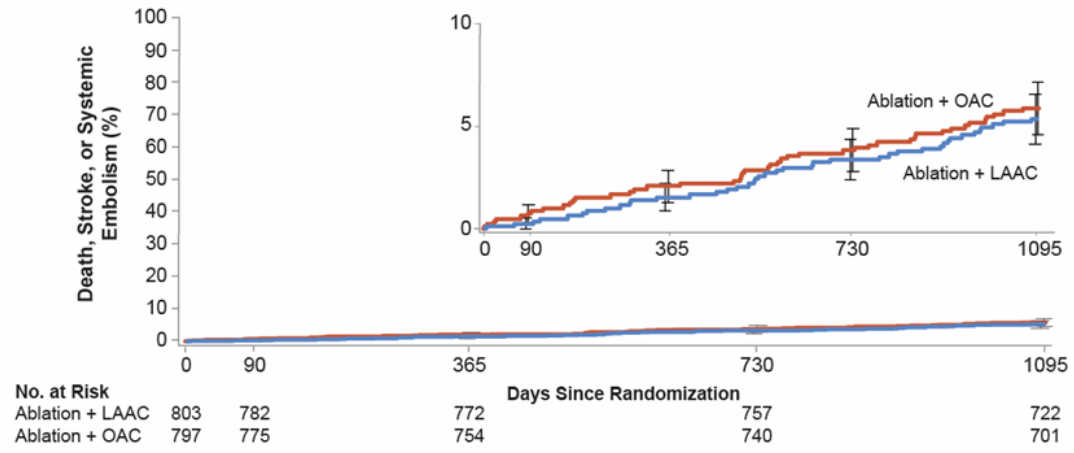

Figure 3: Kaplan Meier Incidence of Primary Effectiveness Endpoint

Secondary effectiveness endpoint

This study also showed statistically significant non-inferiority for the secondary endpoint of occurrence of ISTH major bleeding (including procedural bleeding) at 36 months. In the ITT analysis set, the rate for the WATCHMAN FLX™ group was 3.9% and the rate for the Control group was 5.0%. Non-inferiority was concluded because the one-sided upper 97.5% confidence bound on the difference between treatment groups (WATCHMAN FLX™ - Control; 1.0%) was less than the non-inferiority margin (P<0.001) establishing clinical equivalence. Superiority of WATCHMAN FLX™ to the Control cohort was not demonstrated as the two-sided p-value from the from the log-rank test exceeded the significance threshold.

Figure 4 shows the Kaplan–Meier survival curves for the secondary end point of major bleeding (including procedural bleeding) through 36 months after randomization. Shown are the two primary cohorts, device group (patients who underwent catheter ablation and implantation of a left atrial appendage closure device in blue) and control group (patients who underwent catheter ablation only in red).

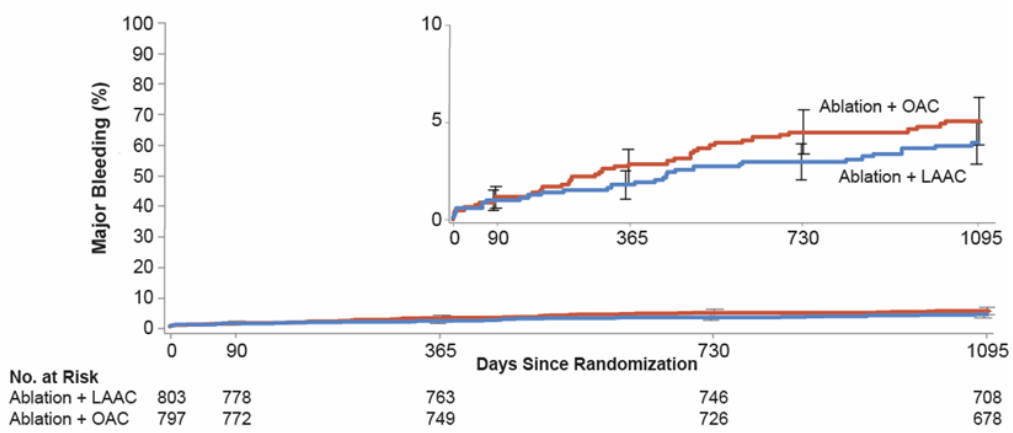

Figure 4: KM Incidence of Secondary Effectiveness Endpoint

Device Success

In the WATCHMAN FLX™ group, implantation was successful in 98.8% of patients; device or procedure-related complications occurred in 22 patients assigned to the device group and one patient in the anticoagulation group that crossed over to receive a device.

3. Subgroup Analyses

Selected baseline characteristics were evaluated for potential association with safety and effectiveness outcomes using a multivariate model Cox proportional hazard model. Variables included in the multivariate modeling analysis included: sex, age, race, prior major bleeding or predisposition to bleeding, previous stroke or transient ischemic attach (TIA), congestive heart failure

(CHF), abnormal renal function, diabetes, abnormal liver function, vascular disease, history of labile International Normalized Ratio (INR) (unstable/high INR or poor time in therapeutic range), alcohol use >8 drinks per week, hypertension, medication usage predisposing to bleeding, uncontrolled hypertension >160 mmHg systolic, left ventricular ejection fraction, and procedure timing (concomitant or sequential). Primary effectiveness and safety endpoint results are summarized and treatment groups compared based on the following subgroups:

- Sequential vs Concomitant subjects
- Male vs female
- Age at time of consent (< 75 years vs. ≥ 75 years)
- Stroke risk (CHA2DS2-VASc score 2-3, 4-5, and >5)
- Bleeding risk (HAS-BLED scores of 0, 1-2, and > 2)
- AF type at baseline (paroxysmal, persistent, permanent)

The study was not specifically powered for subgroups.
Subgroup analyses were intended as exploratory only. There were no significant subgroup interactions in subgroups, except for sex: the treatment effect of lower event rates for the Device group compared to Controls in the primary safety endpoint was more pronounced in males than females (see **Table 17**).

There was no significant subgroup interaction between the sequential and concomitant patients. There were numerical differences in the baseline characteristics and outcomes between the concomitant and sequential subgroups. This information is provided in the section below for reference.

