SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORAMTION

Device Generic Name:	System, Appendage Closure, Left Atrial
Device Trade Name:	Amplatzer™ Amulet™ Left Atrial Appendage Occluder
Device Product Code:	NGV
Applicant's Name and Address:	Abbott Medical 5050 Nathan Lane North, Plymouth, MN 55442, USA
Date(s) of Panel Recommendation:	None
Premarket Approval (PMA) Number:	P200049
Date of FDA Notice of Approval:	August 14, 2021

II. INDICATIONS FOR USE

The Amplatzer™ Amulet™ Left Atrial Appendage Occluder is a percutaneous transcatheter device intended to reduce the risk of thrombus embolization from the left atrial appendage (LAA) in patients who have nonvalvular atrial fibrillation and who are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores, are suitable for short term anticoagulation therapy, and have appropriate rationale to seek a non-pharmacologic alternative to oral anticoagulation, taking into consideration the safety and effectiveness of the device.

III. CONTRAINDICATIONS

The Amplatzer™ Amulet™ Left Atrial Appendage (LAA) Occluder is contraindicated for patients:

- with the presence of intracardiac thrombus
- with active endocarditis or other infections producing bacteremia
- where placement of the device would interfere with any intracardiac or intravascular structures

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Amplatzer Amulet LAA Occluder labeling (Instructions for Use).

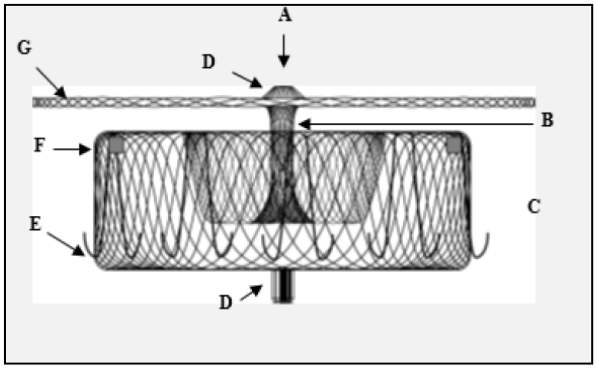
V. DEVICE DESCRIPTION

A. General Description

The Amplatzer™ Amulet™ Left Atrial Appendage Occluder (**Figure 1**) is a percutaneous transcatheter device intended to prevent thrombus embolization from the left atrial appendage (LAA) in patients who have non-valvular atrial fibrillation. It is a permanent implant intended for use in direct contact with the heart.

Figure 1: Amulet LAA Occluder

The device is constructed from a braided Nitinol mesh and consists of a disc and a lobe connected by a central waist. The lobe ranges in diameter from 16 mm to 34 mm and has stabilizing wires for device placement and retention. The disc is larger in diameter than the lobe, ranging from 22mm to 41mm. Both the disc and the lobe contain polyester fabric to facilitate occlusion. There are threaded screw attachments at either end of the device for connection to the delivery and loading cables. Radiopaque marker bands (Platinum/iridium) at either end of the device allow for predictable and visible placement of the device. **Figure 2** depicts the Amulet occluder components.



A=Screw Attachments
B=Waist of Device
C=Lobe
D=Marker Bands
E=Stabilizing Wires
F=Platinum/Iridium Thread
G=Disc

Figure 2: Amplatzer Amulet Left Atrial Appendage Occluder and Key Components

Figure 3 below depicts an Amulet device, attached to the delivery cable, advanced through the delivery sheath.

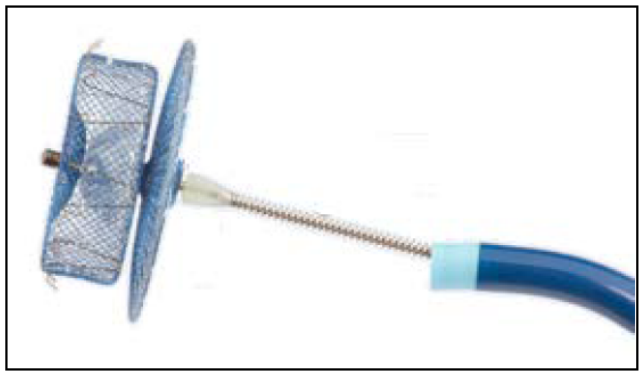
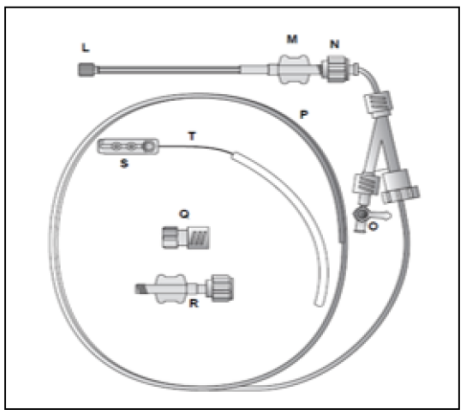


Figure 3: Amulet Device with Delivery Cable and Sheath

B. Accessories

The Amulet occluder is packaged with several accessory components to facilitate the delivery of the implant to the LAA with the recommended 12 French (12F) or 14 French (14F) Amplatzer TV45x45 Delivery Sheath (K163000, cleared 23 December 2016). All Amulet devices are packaged with an implant, loader, delivery cable, delivery cable vise, loading cable, loading cable vise and hemostasis valve. Additionally, a 13F to 14F sheath adaptor is included with device sizes 16-25 mm in order to facilitate connection of the 13F loader to a 14F delivery sheath. A 14F flush adaptor is also included for sizes 28 mm–34 mm to facilitate connection of the 14F loader to the hemostasis valve. **Figure 4** depicts the Amulet accessory components packaged with the device.



L:	Loader with Device	Q:	Delivery Cable Vise
M:	Loader Hub	R:	13-14Fr Sheath Adaptor (for Sizes 16mm – 25mm)
N:	14Fr flush adaptor (for sizes 28mm-34mm)	S:	Loading Cable Vise
O:	Hemostasis Valve	T:	Loading Cable
P:	Delivery Cable		

Figure 4: Amulet Occluder Accessory Components

C. Principles of Operation

Prior to implantation, a transesophageal echocardiography (TEE) is performed to rule out the presence of intracardiac thrombus (including left atrial appendage thrombus) and presence of pericardial effusion.

Implantation of the Amulet device occurs in a catheterization laboratory by interventional cardiologists or electrophysiologists using standard transcatheter techniques. Heparin is administered to achieve a recommended activated clotting time (ACT) of 250 seconds throughout the procedure. The physician performs a transseptal puncture using standard percutaneous techniques, gains access to the left atrium and places an Amplatzer guidewire into the left upper pulmonary vein. The dilator and delivery sheath are advanced over the guidewire to the landing zone. The physician then advances the distal portion of the dilator and delivery sheath approximately 10 mm into the left atrial appendage. The dilator and guidewire are removed from the sheath. The device is introduced into the sheath and advanced to the distal tip of the sheath. The device is guided into the left atrial appendage using fluoroscopy and TEE. Deployment of the lobe of the Amulet device initiates by retracting the delivery sheath to expose the lobe and continuing to deploy the lobe by advancing the delivery cable and/or pulling the delivery sheath back until the lobe is fully deployed within the left atrial appendage at the intended landing zone. While maintaining slight tension on the delivery cable, the sheath is retracted to expose the disc. The device disc should cover the orifice. Proper placement is confirmed using TEE and fluoroscopy. At least 2/3 of the device lobe should be distal to the left circumflex artery on echocardiography. When the device placement is confirmed, the device is released. The device is detached by turning the delivery cable vise counterclockwise and removing the delivery cable and sheath from the patient. If

device repositioning is not satisfactory, the device can be recaptured and repositioned by pulling the delivery cable. **Figure 5** illustrates final device placement.

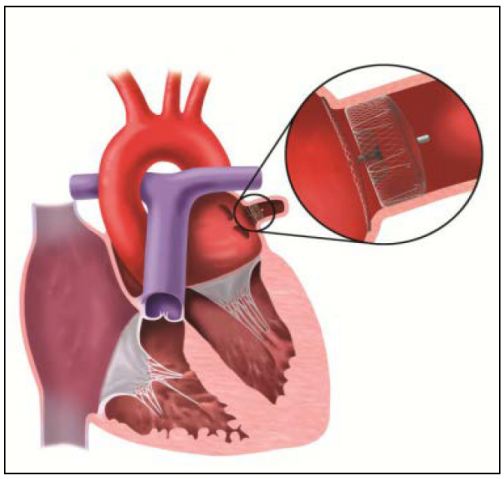


Figure 5: Amulet Device Placement in the LAA

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for preventing thrombus embolization from the left atrial appendage to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

The most common and recommended treatment to prevent stroke in patients with atrial fibrillation is oral anticoagulation. This includes vitamin K antagonists (VKA) such as warfarin, or non-VKA oral anticoagulant medications (NOACs). These oral anticoagulants reduce the blood's ability to clot.

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 July 19, 2021, the Amplatzer Amulet LAA Occluder Device is commercially available in the following countries:

Albania	Egypt	Libya	Reunion
Algeria	Estonia	Liechtenstein	Romania
Andorra	Finland	Lithuania	Rwanda
Argentina	France	Luxembourg	Saudi Arabia

Australia	French Polynesia	Malaysia	Serbia
Austria	French Guiana	Malta	Slovakia
Azerbaijan	Georgia	Martinique	Slovenia
Bahrain	Germany	Mauritius	South Africa
Belgium	Greece	Mexico	South Korea
Bolivia	Guadeloupe	Monaco	Spain
Brazil	Hong Kong	Morocco	Sweden
Bulgaria	Hungary	Netherlands	Switzerland
Canada	Iceland	New Caledonia	Taiwan
Chile	Indonesia	New Zealand	Thailand
Colombia	Ireland	Norway	Tunisia
Croatia	Israel	Palestine	Turkey
Cyprus	Italy	Panama	United Kingdom
Czech Republic	Jordan	Peru	United Arab Emirates
Denmark	Kazakhstan	Poland	Venezuela
Dominican Rep	Latvia	Portugal	Vietnam
Ecuador	Lebanon	Qatar	

The device has not been withdrawn from marketing for any reason related to its safety and 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 Amplatzer Amulet LAA Occluder or the device implantation procedure:

- Air embolism
- Airway trauma
- Allergic reaction
- Anemia
- Anesthesia reaction (nausea, vasovagal reaction confusion/altered mental status or other)
- Arrhythmia
- Atrial septal defect
- Bleeding
- Cardiac arrest
- Cardiac tamponade
- Chest pain/discomfort
- Congestive heart failure
- Death
- Device embolization
- Device erosion
- Device malfunction
- Device malposition

- Device migration
- Device related thrombus
- Fever
- Hematuria
- Hypertension/hypotension
- Infection
- Multi-organ failure
- Myocardial infarction
- Perforation
- Pericardial effusion
- Pleural effusion
- Renal failure/dysfunction
- Respiratory failure
- Seizure
- Significant residual flow
- Stroke
- Thrombocytopenia
- Thromboembolism: peripheral and pulmonary
- Thrombus formation
- Transient ischemic attack
- Valvular regurgitation/insufficiency
- Vascular access site injury (hematoma, pseudoaneurysm, arteriovenous fistula, groin pain or other)
- Vessel trauma/injury

For the specific adverse events that occurred in the clinical study, please see Summary of clinical data sections below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

1. Biocompatibility

Based on the results of the biocompatibility testing performed, the materials used in the Amplatzer Amulet LAA Occluder were determined to be biocompatible, non-mutagenic, non-toxic and, therefore, safe for the devices intended use. Testing was conducted in accordance with ISO 10993-1, Biological Evaluation of Medical Devices. According to ISO 10993, the Amulet Occluder is classified as a long-term implantable device contacting blood for >30 days. The accessory components packaged with the Amulet Occluder are classified as limited exposure (<24 hours) externally communicating, circulating blood contact devices. The required testing for the implant and accessories was determined based on these classifications, in accordance with ISO 10993-1.

A summary of the tests performed, and test results are presented in **Table 1** below.

Table 1: Biocompatibility Tests and Results

Biological Study	Test Name /Description	Implant	Accessory Components	Results
Cytotoxicity	ISO 10993-5 MEM Elution Assay	X	X	**Passed** Non-cytotoxic
Sensitization	ISO 10993-10 Guinea Pig Maximization	X	X	**Passed** Non-sensitizer
Irritation	ISO 10993-10 Intracutaneous Reactivity	X	X	**Passed** Non-irritant
Acute Systemic Toxicity	ISO 10993-11 Systemic Toxicity	X	X	**Passed** No evidence of systemic toxicity
Pyrogenicity	ISO 10993-11 Material Mediated Rabbit Pyrogen	X	X	**Passed** Non-pyrogenic
Genotoxicity	ISO 10993-3 Ames and Mouse Lymphoma	X	N/A	**Passed** Non-mutagenic
Implantation	ISO 10993-6 13 Week Intramuscular Implant Toxicity – Rabbit Model	X	N/A	**Passed** Non-irritant
Subacute/Subchronic Toxicity	ISO 10993-6 13 Week Intramuscular Implant Toxicity – Rabbit Model	X	N/A	**Passed** No patterns of systemic toxicity
Hemocompatibility	ISO 10993-4 Hemolysis (Direct and Indirect), Complement Activation, PTT, Platelet and Leukocyte Counts	X	X	**Passed** Acceptable hemocompatibility profile
Chemical Characterization	ISO 10993-18 GCMS, LCMS, ICPMS, and NVR	X	X	**Passed** Acceptable toxicological risk
Surface Characterization	ISO 10993-19 Scanning Electron Microscopy	X	X	**Passed** Surfaces comparable to control
Nickel Leach Profile	Quantitative assessment of nickel elution from device	X	N/A	**Passed** Acceptable nickel levels

2. In Vitro Engineering Tests

Design verification testing and material characterization was performed on the Amplatzer Amulet LAA Occluder to ensure the design meets all required inputs per the product specifications. The test results demonstrate that the Amulet Occluder meets all design requirements. The testing is summarized in **Table 2** below.