Subgroup Analyses: Sequential vs. Concomitant Subgroup

In the concomitant subgroup, the mean CHA_2DS_2-VASc score was 3.4 ± 1.2, the mean age was 70 years, 37% were female, and 78% were Caucasian in subjects randomized to the WATCHMAN FLX™ arm. The mean CHA_2DS_2-VASc score was 3.5 ± 1.2, the mean age was 70 years, 32% were female, and 80% were Caucasian in subjects randomized to the Control arm.

In the sequential subgroup, the mean CHA_2DS_2-VASc score was 3.6 ± 1.3, the mean age was 69 years, 34% were female, and 88% were Caucasian in subjects randomized to the WATCHMAN FLX™ arm. For subjects randomized to the Control group, the mean CHA_2DS_2-VASc score was 3.6 ± 1.3, the mean age was 69 years, 34% were female, and 90% were Caucasian.

Device success was 99.1% in concomitant WATCHMAN FLX™ subjects and 98.7% in sequential WATCHMAN FLX™ subjects.

Imaging Endpoints:

Table 14 displays the number of evaluable patients with complete seal and device-related thrombus (DRT) at procedure, 90 days, and 1 year for subjects randomized to WATCHMAN FLX™ in the concomitant and sequential ablation timing subgroups. Patients who received WATCHMAN FLX™ implant at the time or within 10 days of ablation (concomitant group) had numerically lower rates of complete seal at 3- and 12-month follow up timepoints than patients who received WATCHMAN FLX™ implantation 90-180 days following ablation (sequential group). The ischemic stroke rates between the two groups were comparable. The core lab adjudicated DRT in 3 subjects in the concomitant ablation group (1.0%) and 5 subjects in the sequential ablation group (1.2%) at 3 months. At 12-months, the core lab adjudicated DRT in 10 subjects (3.5%) in the concomitant group and 3 subjects in the sequential group (0.7%). Most DRT were characterized as non-mobile laminar in either subgroup. No subjects in either ablation timing group who had a DRT at 3 or 12 months experienced a stroke or systemic embolism during follow-up.

Table 13: Core Laboratory Adjudicated Transesophageal Characteristics in Ablation + WATCHMAN FLX™ Patients

	Procedure	90 Days	1 year
Concomitant Subjects*			
LAA seal			
Residual leak — no. (%)			
Complete seal (0mm)	97.3% (255/262)	77.0% (224/291)	78.6% (206/262)
>0mm to ≤3mm	2.7% (7/262)	22.0% (64/291)	18.7% (49/262)
>3mm to ≤5mm	0.0% (0/262)	1.0% (3/291)	2.3% (6/262)
>5mm	0.0% (0/262)	0.0% (0/291)	0.4% (1/262)
Residual flow not assessed	0.0% (0/262)	0.7% (2/293)	1.5% (4/266)
Device-related thrombus — no. (%)	N/A	1.0% (3/304)	3.5% (10/282)
Laminar	N/A	0.3% (1/304)	2.8% (8/282)
Mobile	N/A	0.0% (0/304)	0.7% (2/282)
Non-mobile	N/A	0.3% (1/304)	1.8% (5/282)
Pedunculated	N/A	0.7% (2/304)	0.4% (1/282)
Mobile	N/A	0.3% (1/304)	0.4% (1/282)
Non-mobile	N/A	0.0% (0/304)	0.0% (0/282)
Sequential Subjects†			
LAA seal			
Residual leak — no. (%)			
Complete seal (0mm)	97.1% (395/407)	83.9% (348/415)	80.3% (323/402)
>0mm to ≤3mm	2.7% (11/407)	14.5% (60/415)	17.7% (71/402)
>3mm to ≤5mm	0.0% (0/407)	1.2% (5/415)	2.0% (8/402)
>5mm	0.2% (1/407)	0.5% (2/415)	0.0% (0/402)
Residual flow not assessed	0.0% (0/407)	0.5% (2/417)	0.2% (1/403)
Device-related thrombus — no. (%)	N/A	1.2% (5/430)	0.7% (3/420)
Laminar	N/A	0.5% (2/430)	0.2% (1/420)
Mobile	N/A	0.0% (0/430)	0.0% (0/420)
Non-mobile	N/A	0.5% (2/430)	0.2% (1/420)
Pedunculated	N/A	0.5% (2/430)	0.5% (2/420)
Mobile	N/A	0.5% (2/430)	0.5% (2/420)
Non-mobile	N/A	0.0% (0/430)	0.0% (0/420)

Core laboratory adjudicated; N/A indicates not assessed

*defined as concomitant ablation and LAAC within 10 days of randomization in the WATCHMAN FLX™ arm and as ablation within 10 days of randomization in the control arm

†defined as ablation 90 to 180 days before LAAC in WATCHMAN FLX™ subjects and as ablation occurring 90 to 180 days before randomization in control patients

For the primary safety and effectiveness endpoints and the secondary endpoint, concomitant and sequential ablation timing did not significantly interact with treatment group (**Table 15**).

Table 14: Primary and Secondary Endpoints - Interaction Analysis with Ablation Timing, Intent-to-Treat Subjects (N=1600)

	Control (N=797)	WATCHMAN FLX™ (N=803)	Hazard Ratio [95% C.I.]	*P* value	Interaction *P* value
Primary Safety Endpoint[a]					
Sequential	(N=471)	(N=475)			0.2411
	21.5% (95)	8.8% (40)	0.38 [0.27, 0.56]	<.0001	
Concomitant	(N=326)	(N=328)			
	13.3% (42)	8.0% (25)	0.56 [0.34, 0.92]	0.0200	
Primary Effectiveness Endpoint[b]					
Sequential	(N=471)	(N=475)			0.5393
	5.3% (23)	4.2% (19)	0.79 [0.43, 1.45]	0.4490	
Concomitant	(N=326)	(N=328)			
	6.7% (21)	7.0% (22)	1.04 [0.57, 1.88]	0.9083	
Secondary Endpoint[c]					
Sequential	(N=471)	(N=475)			0.1055
	5.7% (25)	3.1% (14)	0.54 [0.28, 1.04]	0.0608	
Concomitant	(N=326)	(N=328)			
	4.1% (13)	5.1% (16)	1.22 [0.59, 2.53]	0.5965	

Kaplan Meier event rates. Numbers are % (number of events)

a: Composite of non-procedural bleeding through 36 months (ISTH major bleeding and clinically relevant non-major bleeding), non-procedural events are those occurring after 3 days post procedure.

b: Composite of stroke (including ischemic and/or hemorrhagic), all cause death, and systemic embolism through 36 months.

c: ISTH major bleeding through 36 months (including procedural bleeding).

P-value from Cox regression

Clinical Events:

Table 16 shows mortality, stroke, and bleeding rates in sequential and concomitant subjects at 36 months post randomization. The rate of clinically relevant non-major bleeding was numerically lower in the WATCHMAN FLX™ group compared to Control for each of the sequential and concomitant subgroups.

In concomitant compared descriptively to sequential WATCHMAN FLX™ subjects at 36 months of follow-up, mortality was higher due to increased cardiovascular/unknown death. One death 342 days post index procedure with unknown cause for a subject in the concomitant WATCHMAN FLX™ group was considered by the site to be related to the device and related to the study medication. None of the deaths in the study were related to the procedure, and all occurred more than 166 days after WATCHMAN FLX™ implantation. All Stroke, Ischemic Stroke, Hemorrhagic Stroke, Non-disabling (site-reported) Stroke, and ISTH major bleeding rates were numerically higher in the concomitant WATCHMAN FLX™ subjects when compared to the sequential WATCHMAN FLX™ subjects. Conversely, Systemic Embolism and Clinically Relevant Non-Major Bleeding rates were numerically higher in

the sequential WATCHMAN FLX™ subjects when compared to the concomitant WATCHMAN FLX™ subjects. Through three years of follow-up, site-reported device related thrombus and both site-reported device- and procedure-related serious adverse events trended higher in concomitant when compared to sequential WATCHMAN FLX™ subjects (2.2%, 2.5%, and 5.5%, respectively, for concomitant and 0.9%, 1.5%, and 2.4%, respectively, for sequential). Additional details related to outcomes are below in **Table 16**.

When comparing concomitant to sequential control subjects descriptively, ISTH major bleeding and clinically relevant non-major bleeding were numerically increased in the sequential ablation subgroup.

Adverse events were not collected between ablation and LAAC in sequential patients, and procedure-related adverse events were not assessed for relatedness to the ablation procedure.

Table 15: Mortality, Stroke and Bleeding by Sequential and Concomitant Ablation Timing; Intention-to-Treat Analysis Set at 36 Months Follow-Up

	Sequential Subjects		Concomitant Subjects	
Event	**Control (N=471)**	**WATCHMAN FLX™ (N=475)**	**Control (N=326)**	**WATCHMAN FLX™ (N=328)**
All-cause death	3.9% (17)	2.7% (12)	5.4% (17)	5.4% (17)
Cardiovascular/unknown	2.1% (9)	1.1% (5)	1.9% (6)	3.2% (10)
Cardiovascular	1.4% (6)	0.2% (1)	1.3% (4)	2.5% (8)
Unknown	0.7% (3)	0.9% (4)	0.7% (2)	0.6% (2)
Non-cardiovascular	1.9% (8)	1.6% (7)	3.6% (11)	2.3% (7)
Stroke or Systemic Embolism	1.6% (7)	1.6% (7)	2.9% (9)	2.3% (7)
Ischemic stroke or Systemic Embolism	1.1% (5)	1.3% (6)	1.9% (6)	1.6% (5)
All stroke	1.6% (7)	1.1% (5)	2.5% (8)	2.3% (7)
Ischemic	1.1% (5)	0.9% (4)	1.6% (5)	1.6% (5)
Hemorrhagic	0.4% (2)	0.2% (1)	0.3% (1)	0.6% (2)
Systemic embolism	0.0% (0)	0.4% (2)	0.3% (1)	0.0% (0)
Transient ischemic attack	1.6% (7)	1.6% (7)	1.3% (4)	1.6% (5)
ISTH major bleeding or clinically relevant non-major bleeding	21.5% (95)	9.7% (44)	13.3% (42)	9.2% (29)
ISTH major bleeding	5.7% (25)	3.1% (14)	4.1% (13)	5.1% (16)
Clinically relevant non-major bleeding	17.3% (76)	7.0% (32)	10.8% (34)	4.4% (14)
Pericardial effusion resulting in an intervention	0.5% (2)	0.2% (1)	0.9% (3)	0.3% (1)

Kaplan Meier event rates. Numbers are % (n)
Abbreviations: CEC=clinical events committee; TIA=transient ischemic attack; ISTH=international society on thrombosis and Haemostasis

Subgroup Analyses: Sex Differences

A total of 1053 male subjects (65.8%) were enrolled in the ITT analysis set; 520 were randomized to WATCHMAN FLX™ and 533 were randomized to Control. There were 546 female subjects (34.1%) in the ITT analysis set; 283 were in the WATCHMAN FLX™ arm and 263 were in the Control arm. One subject identified as intersex and was not included in this subgroup analysis.

Overall, at 3 years, no differences in rates of mortality, ischemic stroke, and systemic embolism were found between treatment arms in females or in males. The device group reduction in post-procedure bleeding compared to controls was larger for males as compared to females. Females had numerically higher ISTH major bleeding and clinically relevant non-major bleeding than males in the device group (**Table 17).**