Table 2: Design Verification Testing

Test	Test Description	Results
Radial Force	These tests quantitatively assessed the outward radial force of the Amulet occluder.	**Pass**
Anchoring Force	This test quantitatively assessed the force to dislodge the Amulet occluder.	**Pass**
Stabilizing Wire Retention Force	This test quantitatively assessed the force required to remove a stabilizing wire from the Amulet occluder.	**Pass**
Occluder Tensile	This test assessed the tensile strength of the Amulet occluder.	**Pass**
System Preparation	These tests assessed the ability to flush the occluder properly.	**Pass**
Loading Force and Loading Requirements	These tests assessed the force required to load the Amulet occluder and the ability to load the Amulet occluder properly.	**Pass**
Advancement and Deploy Force	This test quantitatively assessed the force required to advance the Amulet occluder through the delivery sheath and deploy the occluder.	**Pass**
Partial and Full Recapture Forces	These tests quantitatively assessed the force required to partially and fully recapture the Amulet occluder into the delivery sheath.	**Pass**
Delivery Cable Detachment	These tests assessed the ability to detach the Amulet delivery cable from the occluder and ensured the delivery cable would not detach from the occluder unintentionally.	**Pass**
Inspection After Simulated Use	These tests assessed the Amulet occluder after simulated use testing to ensure the occluder met requirements.	**Pass**
MRI Compatibility Testing	This test assessed the compatibility of the Amulet occluder with MRI scanning. Additional MRI information is provided below this table.	**Pass**

Test	Test Description	Results
Occluder Fatigue Resistance	This test assessed the ability of the Amulet occluder to resist fatigue-related damage. The occluders were cycled to 400 million cycles, the equivalent of 10 years.	**Pass**
Occluder Corrosion Resistance	These tests assessed the ability of the Amulet occluder to resist corrosion	**Pass**
Particulate Testing	This test assessed the particulate levels generated from the Amulet occluder and delivery components during simulated clinical use.	**Pass**
Delivery Cable Tensile	This test quantitatively assessed the tensile strength of the Amulet delivery cable.	**Pass**
Delivery Cable Torque	This test quantitatively assessed the torque strength	**Pass**
Delivery Cable Flexibility	This test quantitatively assessed the flexibility of the distal end of the Amulet delivery cable	**Pass**
Delivery Cable Length	This test quantitatively assessed the length of the Amulet delivery cable.	**Pass**
Delivery Cable Leak	This test assessed the ability of the Amulet delivery cable to remain leak free.	**Pass**
Delivery Cable Distal Feature Tensile	This test quantitatively assessed the tensile strength of the distal feature of the Amulet delivery cable.	**Pass**
Accessories Corrosion Resistance	This test assessed the ability of the Amulet accessories to resist corrosion	**Pass**
Loading Cable Tensile	This test quantitatively assessed the tensile strength of the Amulet loading cable.	**Pass**
Loading Cable Length	This test quantitatively assessed the length of the Amulet loading cable.	**Pass**
Loader Tensile	This test quantitatively assessed the tensile strength of the Amulet loader.	**Pass**
Sheath Adapter Tensile	This test quantitatively assessed the tensile strength of the Amulet sheath adapter.	**Pass**
System Compatibility	These tests assessed the ability of the connections between components of the system to join properly and remain leak-free	**Pass**
Label Requirements	These tests assessed the ability of the labels of the Amulet occluder package to remain adhered and legible	**Pass**
Sterile Barrier	These tests assessed the ability of the Amulet occluder packaging system to maintain sterility of the package.	**Pass**

Magnetic Resonance Imaging (MRI) Compatibility

Non-clinical testing has demonstrated the Amplatzer Amulet Left Atrial Appendage Occluder is MR Conditional. A patient with the Amplatzer Amulet device can be safely scanned in an MR system under the following conditions:

- Static magnetic field of 1.5 Tesla (1.5T) and 3.0 Tesla (3.0T)
- Maximum spatial gradient field of 19 T/m (1900 G/cm)
- Maximum MR system reported, whole-body averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode)

Under the scan conditions defined above, the device is expected to produce a maximum temperature rise of less than or equal to 4°C after 15 minutes of continuous scanning. In non-clinical testing the image artifact caused by the device extends radially up to 20mm from the device when imaged with a gradient echo pulse sequence in a 3.0T MR system.

3. Sterilization

The Amplatzer Amulet Occluder is provided sterile and for single use only. The Amulet occluder is sterilized via ethylene oxide. The sterilization cycle was validated to meet a minimum Sterility Assurance Level (SAL) of 10^{-6}.

4. Shelf Life /Packaging

The Amulet device was validated to ensure that both device performance and package integrity were maintained for the shelf life of the product (5 years). Both the device and the packaging passed the 5-year accelerated aging shelf-life testing. Prior to the 5 years accelerated aging, the device and the packaging were subjected to 2x sterilization, distribution cycling and environmental conditioning that were in accordance with the applicable ASTM standards. At the end of the accelerated aging, performance verification testing was conducted, and all the samples met the pre-defined acceptance criteria.

B. Animal Studies

In vivo GLP animal testing was performed to evaluate the Amulet device for delivery, handling and device implant safety and performance. The animal validation activities included an acute study in a porcine model to assess the performance of the occluder with a delivery sheath, and a chronic implant study in a canine model to assess the safety and performance of transcatheter left atrial appendage occlusion. All requirements were met and demonstrated the Amulet device met customer requirements and intended use. In addition, a supplemental acute validation study was performed as part of validation activities for the Amulet design change which implemented a one-piece delivery cable as well as other modified accessory components for the acute delivery of the device to ensure the device and delivery system continued to meet performance requirements. In

totality, all studies met the protocol specified safety and performance criteria.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish reasonable assurance of safety and effectiveness of transcatheter left atrial appendage (LAA) closure with the Amulet left atrial appendage occluder to prevent thrombus embolization from the LAA in subjects with non-valvular atrial fibrillation in the US, Europe, Australia, and Canada under IDE G080150. Data from the Amulet IDE clinical trial were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between September 8, 2016 and March 8, 2019. The database for this PMA reflected data collected through October 26, 2020 and included 1878 randomized subjects (US: 1598, OUS: 280). There were 78 sites in the US and 30 sites outside the US.

The Amulet IDE Trial was a prospective, multi-center, randomized, controlled, pivotal trial comparing the safety and effectiveness of the Amulet device to the FDA-approved and commercially available Boston Scientific LAA closure device (Watchman; P130013). The study enrolled subjects with non-valvular AF who were eligible for short-term anticoagulation therapy but had a rationale to seek a non-pharmacologic alternative. Subjects were randomized 1:1 to transcatheter LAA occlusion with either the Amulet device or the Watchman device. After the study procedure, subjects were followed for up to 5 years.

The study success was assessed based on demonstrating non-inferiority of the Amulet device to the control device for the following: (1) rate of ischemic stroke or systemic embolism at 18 months, (2) composite of procedure-related complications, all-cause death or major bleeding at 12 months, and (3) effective closure at 45 days.