Table 16: Mortality, Stroke and Bleeding by Sex; Intention-to-Treat Analysis Set

Outcomes at 36 Months	**Male Subjects**		**Female Subjects**	
	Control (N=533)	**WATCHMAN FLX™ (N=520)**	**Control (N=263)**	**WATCHMAN FLX™ (N=283)**
All-cause death	4.6% (23)	3.6% (18)	4.5% (11)	4.2% (11)
Cardiovascular	1.4% (7)	1.0% (5)	1.2% (3)	1.5% (4)
Non-cardiovascular	2.4% (12)	2.0% (10)	2.9% (7)	1.5% (4)
Unexplained	0.8% (4)	0.6% (3)	0.4% (1)	1.2% (3)
All stroke	1.6% (8)	1.8% (9)	2.8% (7)	1.2% (3)
Ischemic	0.8% (4)	1.4% (7)	2.4% (6)	0.8% (2)
Hemorrhagic	0.4% (2)	0.4% (2)	0.4% (1)	0.4% (1)
Systemic embolism	0.2% (1)	0.2% (1)	0.0% (0)	0.4% (1)
ISTH major bleeding or clinically relevant non-major bleeding	19.1% (97)	7.7% (39)	16.2% (40)	12.8% (34)
ISTH major bleeding	4.2% (21)	3.0% (15)	6.8% (17)	5.6% (15)
Clinically relevant non-major bleeding	16.4% (83)	5.3% (27)	11.1% (27)	7.2% (19)

Values are % (count/sample size)

4. Pediatric Extrapolation

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

XI. 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 OPTION clinical study included 380 Principal and Sub-investigators over time, of which none were full-time or part-time employees of the sponsor; 25 of the 380 investigators 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: 0
- Significant payment of other sorts: 23
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 2

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.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. WATCHMAN FLX-SURPASS Discharge Medication Sub-Analysis

Primary Objective:
The objective of the WATCHMAN FLX™ Device SURveillance Post Approval AnalySiS Plan (SURPASS) analysis is to assess long-term safety and effectiveness outcomes associated with the use and implantation of the WATCHMAN FLX™ Left Atrial Appendage (LAA) Closure Device with Delivery System in a routine clinical setting. This surveillance analysis utilizes data captured in the Left Atrial Appendage Occlusion Registry (LAAO Registry) within the American College of Cardiology Foundation's (ACCF) National Cardiovascular Data Registry (NCDR).

The primary objective of the SURPASS discharge medication sub-analysis was to assess safety outcomes associated with the use of non-vitamin K oral anticoagulant (NOAC) alone as an alternative to an oral anticoagulant (OAC) and aspirin as the post-implant medication regimen after LAA closure in a routine clinical setting.

Design:
SURPASS data collection is ongoing and began in August 2020 with the US commercial release of WATCHMAN FLX™. The SURPASS discharge medication sub-analysis data set includes all patients enrolled in the LAAO Registry who had a WATCHMAN FLX™ Device implant attempt and were discharged from Aug 5, 2020 to September 30, 2022. The LAAO Registry is observational in nature and the data collected reflects the real-world setting and does not reflect a required clinical regimen. Discharge medication availability was the only inclusion criteria of the sub-analysis.

Key Safety Endpoint:
The occurrence of one of the following events between the time of the first implant procedure and within seven days of 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.

Additional Endpoints:
Additional analyses included the occurrence of the following endpoints at each LAAO Registry follow-up time points (discharge, 45 days, 6 months, and 12 months post-procedure):

- Death
- Stroke (Ischemic, Hemorrhagic)
- Systemic embolism
- Major bleeding

Enrollment Demographics: Among 97,325 subjects, the mean age was 76.4 ±7.9 years, 41% were female, and the mean CHA_2DS_2-VASc and HAS-BLED scores were 4.8±1.5 and 2.8±1.0, respectively. NOAC + aspirin is the most often prescribed discharge medication regimen post LAAC (47%), followed by NOAC alone (24%), and DAPT (9%) (**Table 18**).

Table 17: Summary of Baseline Characteristics SURPASS Discharge Medications Sub-Analysis

Characteristics	NOAC Alone (N = 23404)	NOAC+ Aspirin (N = 46169)	Warfarin Alone (N = 2303)	Warfarin+ Aspirin (N = 6270)	DAPT (N = 8974)
Age, years	76.5 ± 7.96 (23404)	76.2 ± 7.75 (46169)	76.7 ± 7.99 (2303)	76.7 ± 7.69 (6270)	76.9 ± 8.01 (8974)
Sex					
Female	45.31% (10605/23403)	40.60% (18742/46167)	45.59% (1050/2303)	39.44% (2473/6270)	41.63% (3736/8974)
Male	54.69% (12798/23403)	59.40% (27425/46167)	54.41% (1253/2303)	60.56% (3797/6270)	58.37% (5238/8974)
Race/Ethnicity					
American Indian or Alaskan	0.17% (40/22913)	0.22% (99/45491)	0.44% (10/2275)	0.19% (12/6194)	0.12% (11/8856)
Asian	1.49% (342/22913)	0.98% (444/45491)	0.92% (21/2275)	0.77% (48/6194)	1.31% (116/8856)
Black/African American	3.95% (904/22913)	3.82% (1740/45491)	3.52% (80/2275)	3.04% (188/6194)	5.23% (463/8856)
Caucasian	89.80% (20575/22913)	92.11% (41904/45491)	92.31% (2100/2275)	93.85% (5813/6194)	89.98% (7969/8856)
Hispanic / Latino	4.35% (997/22913)	2.67% (1215/45491)	2.59% (59/2275)	2.02% (125/6194)	3.05% (270/8856)
Hawaiian / Pacific Islander	0.11% (25/22913)	0.09% (39/45491)	0.09% (2/2275)	0.05% (3/6194)	0.15% (13/8856)
Other	0.13% (30/22913)	0.11% (50/45491)	0.13% (3/2275)	0.08% (5/6194)	0.16% (14/8856)

Characteristics	NOAC Alone (N = 23404)	NOAC+ Aspirin (N = 46169)	Warfarin Alone (N = 2303)	Warfarin+ Aspirin (N = 6270)	DAPT (N = 8974)
AF Pattern					
Paroxysmal AF	61.87% (14356/23205)	62.26% (28556/45864)	55.71% (1274/2287)	56.48% (3523/6238)	65.09% (5787/8891)
Persistent AF	21.18% (4915/23205)	21.73% (9966/45864)	19.94% (456/2287)	18.93% (1181/6238)	18.22% (1620/8891)
Permanent AF	10.73% (2489/23205)	11.07% (5079/45864)	17.18% (393/2287)	18.40% (1148/6238)	11.51% (1023/8891)
CHA2DS2-VASc Score	4.6 ± 1.50 (23357)	4.7 ± 1.48 (46087)	4.7 ± 1.51 (2296)	4.9 ± 1.47 (6261)	4.9 ± 1.52 (2523)
Congestive heart failure	35.36% (8272/23394)	36.11% (16662/46142)	41.36% (952/2302)	43.14% (2703/6265)	39.38% (3533/8971)
Hypertension	90.79% (21245/23401)	91.55% (42260/46162)	90.75% (2090/2303)	92.23% (5781/6268)	92.15% (8269/8973)
Diabetes	32.42% (7585/23399)	34.30% (15829/46150)	34.87% (802/2300)	38.26% (2398/6268)	37.20% (3336/8968)
Vascular disease	41.86% (9794/23398)	52.01% (24007/46157)	43.63% (1004/2301)	53.97% (3383/6268)	56.43% (5063/8972)
HAS-BLED Score	2.5 ± 1.10 (23357)	2.8 ± 1.12 (46069)	2.7 ± 1.15 (2298)	3.1 ± 1.16 (6259)	3.0 ± 1.10 (8948)

Results: The composite rate of major adverse events was lowest in NOAC alone and warfarin alone at 45 days (**Table 19)**. The main driver of this composite event rate was major bleeding, which was lowest at 45 days in subjects receiving NOAC alone (1.49%) or warfarin alone (1.37%) compared to patients receiving NOAC + aspirin (2.50%), warfarin + aspirin (2.10%), and DAPT (2.83%). The rate of death was lowest in subjects discharged on NOAC alone or NOAC + aspirin (**Table 19**).

Table 18: Events Post Discharge to 45 days

Description	NOAC Alone (N = 23404)	NOAC+ Aspirin (N = 46169)	Warfarin Alone (N = 2303)	Warfarin+ Aspirin (N = 6270)	DAPT (N = 8974)
Any major adverse events	2.46% (533)	3.40% (1514)	2.76% (59)	3.14% (192)	4.21% (358)
All death	0.55% (120)	0.59% (262)	1.26% (27)	0.73% (45)	0.93% (79)
Cardiovascular death/unknown cause death	0.28% (61)	0.27% (119)	0.66% (14)	0.34% (21)	0.48% (41)
Cardiovascular death	0.22% (47)	0.21% (92)	0.51% (11)	0.34% (21)	0.40% (34)
Death cause unknown/missing	0.06% (14)	0.06% (27)	0.14% (3)	0.00% (0)	0.08% (7)
Non-cardiovascular death	0.27% (59)	0.32% (143)	0.61% (13)	0.39% (24)	0.45% (38)
Pericardial effusion requiring surgical or percutaneous	0.08% (18)	0.13% (59)	0.14% (3)	0.08% (5)	0.08% (7)
Ischemic stroke or systemic thromboembolism	0.20% (43)	0.14% (62)	0.14% (3)	0.16% (10)	0.27% (23)
Any stroke or TIA	0.34% (74)	0.28% (126)	0.37% (8)	0.33% (20)	0.50% (43)
All stroke	0.22% (48)	0.19% (86)	0.33% (7)	0.21% (13)	0.40% (34)
Ischemic stroke	0.20% (43)	0.13% (59)	0.14% (3)	0.15% (9)	0.26% (22)
Hemorrhagic stroke	0.02% (4)	0.05% (24)	0.19% (4)	0.07% (4)	0.13% (11)
Undetermined stroke	0.00% (1)	0.01% (4)	0.00% (0)	0.00% (0)	0.01% (1)

Description	NOAC Alone (N = 23404)	NOAC+ Aspirin (N = 46169)	Warfarin Alone (N = 2303)	Warfarin+ Aspirin (N = 6270)	DAPT (N = 8974)
Transient ischemic attack	0.12% (26)	0.09% (41)	0.05% (1)	0.11% (7)	0.11% (9)
Systemic thromboembolism	0.00% (0)	0.01% (3)	0.00% (0)	0.02% (1)	0.01% (1)
Major bleeding	1.49% (322)	2.50% (1108)	1.37% (29)	2.10% (128)	2.83% (240)

Kaplan Meier event rates; Numbers are % (number of events)

Any major adverse event included death, cardiac arrest, ischemic stroke, hemorrhagic stroke, undetermined stroke, transient ischemic attack, intracranial hemorrhage, systemic arterial embolism, major bleeding, major vascular complication, myocardial infarction, pericardial effusion requiring intervention, and device embolization.

At 6 months, the lowest rates of major adverse events were found in subjects receiving NOAC alone or NOAC + aspirin at discharge; major bleeding was lowest in subjects receiving NOAC alone or warfarin alone at discharge (**Table 20)**. The rate of death was lowest in subjects discharged on NOAC alone or NOAC + aspirin. Any stroke or TIA occurred at the lowest rates in the NOAC alone or warfarin alone groups; however, the rate of stroke and TIA was also very low in the NOAC + aspirin at discharge group (**Table 20**).

Table 19: Events Post Discharge to 6 months

Description	NOAC Alone (N = 23404)	NOAC+ Aspirin (N = 46169)	Warfarin Alone (N = 2303)	Warfarin+ Aspirin (N = 6270)	DAPT (N = 8974)
Any major adverse events	7.39% (1491)	8.10% (3465)	9.38% (184)	9.31% (551)	10.73% (870)
All death	3.23% (637)	3.14% (1319)	5.45% (106)	4.39% (257)	4.73% (376)
Cardiovascular death/unknown cause death	1.27% (250)	1.19% (497)	2.39% (46)	1.55% (90)	1.78% (140)
Cardiovascular death	1.01% (199)	0.92% (385)	1.71% (33)	1.23% (72)	1.50% (118)
Death cause unknown/missing	0.26% (51)	0.27% (112)	0.69% (13)	0.32% (18)	0.28% (22)
Non-cardiovascular death	1.98% (387)	1.97% (822)	3.14% (60)	2.88% (167)	3.00% (236)
Ischemic stroke or systemic thromboembolism	0.59% (117)	0.63% (260)	0.31% (6)	0.61% (35)	0.67% (53)
Pericardial effusion requiring surgical or percutaneous	0.16% (32)	0.22% (94)	0.25% (5)	0.17% (10)	0.16% (13)
Ischemic stroke or systemic thromboembolism	0.59% (117)	0.63% (260)	0.31% (6)	0.61% (35)	0.67% (53)
Any stroke or TIA	0.95% (190)	0.99% (416)	0.88% (17)	1.23% (71)	1.21% (97)
All stroke	0.70% (140)	0.76% (317)	0.61% (12)	0.90% (52)	0.99% (79)
Ischemic stroke	0.53% (107)	0.59% (246)	0.31% (6)	0.55% (32)	0.60% (48)
Hemorrhagic stroke	0.15% (29)	0.15% (63)	0.30% (6)	0.29% (17)	0.34% (27)
Undetermined stroke	0.02% (4)	0.03% (14)	0.00% (0)	0.07% (4)	0.05% (4)
Transient ischemic attack	0.24% (50)	0.24% (102)	0.27% (5)	0.34% (20)	0.22% (18)
Systemic thromboembolism	0.05% (10)	0.04% (17)	0.00% (0)	0.05% (3)	0.08% (6)
Major bleeding	3.27% (664)	4.22% (1818)	3.73% (73)	4.34% (256)	5.22% (424)