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) to adjudicate endpoint events, and an independent Echocardiography Core Lab for the interpretation of all echocardiographic data.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the Amulet IDE Trial was limited to patients who met the following inclusion criteria:

- 18 years of age or older
- Documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation and the patient has not been diagnosed with rheumatic mitral valvular heart disease
- At high risk of stroke or systemic embolism defined as $CHADS_2$ score $\geq$ 2 or a CHA_2DS_2-VASc score of $\geq$ 3

- Has an appropriate rationale to seek an alternative to warfarin or other anticoagulant medication
- Deemed by investigator to be suitable for short term warfarin therapy but deemed unable to take long term anticoagulation, following the conclusion of shared decision making (see next inclusion criterion)
- Deemed suitable for LAA closure by a multidisciplinary team of medical professionals (including an independent non-interventional physician) involved in the formal and shared decision-making process, and by use of an evidence-based decision tool on oral anticoagulation (final determination must be documented in the subject's medical record)
- Able to comply with the required medication regimen post-device implant
- Able to understand and is willing to provide written informed consent to participate in the trial
- Able and willing to return for required follow-up visits and examinations

Patients were <u>not</u> permitted to enroll in the Amulet IDE Trial if they met any of the following key exclusion criteria:

- Requires long-term oral anticoagulation therapy for a condition other than atrial fibrillation
- Contraindicated for or allergic to aspirin, clopidogrel, or warfarin use
- Has undergone atrial septal defect (ASD) repair or has an ASD closure device present
- Has undergone patent foramen ovale (PFO) repair or has a PFO closure device implanted
- Stroke or transient ischemic attack (TIA) within 90 days prior to randomization or implant procedure (as applicable)
- New York Heart Association Class IV Congestive Heart Failure
- Left ventricular ejection Fraction (LVEF) $\leq$ 30%
- Thrombocytopenia or anemia requiring transfusions
- Hypersensitivity to any portion of the device material or individual components of either the Amulet or Boston Scientific LAA closure device (e.g. nickel allergy)
- Active endocarditis or other infection producing bacteremia
- Subjects with severe renal failure (estimated glomerular filtration rate <30 ml/min/1.73m^2)
- Intracardiac thrombus visualized by echocardiographic imaging
- Existing circumferential pericardial effusion >2mm
- Cardiac tumor
- LAA anatomy cannot accommodate either a Boston Scientific LAA closure device or Amulet device, as per manufacturer's IFU. (i.e., the LAA anatomy and sizing must be appropriate for both devices in order to be enrolled in the trial. This is applicable to all roll-in and randomized subjects).
- Placement of the device would interfere with any intracardiac or intravascular structure

2. Follow-up Schedule

All patients were scheduled to return for clinical follow-up at discharge, 45 days, 3, 6, 9, 12 and 18 months, and 2, 3, 4 and 5 years. The key timepoints and evaluations conducted in the trial are shown in **Table 3**. Adverse events and complications were recorded at all visits.

Table 3: Study Visits and Assessments

Study Evaluation	Baseline	Procedure[2]	Discharge	45-day visit (± 5 days)	3-month visit (± 30 days) Phone Contact	6-month visit (± 30 days)	9-month visit (± 30 days) Phone Contact	12-month visit (±30 days)	**18-month visit	24-month visit (±30 days)	Annual visits 3, 4 and 5 years(±60 days) Phone Contact	Stroke Assessment Visit
Informed Consent Process	X											
History & Physical	X											
Cardiovascular & Medical Exam	X											
Neurological exam	X											
$CHADS_2$ and CHA_2DS_2-VASc scores	X											
HAS-BLED score	X											
Reason for seeking an alternative to Warfarin/OAC therapy	X											
INR assessment (as applicable)	X			X		X		X	X	X		X
12-lead ECG	X											
Pregnancy Test[1]	X											
Medication Assessment	X		X	X	X	X	X	X	X	X	X	X
MRI (CT if contraindicated)	X[3]											X
Modified Rankin Scale, NIHSS, & Barthel Index[4]	X											X
QVSFS	X			X	X	X	X	X	X	X	X	
EQ-5D-5L	X			X		X		X	X			
Angiography		X										
TTE			X									
TEE/TOE	X*	X		X		X[5]		X[6]				X[7]
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X	X

*Echoes performed within 90 days prior to consent will be accepted; otherwise, TEE/TOE must be conducted after consent;
[1]Pregnancy test for women of childbearing potential;
[2] Procedure must occur within 14 days from the date of randomization. Follow-up visit windows for implanted subjects will be calculated based on the date of procedure;
[3]MRI (CT if contraindicated) is required for subjects with a documented history of TIA or stroke. Previous imaging done post-neurological event is acceptable; otherwise must be repeated;
[4]Perform additional Neurological assessments after a confirmed stroke or TIA and repeat within 90 days of stroke confirmation.
[5] TEE/TOE is not required if closure was confirmed at 45 days (defined as residual jet <5mm);
[6] TEE/TOE is required for all subjects at 12 months;

[7] TEE/TOE is required at stroke visit only if stroke is confirmed by MRI/CT **As an endpoint visit, the 18-month visit window is -7/+45 days based on the date of implant procedure. Note: Subjects that are randomized but do not have a procedure or do not receive a device will be followed according to Table 3; however, medication requirements and follow-up TEE/TOEs are not required

3. Clinical Endpoints

Primary Safety Endpoint

The primary safety endpoint was a composite of procedure-related complications, all-cause death, or major bleeding (Type 3 or greater per Bleeding Academic Research Consortium (BARC) definition) at 12 months. The primary safety endpoint was analyzed based on event adjudication by the CEC.

For the primary safety endpoint, the following hypothesis was tested:

$$H_0: p_1(\text{Amulet}) - p_1(\text{Watchman}) \geq \Delta_1$$
$$H_1: p_1(\text{Amulet}) - p_1(\text{Watchman}) < \Delta_1$$

where p_1(device) is the probability of a primary safety endpoint event in the respective device group estimated by the Kaplan-Meier method, and Δ_1 is the absolute value of the non-inferiority margin for the safety endpoint. The non-inferiority margin (Δ_1) was prespecified to be 5.8%. The null hypothesis was tested at a significance level of 0.025.

The primary safety analysis was based on the per-protocol (PP) population which consisted of subjects who met all inclusion and none of the exclusion criteria, who underwent an implant attempt with the device as randomized.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was a composite of ischemic stroke and systemic embolism at 18 months.

For the primary effectiveness endpoint, the following hypothesis was tested:

$$H_0: p_2(\text{Amulet}) - p_2(\text{Watchman}) \geq \Delta_2$$
$$H_1: p_2(\text{Amulet}) - p_2(\text{Watchman}) < \Delta_2$$

where p_2(device) is the probability of a subject experiencing a primary effectiveness endpoint event in the respective device group estimated by the Kaplan-Meier method, and Δ_2 is the absolute value of the non-inferiority margin for the effectiveness endpoint. The non-inferiority margin (Δ_2) was prespecified to be 3.2%. The null hypothesis was tested at a significance level of 0.025.

The primary effectiveness analysis was based on the intention to treat (ITT) population, which includes all randomized subjects.

Primary Mechanism of Action Endpoint

The primary mechanism of action endpoint was device closure (defined as residual jet around the device ≤ 5 mm) as assessed by an independent core laboratory on transesophageal echocardiography (TEE) at the 45-day visit.