Kaplan Meier event rates; Numbers are % (number of events)

Any major adverse event included death, cardiac arrest, ischemic stroke, hemorrhagic stroke, undetermined stroke, transient ischemic attack, intracranial hemorrhage, systemic arterial embolism, major bleeding, major vascular complication, myocardial infarction, pericardial effusion requiring intervention, and device embolization.

At 1 year, the lowest rates of major adverse events were found in subjects discharged on NOAC alone and NOAC + aspirin; the rates of death were also lowest in these two groups (**Table 21**). The rate major bleeding continued to be lower in the NOAC alone and warfarin alone discharge medication groups.

Table 20: Events Post Discharge to 1 year

Description	NOAC Alone (N = 23404)	NOAC+ Aspirin (N = 46169)	Warfarin Alone (N = 2303)	Warfarin+ Aspirin (N = 6270)	DAPT (N = 8974)
Any major adverse events	12.52% (2334)	12.66% (5127)	14.87% (275)	14.73% (833)	16.67% (1252)
All death	6.95% (1249)	6.33% (2483)	9.37% (171)	8.36% (464)	9.30% (669)
Cardiovascular death/unknown cause death	2.62% (464)	2.45% (944)	4.07% (73)	3.18% (172)	3.70% (258)
Cardiovascular death	2.07% (365)	1.85% (713)	3.14% (56)	2.48% (134)	3.08% (214)
Death cause unknown/missing	0.57% (99)	0.61% (231)	0.96% (17)	0.72% (38)	0.65% (44)
Non-cardiovascular death	4.44% (785)	3.98% (1539)	5.53% (98)	5.35% (292)	5.81% (411)
Pericardial effusion requiring surgical or percutaneous	0.22% (42)	0.27% (112)	0.31% (6)	0.21% (12)	0.23% (17)
Ischemic stroke or systemic thromboembolism	1.22% (216)	1.28% (486)	0.94% (16)	1.34% (71)	1.16% (82)
Any stroke or TIA	1.82% (326)	1.87% (722)	1.81% (32)	2.11% (115)	2.04% (146)
All stroke	1.42% (253)	1.46% (560)	1.42% (25)	1.67% (90)	1.54% (112)
Ischemic stroke	1.14% (202)	1.18% (449)	0.94% (16)	1.22% (65)	1.04% (74)
Hemorrhagic stroke	0.25% (45)	0.25% (99)	0.48% (9)	0.37% (21)	0.42% (32)
Undetermined stroke	0.05% (9)	0.06% (22)	0.00% (0)	0.09% (5)	0.10% (7)
Transient ischemic attack	0.40% (74)	0.45% (174)	0.39% (7)	0.51% (28)	0.50% (34)
Systemic thromboembolism	0.09% (16)	0.11% (40)	0.00% (0)	0.12% (6)	0.15% (10)
Major bleeding	4.22% (816)	5.05% (2111)	4.59% (86)	5.34% (305)	6.34% (492)

Kaplan Meier event rates; Numbers are % (number of events)

Any major adverse event included death, cardiac arrest, ischemic stroke, hemorrhagic stroke, undetermined stroke, transient ischemic attack, intracranial hemorrhage, systemic arterial embolism, major bleeding, major vascular complication, myocardial infarction, pericardial effusion requiring intervention, and device embolization.

At 45 days, effective device closure, defined as "Complete Seal" or 0 < Device Margin Residual leak (mm) ≤5mm, was greater than 99% for all groups.

At 1 year, device-related thrombus rates in evaluable patients who had a TEE or CT at the 12-month timepoint were 1.29% (31/2409) for NOAC Alone, 1.67% (109/6520) for NOAC + aspirin, 4.37% (10/229) for Warfarin Alone, 3.25% (29/891) for Warfarin + aspirin, and 1.79% (13/727) for DAPT patients.

Overall rates of any major adverse events were highest at all time points (45 days, 6 months and 1 year) in the DAPT group.

After adjusting for differences in baseline characteristics, the use of NOAC alone compared with the reference of NOAC + aspirin was associated with a significantly lower rate of major adverse events through 6 months and major bleeding between through 1 year of follow-up (**Table 22**). The risk of death was increased for the warfarin alone treated subjects at 1 year. The risk of stroke or TIA was increased in DAPT-treated subjects through 6 months and in warfarin + aspirin treated subjects at 1 year (**Table 22**).

Table 21: Adjusted Risk of Adverse Events in Mutually Exclusive Discharge Medication Groupings Compared With NOAC + Aspirin

	45 day		6 month		1 year	
	Univariate HR [95% CI]	**Multivariate HR [95% CI]**	**Univariate HR [95% CI]**	**Multivariate HR [95% CI]**	**Univariate HR [95% CI]**	**Multivariate HR [95% CI]**
Major adverse events						
NOAC alone	**0.87 [0.80, 0.94]**	**0.80 [0.71, 0.90]**	0.96 [0.90, 1.01]	**0.92 [0.85, 0.99]**	0.97 [0.92, 1.01]	0.96 [0.90, 1.02]
Warfarin + aspirin	1.07 [0.94, 1.22]	0.85 [0.72, 1.01]	1.20 [1.11, 1.31]	0.99 [0.88, 1.11]	1.17 [1.09, 1.25]	1.00 [0.91, 1.10]
Warfarin alone	0.91 [0.73, 1.14]	0.78 [0.60, 1.02]	1.16 [1.01, 1.34]	0.92 [0.78, 1.10]	1.16 [1.04, 1.31]	0.99 [0.86, 1.15]
DAPT	1.47 [1.33, 1.62]	0.94 [0.81, 1.10]	1.44 [1.35, 1.55]	0.93 [0.84, 1.04]	1.28 [1.21, 1.36]	0.94 [0.86, 1.03]
Death						
NOAC alone	0.94 [0.76, 1.17]	0.93 [0.71, 1.22]	1.03 [0.93, 1.13]	1.00 [0.88, 1.13]	1.01 [0.95, 1.08]	1.02 [0.93, 1.12]
Warfarin + aspirin	1.25 [0.91, 1.71]	0.92 [0.61, 1.41]	1.41 [1.23, 1.61]	1.06 [0.89, 1.26]	1.23 [1.11, 1.36]	1.06 [0.94, 1.21]
Warfarin alone	2.15 [1.45, 3.20]	1.61 [0.98, 2.63]	1.77 [1.45, 2.15]	1.22 [0.95, 1.56]	1.51 [1.29, 1.76]	**1.24 [1.02, 1.51]**
DAPT	1.58 [1.23, 2.03]	0.84 [0.58, 1.23]	1.52 [1.36, 1.71]	0.95 [0.80, 1.13]	1.21 [1.11, 1.32]	1.00 [0.88, 1.14]
Stroke or TIA						
NOAC alone	1.10 [0.85, 1.42]	1.10 [0.85, 1.43]	0.95 [0.81, 1.12]	0.97 [0.82, 1.15]	0.98 [0.86, 1.11]	1.04 [0.88, 1.24]
Warfarin + aspirin	1.04 [0.68, 1.60]	1.08 [0.70, 1.66]	1.19 [0.93, 1.52]	1.17 [0.91, 1.50]	1.29 [1.06, 1.56]	**1.31 [1.04, 1.65]**
Warfarin alone	1.11 [0.57, 2.17]	1.16 [0.59, 2.26]	0.85 [0.53, 1.36]	0.91 [0.57, 1.46]	1.21 [0.85, 1.71]	1.45 [0.99, 2.11]
DAPT	**1.77 [1.31, 2.39]**	**1.80 [1.33, 2.44]**	**1.29 [1.05, 1.59]**	**1.25 [1.01, 1.54]**	1.13 [0.95, 1.34]	1.27 [0.99, 1.64]
Major Bleeding						
NOAC alone	**0.79 [0.72, 0.88]**	**0.73 [0.64, 0.84]**	**0.87 [0.80, 0.94]**	**0.82 [0.73, 0.91]**	**0.89 [0.83, 0.96]**	**0.84 [0.76, 0.93]**
Warfarin + aspirin	1.05 [0.91, 1.23]	0.92 [0.76, 1.11]	**1.14 [1.01, 1.28]**	0.97 [0.83, 1.14]	1.10 [0.99, 1.23]	0.95 [0.82, 1.11]
Warfarin alone	**0.72 [0.54, 0.96]**	**0.62 [0.44, 0.87]**	0.93 [0.75, 1.14]	**0.72 [0.55, 0.93]**	0.90 [0.74, 1.09]	**0.78 [0.61, 0.99]**
DAPT	1.45 [1.30, 1.63]	0.84 [0.70, 1.00]	1.43 [1.30, 1.57]	**0.81 [0.69, 0.94]**	1.38 [1.26, 1.51]	**0.81 [0.70, 0.93]**

Reference NOAC + aspirin

HR=hazard ratio

To adjust for differences in baseline characteristics, multivariable Cox regression was performed using NOAC plus aspirin as the reference group. Variables were included in the regression analysis if they had a P value <0.05 in univariate analysis or were clinically known to be associated with the study outcomes. The final variables included in the analysis included age, sex, race, CHA2DS2-VASc score components (congestive heart failure, left ventricular dysfunction, hypertension, diabetes mellitus, transient ischemic. The confidence intervals are exploratory in nature and should not be used in place of hypothesis testing.

XIII. 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 Supplement 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.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint of OPTION was the composite rate of stroke (including ischemic and/or hemorrhagic), all cause death, and systemic embolism through 36 months. Device non-inferiority was considered achieved for the primary effectiveness endpoint.

The OPTION clinical trial results confirm the effectiveness of LAAC with the WATCHMAN FLX™ Device and indicate implantation of the device is a reasonable alternative to oral anticoagulation following percutaneous catheter ablation for high-risk subjects with non-valvular atrial fibrillation.

B. Safety Conclusions

The risks of the device are based on data collected in clinical studies conducted to support PMA approval as described above. The primary safety endpoint of the OPTION study was non-procedural ISTH major and clinically relevant non-major bleeding through 36 months. The device group was superior to the control group. The superiority result was driven primarily by higher rates of ISTH clinically relevant non-major bleeding in the Control arm compared to the Device arm. The secondary endpoint, defined as the Kaplan-Meier rate of ISTH major bleeding (including procedural bleeding) through 36 months, was also achieved. The 36-month rate of major bleeding among Control subjects was 5.0% (38 subjects). For subjects randomized to WATCHMAN FLX™ Device, this rate was 3.9% (30 subjects). Device non-inferiority was considered achieved for the secondary endpoint.

Outcomes stratified by discharge medication regimen were assessed in an observational study (WATCHMAN FLX-SURPASS discharge medication sub-analysis). The totality of clinical data from patients receiving NOAC alone therapy versus NOAC plus aspirin following WATCHMAN and WATCHMAN FLX™ implantation demonstrate a NOAC-only post-procedure antithrombotic regimen results in clinically acceptable rates of death, stroke or TIA, and major bleeding after device implantation.