The following hypothesis was tested for this endpoint:

H_0: p_3(Amulet) – p_3(Control) ≤ $-\Delta_3$
H_1: p_3(Amulet) – p_3(Control) > $-\Delta_3$

where p_3(Amulet) is the 45-day closure probability in the Amulet group, p_3(Watchman) is the corresponding probability in the Watchman group, and Δ_3 is the absolute value of the non-inferiority margin. The non- inferiority margin (Δ_3) was chosen to be -3%. The null hypothesis was tested at a significance level of 0.025.

The analysis population for the primary mechanism of action endpoint includes subjects who received the device (i.e., successfully implanted) as randomized and who had closure status determined by the Echocardiography Core Lab reviewed 45-day TEE.

Secondary Endpoint

If all three primary endpoints of non-inferiority of are met, the Hochberg procedure is used to adjust for multiple comparisons for testing the following secondary endpoints (including superiority of primary endpoints):

- A composite of all stroke, systemic embolism, or cardiovascular/unexplained death through 18 months (non-inferiority analysis with a prespecified non-inferiority margin of 4.5%)

- Major bleeding rate through 18 months, defined as Type 3 or greater based on BARC definition (superiority analysis)

- A composite of procedure-related complications, or all-cause death, or major bleeding through 12 months (superiority analysis)

- A composite of ischemic stroke or systemic embolism through 18 months (superiority analysis)

- Device closure (defined as residual jet around the device ≤5 mm) at the 45-day visit documented by TEE/TOE, defined by Doppler flow (superiority analysis)

With regard to success/failure criteria, the study would be considered a success when all three primary endpoints were met.

B. Accountability of PMA Cohort

At the time of database lock, of 1878 randomized patients in the Amulet IDE study, 81.9% (N = 1538) of patients were available for analysis at the 18-month post-procedure visit. Subject accountability is shown in **Figure 6** and **Table 4**. Through the 18-month follow-up, visit compliance (i.e., Actual Follow-up Rate) in subjects with an implant attempt was 93.3% in the Amulet group and 89.3% in the Watchman group.

Figure 6: Disposition of Randomized Subject

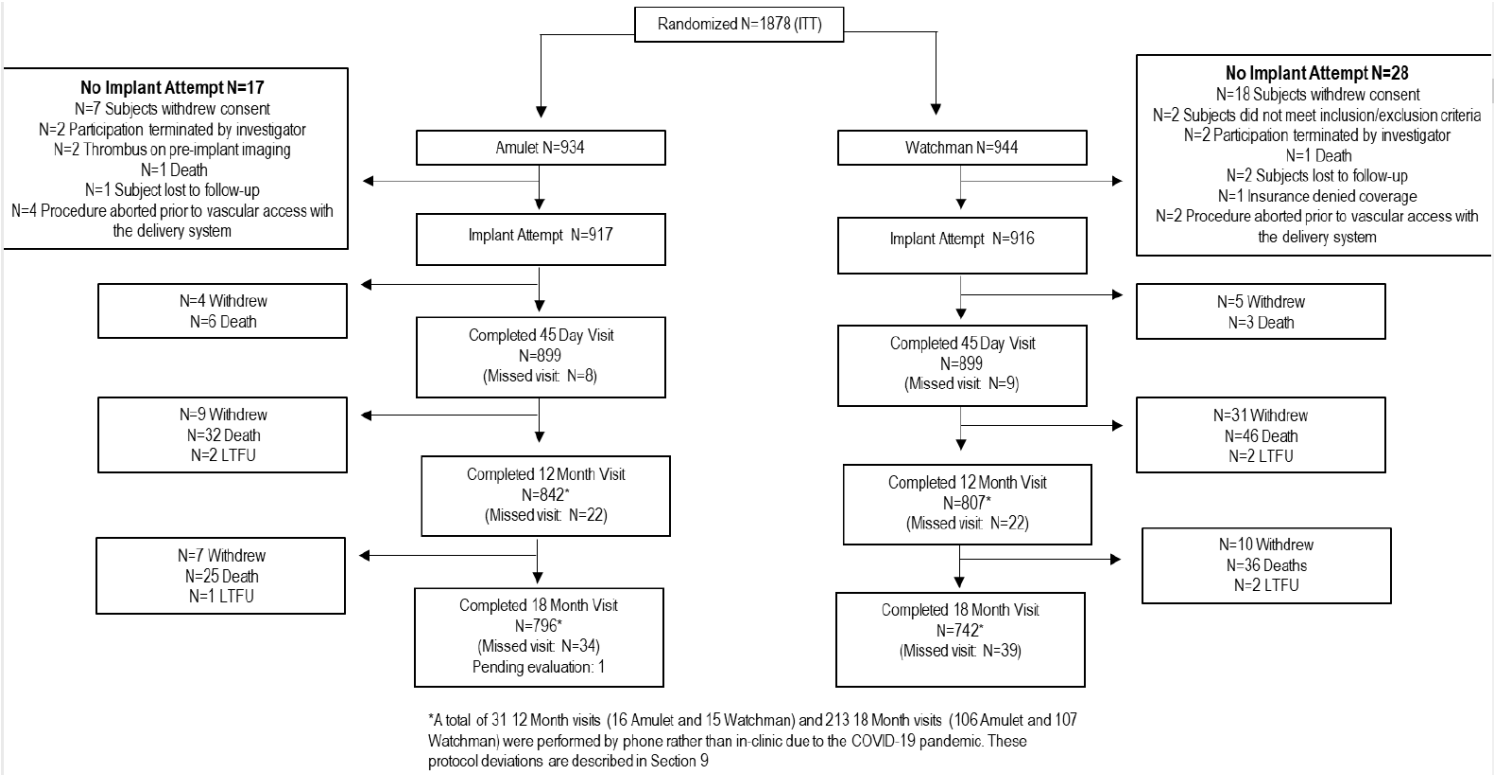


Table 4: Follow-up Visit Accountability

	Visit Complete	Deaths (Incremental)	Withdrawal (Incremental)	Lost to Follow- up (Incremental)	Missed Visit	Actual Follow-up Rate (%)
Amulet						
Procedure	917	0	0	0	0	100.0
Discharge	912	3	0	0	2	99.8
45 Day	899	3	4	0	8	98.7
3 Month	886	7	1	0	13	98.0
6 Month	864	9	4	2	20	96.5
9 Month	858	7	0	0	19	96.6
12 Month	842	9	4	0	22	95.8
18 Month	796	25	7	1	34	93.3
Watchman						
Procedure	916	0	0	0	0	100.0
Discharge	914	1	0	0	1	99.9
45 Day	899	2	5	0	9	98.5
3 Month	877	8	5	0	18	96.9
6 Month	847	12	11	1	24	94.8
9 Month	826	10	3	0	32	93.5
12 Month	807	16	12	1	22	93.1
18 Month	742	36	10	2	39	89.3

Incremental Death/Withdrawn/Lost to Follow Up (LTFU) -Number of subjects discontinued (Death/Withdrawn/LT FU) after the end of previous visit window but prior to the end of current visit window without a visit.

Missed Visits - Number of subjects without a follow-up visit after closure of visit window.

Actual Follow-up Rate % - Visit Complete / (Visit Complete + Missed Visits + Withdrawal (cumulative) + Lost to Follow- up (cumulative)).

Table 5 summarizes the definition of primary endpoint analysis populations.