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. 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 compared with chronic anticoagulation use. Based on the OPTION study results, a significant portion of patients undergoing LAA closure with the WATCHMAN FLX™ Device are expected to gain these probable benefits. Based on the WATCHMAN FLX-SURPASS Discharge Medication Sub-analysis, a significant portion of patients prescribed NOAC alone after device implantation 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. Cumulative clinical experience with the WATCHMAN FLX™ Closure Device with Delivery System were also considered. The probable risks of the WATCHMAN FLX™ Closure Device with Delivery System include device- and 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.

Additional factors to be considered in determining probable risk and benefits for the device included considering generalizability of results to real-world use, patient tolerance for risks of the device compared to medical therapies, timing of procedures, and patient sex.

1. Patient Perspective
   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support 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 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.

The WATCHMAN FLX™ Closure Device with Delivery System and WATCHMAN FLX™ Pro Closure Device with Delivery System 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 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.

Following catheter ablation for non-valvular atrial fibrillation (concomitantly or sequentially with WATCHMAN FLX™ or WATCHMAN FLX™ Pro implantation):

The WATCHMAN FLX™ and WATCHMAN FLX™ Pro Devices 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 CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for anticoagulation therapy

There is reasonable assurance that the probable benefits of the WATCHMAN FLX™ and WATCHMAN FLX™ Pro devices of reducing the risk of thromboembolism in patients while allowing most patients to discontinue long-term oral anticoagulation therapies outweigh the probable risks of device- and procedure-related adverse events (e.g., device-related thrombus, device leak or failures, procedural bleeding, etc.). For high-risk patients with non-valvular atrial fibrillation who have undergone catheter ablation, the device has demonstrated lower rates of non-procedural bleeding and similar all bleeding (including procedural bleeding) compared to medical therapy of oral anticoagulation after ablation.

XV. CDRH DECISION

CDRH issued an approval order on July 16, 2025. The final conditions of approval cited in the approval order are described below.

In addition to the Annual Report requirements, the applicant must provide the following data in post-approval study (PAS) reports for each PAS listed below.

1. **WATCHMAN FLX™ Pro OPTION PAS** – The applicant has agreed to work with the American College of Cardiology (ACC) Left Atrial Appendage Occlusion (LAAO) Registry to ensure that FDA surveillance occurs for commercial use of the WATCHMAN FLX™ Pro Left Atrial Appendage Device with Delivery System. The OPTION Post Approval Analysis will be carried out to continue to characterize clinical outcomes associated with concomitant ablation and WATCHMAN implant in real world use.

Surveillance of real-world use will include a minimum of 3,000 consecutive subjects entered into the LAAO Registry. Of these subjects, at least 1,500 subjects will be subjects in whom a WATCHMAN FLX™ Pro device was successfully implanted during a concomitant ablation procedure. The remaining subjects will be subjects in whom a WATCHMAN FLX™ Pro device was successfully implanted following a historical ablation procedure that occurred between 3-12 months prior to the WATCHMAN FLX™ Pro implant. This surveillance should monitor the following registry collected data: procedure related events, including pericardial effusion, and device margin residual leak, device related thrombus, the rate of all-cause death, cardiovascular death, stroke (ischemic and/or hemorrhagic), major bleed, systemic embolism. Assessments should occur at hospital discharge, 45 days, 6 months, 1 year and 2 years. Event rates and patient baseline characteristics will be descriptively reported.

2. **WATCHMAN FLX™ Pro NOAC Alone PAS –** The applicant has agreed to work with the American College of Cardiology (ACC) Left Atrial Appendage Occlusion (LAAO) Registry to ensure that FDA surveillance occurs for commercial use of the WATCHMAN FLX™ Pro Left Atrial Appendage Device with Delivery System. The NOAC Alone Post Approval Study will be carried out to continue to characterize clinical outcomes associated with the use of non-vitamin K oral anticoagulant (NOAC) alone as an alternative to an oral anticoagulant (OAC) and aspirin as the post-implant medication regimen for the WATCHMAN FLX™ Pro Left Atrial Appendage (LAA) Closure Device with Delivery System in a routine clinical setting. Surveillance of real-world use will include all consecutive subjects entered into the LAAO Registry who were successfully implanted with a WATCHMAN FLX™ Pro device, discharged, and prescribed NOAC alone, NOAC + aspirin, or dual antiplatelet therapy (DAPT) for 6 months from the date of the approval. This surveillance should monitor the following registry collected data: device- and procedure-related events, including pericardial effusion, and device margin residual leak, device related thrombus, device embolization, the rate of all-cause death, cardiovascular death, stroke (ischemic and/or hemorrhagic), major bleed, systemic embolism. Assessments should occur at hospital discharge, 45 days, 6 months, 1 year and 2 years. The above events will be descriptively compared between the cohorts of patients successfully implanted with a WATCHMAN FLX™ Pro device and discharged on NOAC Alone, NOAC + aspirin, and DAPT. The above event rates and baseline characteristics in the NOAC Alone, NOAC + aspirin, and DAPT cohorts will also be compared to the event rates in previously acquired LAAO Registry data prior to the NOAC Alone labeling implementation at hospital discharge, 45 days, 6 months, 1 year and 2 years. Patient baseline characteristics and event rates will also be descriptively reported and compared to those of patients in the SURPASS (WATCHMAN FLX) post approval analysis.

   From the date of study protocol approval, the applicant must meet the following timelines for OPTION PAS:

   - First subject enrolled within 6 months

- 20% of subjects enrolled within 12 months
- 50% of subjects enrolled within 18 months
- 100% of subjects enrolled within 24 months

In addition, the applicant must submit separate periodic reports on the progress of OPTION PAS and the WATCHMAN FLX™ PRO NOAC Alone PAS as follows:

- PAS Progress Reports every six (6) months until subject enrollment has been completed, and annually thereafter, from the date of the PMA approval letter, unless otherwise specified by FDA.
- If any enrollment milestones are not met, you must begin submitting quarterly enrollment status reports every 3 months in addition to your periodic (6-month) PAS Progress Reports, until FDA notifies you otherwise.
- Submit the Final PAS Report three (3) months from study completion (i.e., last subject's last follow-up date).

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

XVI. 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.