Table 5: Analysis Population

Study Population	Definition	Amulet	Watchman
Intention to Treat (ITT)	All randomized subjects	934	944
As Attempted (AT)	ITT subjects who underwent an implant attempt regardless of the device attempted or implanted.	917	916
Attempt as Randomized	Subjects who underwent an implant attempt with the device as randomized	915	916
Per Protocol (PP)	ITT subjects who met all inclusion criteria and none of the exclusion criteria, who underwent an implant attempt with the device as randomized	903	896

Success as Randomized	Subjects who received a device as randomized (including reattempt procedures, based on last procedure)	903	885

C. Demographics and Baseline Parameters

The demographics of the study population are typical for a non-valvular atrial fibrillation study performed in the US. The mean age was 75 ± 7.6 years, and 40% were female. The groups were balanced in demographics and baseline characteristics. **Table 6** summarizes the subject demographics and baseline characteristics.

Table 6: Demographics and Baseline Characteristics (ITT)

Characteristic	Amulet (N=934)	Watchman (N=944)
Age (years)		
Mean ± SD (n)	75.0 ± 7.6 (934)	75.1 ± 7.6 (944)
Range (Min, Max)	(38.0, 92.0)	(46.0, 96.0)
Female Sex	41.2% (385/934)	38.7% (365/944)
Race/Ethnicity		
White	89.7% (838/934)	90.1% (851/944)
Black or African American	2.2% (21/934)	2.1% (20/944)
Asian	0.4% (4/934)	0.7% (7/944)
American Indian or Alaska Native	0.4% (4/934)	0.2% (2/944)
Native Hawaiian or Other Pacific Islander	0.0% (0/934)	0.3% (3/944)
Other	1.1% (10/934)	1.0% (9/944)
Declined or Unable to Disclose Due to Local Regulation	6.1% (57/934)	5.5% (52/944)
AF Classification		
Paroxysmal	56.5% (528/934)	53.9% (509/944)
Persistent	26.8% (250/934)	29.3% (277/944)
Permanent	16.7% (156/934)	16.6% (157/944)
BMI (kg/m^2)		
Mean ± SD (n)	30.0 ± 6.3 (934)	30.0 ± 6.5 (943)
Range (Min, Max)	(13.0, 68.4)	(16.0, 57.3)
New York Heart Association (NYHA)		
No Heart Failure	50.4%	46.4%
I	15.8%	18.0%
II	27.0%	27.5%
III	6.8%	8.1%
IV	0%	0%

Subjects had a mean CHA_2DS_2-VASc score of 4.5 and 4.7 in the Amulet and Watchman groups, respectively. Similar proportion of subjects in each group had a prior history of stroke (Amulet 18% vs. Watchman 19.9%). **Figure 7** presents the distribution of $CHADS_2$/CHA_2DS_2-VASc score and HAS-BLED score in both groups. Further, **Table 7** summarizes the primary reason for seeking an alternative to OAC. Most frequently, subjects pursued LAA closure due to a history of major or minor bleeding.

Figure 7: Stroke Risk and Bleeding Risk (ITT)

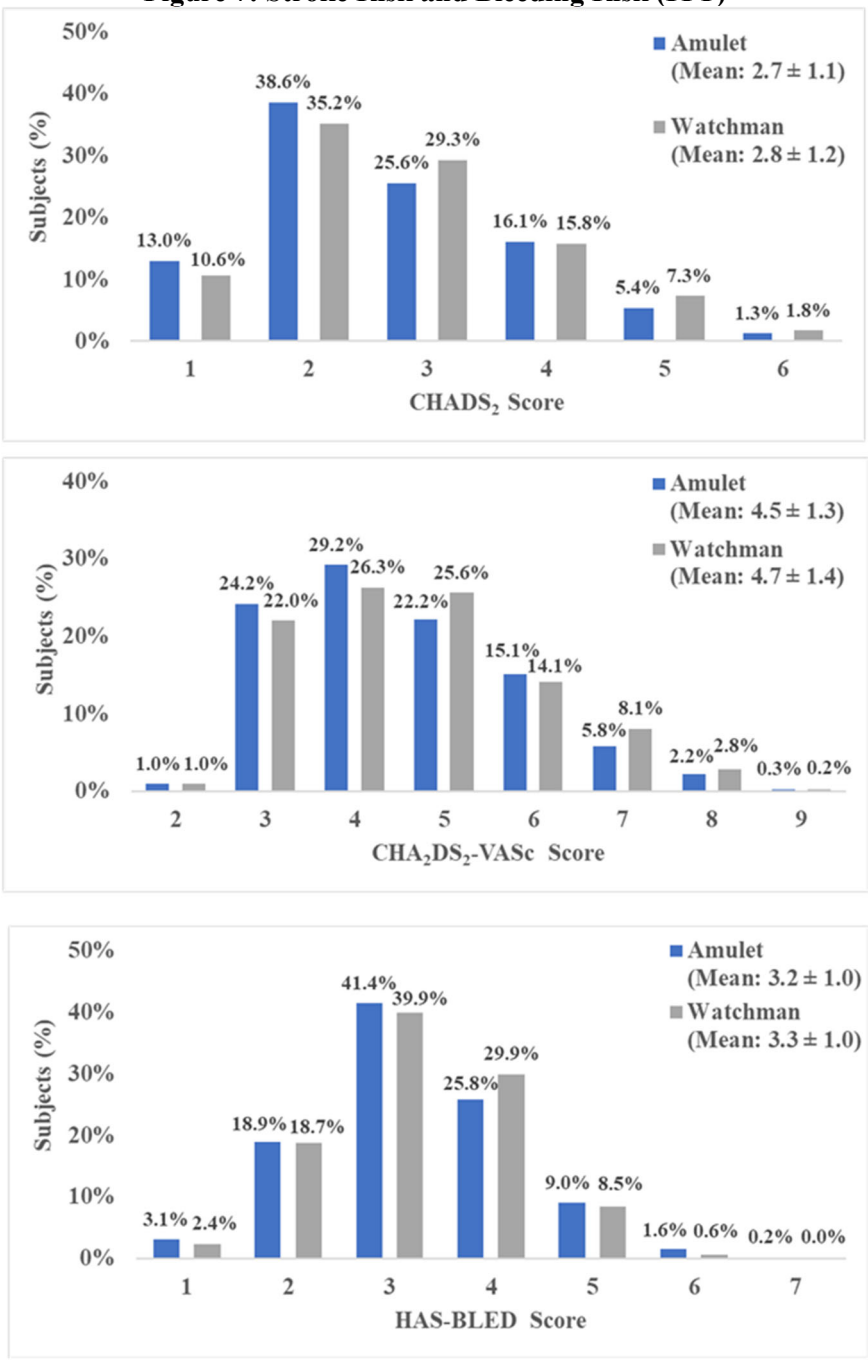


Table 7: Primary Reasons for Seeking an Alternative to OAC

Characteristic	**Amulet (N=934)**	**Watchman (N=944)**
History of major or minor bleeding	55.1% (515/934)	53.3% (503/944)
High bleeding risk	21.8% (204/934)	20.4% (193/944)
Risk of falls	11.5% (107/934)	13.3% (126/944)

Subject's preference/lifestyle	5.5% (51/934)	4.0% (38/944)
Prior stroke on anticoagulant	1.9% (18/934)	3.4% (32/944)
Labile/unstable International Normalized Ratio (INR)	1.6% (15/934)	3.1% (29/944)
Drug interactions	1.3% (12/934)	1.3% (12/944)
Renal or hepatic disease	0.6% (6/934)	0.4% (4/944)
Other	0.6% (6/934)	0.7% (7/944)

D. Procedure Outcomes and Follow-up Medications

Acute procedural outcomes and key parameters of the index procedures in the Attempt as Randomized population are summarized in **Tables 8** and **9**. In each group, technical success was achieved in a vast majority (> 95%) of subjects.

Table 8: Procedural Outcomes

Characteristic	Amulet (N=915)	Watchman (N=916)
Device Success [95% Confidence Interval][1]	98.4% (900/915) [97.31%, 99.08%]	96.4% (883/916) [94.98%, 97.51%]
Technical Success [95% Confidence Interval][1]	97.2% (889/915) [95.86%, 98.14%]	95.3% (873/916) [93.73%, 96.58%]
Procedural Success [95% Confidence Interval][1]	96.0% (878/915) [94.47%, 97.14%]	94.5% (866/916) [92.87%, 95.92%]
Site Reported Residual Jet Post Implant (among subjects with successful implant)		
None	94.2% (848/900)	93.1% (822/883)
>0 and ≤5 mm	5.8% (52/900)	6.9% (61/883)
>5 mm	0.0% (0/900)	0.0% (0/883)

[1]By Clopper-Pearson exact confidence interval. Device success is defined as device deployed and implanted in correct position. Technical success is exclusion of the LAA with no device-related complications through discharge or 7 days whichever is earlier. Procedural success is technical success with no procedure-related complications through discharge or 7 days whichever is earlier.

Table 9: Procedural Characteristics

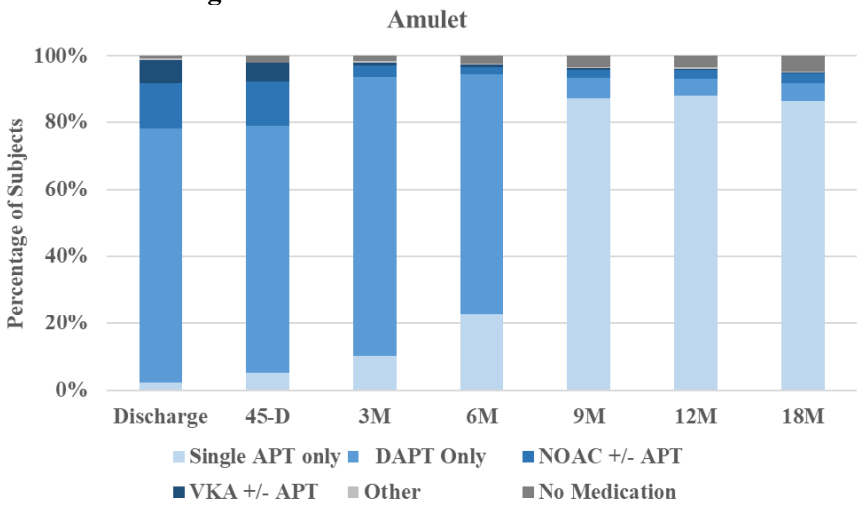
Characteristic	Amulet (N=915)	Watchman (N=916)
Anesthesia Type		
General	92.1% (843/915)	91.4% (837/916)
Conscious Sedation	7.9% (72/915)	8.6% (79/916)
Total Procedure Time (min)*		
Mean ± SD (*n*)	39.9 ± 23.8 (913)	29.5 ± 18.8(915)
Median	35.0	25.0
Range (Min, Max)	(4, 193)	(3, 126)
Contrast Dose (cc)		
Mean ± SD (*n*)	88.53 ± 58.8 (911)	77.47 ± 59.5 (910)
Median	75.0	60.0
Range (Min, Max)	(0.0, 400.0)	(0.0, 509.0)

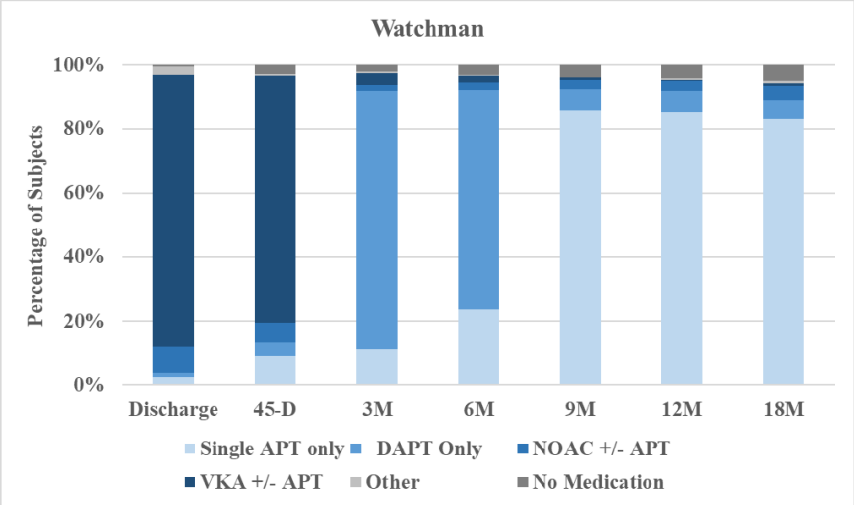
Fluoroscopy time (min)		
Mean ± SD (*n*)	13.8 ± 8.9 (907)	10.3 ± 7.0 (911)
Median	11.1	8.5
Range (Min, Max)	(0.0, 64.8)	(0.0, 69.0)
Number of Devices Attempted		
Mean ± SD (n)	1.2 ± 0.5 (915)	1.3 ± 0.6 (916)
Median	1.0	1.0
Range (Min, Max)	(0, 4)	(0, 5)

*Additional angiogram views and measurements were required in the Amulet group per the IFU

The study required that Amulet subjects be discharged on either dual antiplatelet therapy (DAPT; aspirin plus clopidogrel) or aspirin plus oral anticoagulation (OAC including NOAC or VKA) at physician discretion. Watchman subjects were required to be discharged on aspirin plus warfarin (or other VKA outside the US, if warfarin was not available) in accordance with the approved labeling. **Figure 8** summarizes the post-implant antithrombotic medication use in both groups. At the time of 45-day TEE, 18.8% Amulet subjects and 83.2% Watchman subjects were on an oral anticoagulant.

Figure 8: Antithrombotic Medication Use





E. Safety and Effectiveness Results

1. Safety Results

Primary Safety Endpoint

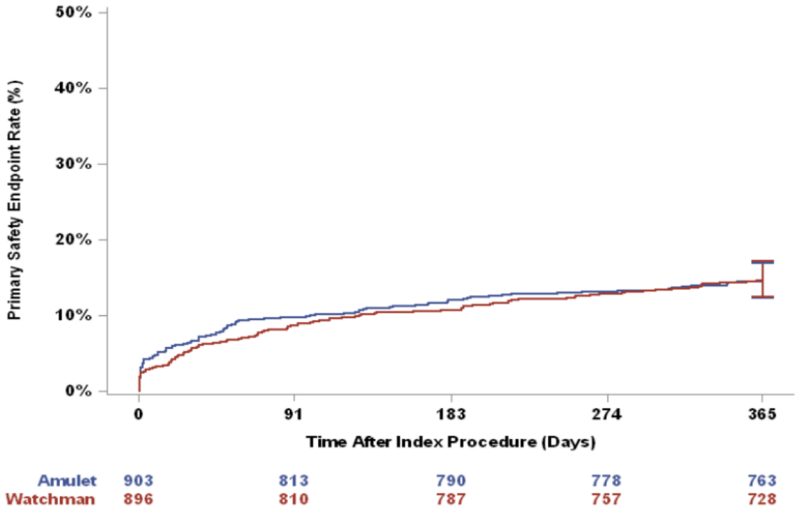
The primary safety analysis was based on the PP population of 903 Amulet and 896 Watchman subjects who underwent an implant attempt with the device as randomized and who met all inclusion and none of the exclusion criteria. The results of the primary safety endpoint are presented in **Table 10** and **Figure 9**. A total of 131 Amulet subjects and 130 Watchman subjects experienced one or more components of the primary safety endpoint, resulting in a Kaplan-Meier estimated primary composite endpoint rate of 14.5% and 14.7% respectively. The 97.5% upper confidence limit for the difference was 3.13% and less than the non-inferiority margin of 5.8%; therefore, the primary safety endpoint was met (p = 0.0002).

Table 10: Primary Safety Endpoint (PP Population)

	Amulet (N=903)	Watchman (N=896)	97.5% Upper Confidence Limit (UCB)	P-value (Non-inferiority margin: 5.8%)	Result
Primary Safety Endpoint*	14.5% (n=131)	14.7% (n=130)	3.13%	0.0002	Pass

*Composite endpoint of procedure-related complications, or all-cause death or major bleeding (defined as Type 3 or greater based on the Bleeding Academic Research Consortium (BARC) definition) at 12 months.
Kaplan-Meier method is used to estimate the event rate (number of subjects with events) with Greenwood standard error.

Figure 9: Primary Safety Endpoint KM Survival (PP Population)



There was an early separation of Kaplan-Meier curves driven by a difference in peri-procedural events.

Individual components of the primary safety endpoint are shown in **Table 11**. The rate of procedure related complications was 4.5% in the Amulet group and 2.5% in the Watchman group, and rate of major bleeding was 10.6% in the Amulet group and 10.0% in the Watchman group, while the rate of all-cause death was 3.9% in the Amulet group and 5.1% in the Watchman group

Table 11: Components of the Primary Safe ty Endpoint (PP population)

	Amulet (N=903)	Watchman (N=896)
Procedure Related Complications	4.5% (n=41)	2.5% (n=22)
Major Bleeding (BARC Type 3 or greater)	10.6% (n=95)	10.0% (n=88)
Procedure-related Major bleeding	3.1% (n = 28)	2.1% (n = 19)
Non-procedure Related Major Bleeding	7.9% (n=70)	8.0% (n=70)
All-Cause Death	3.9% (n=35)	5.1% (n=45)

Kaplan-Meier method is used to estimate the event rate (number of subjects with events). Categories are not mutually exclusive.

Procedure Related Complications

Procedure related complications, defined as adverse events adjudicated by the CEC as procedure related and requiring either invasive surgical or percutaneous intervention, occurred in 41 Amulet and 22 Watchman PP subjects (41 Amulet and 23 Watchman subjects in the As Treated Population). **Table 12** summarizes the first event that each subject experienced that met the primary safety endpoint as a procedure related complication. Pericardial effusion events within 2 days of the procedure occurred in

about the same number of subjects in the two groups, however, late pericardial effusion (i.e., occurred > 2 days post procedure) and device embolization occurred more commonly in Amulet than Watchman subjects. Other events occurred at low numbers in both groups and constitute a variety of procedure related complications such as pleural effusion, air embolus and esophageal injury.

Table 12: Procedure Related Complication at 12 Months (First Event, PP Population)

Event Description	Amulet (N=903)	Watchman (N=896)
Pericardial Effusion/Tamponade 0-2 days post procedure	12	10
Pericardial Effusion/Tamponade >2 days post procedure	10	1
Device Embolization	6	2
Vascular Access-Related Complications	3	3
Air Embolus	0	2
Cardiac Perforation	1	1
Esophageal Laceration and Rupture	1	1
Hematoma	1	1
Pleural Effusion	2	0
Third Degree Heart Block/Asystole	1	1
Acute Peritonitis	1	0
Gastrointestinal Bleeding	1	0
Hematuria	1	0
Inferior Myocardial Infarction	1	0
Ischemic Stroke	0	1
Peripheral Arterial Occlusion	1	0
Total Number of Subjects*	**41**	**22**

*One Amulet subject experienced both pericardial effusion and pleural effusion on POD 20. One Watchman subject experienced both air embolism and ischemic stroke on POD 0. Therefore, these totals are not equal to the sum of the numbers in the rows above.

Major Bleeding

Table 13 presents the major bleeding events through 12 months by bleeding site and CEC adjudicated relatedness to the procedure. The most common procedure related bleeding site was pericardial, and the numerically higher rate of late pericardial effusion observed in the Amulet group accounted for the difference in pericardial bleeding event rate between the two groups. Non-procedure related major bleeding events was similar across the two groups and were most commonly gastrointestinal.

Table 13: Major Bleeding Events through 12 Months by Bleeding Site and Procedure Relatedness (PP Population; First Event)

Events	Procedure related		Non-Procedure Related	
	Amulet	Watchman	Amulet	Watchman
Epistaxis	0	0	4	2
Gastrointestinal	1	0	48	50
Genitourinary	0	0	2	1
Intracranial*	1	1	6	7
Intraocular	0	0	1	0
Pericardial	18	11	3	1
Retroperitoneal	0	0	0	2
Soft Tissue	8	7	5	6
Pulmonary	0	0	2	1
Total	**28**	**19**	**70**	**70**

This analysis includes the first procedure related and first non-procedure related major bleeding event for each subject. One Amulet subject experienced non-procedural related gastrointestinal and intracranial bleeding on the same day and is counted in both bleeding site categories.
*6 intracranial bleeding events are also hemorrhagic strokes.

Mortality

Table 14 summarizes the mortality events at 12 months by adjudicated cause of death (cardiovascular or non-cardiovascular) and relationship to the device and/or procedure. Of 80 subjects (35 Amulet, 45 Watchman) in the PP population who died at 12 months, 41 were adjudicated as cardiovascular/ unexplained and 8 were adjudicated as device or procedure-related.

Table 14: Death at 12 Months (PP Population)

	Amulet (N=903)	Watchman (N=896)
Cardiovascular or Unexplained Death	17	24
Non-Cardiovascular Death	18	21
Device/Procedure Related	5	3
Non-Device/Procedure Related	30	42*

*2 unexplained deaths within 45 days and one death related to LAA tear during CABG in the Watchman arm were adjudicated as with unknown relatedness.

In the Amulet group, procedure/device related deaths (n = 5) were due to inferior myocardial infarction, acute femoral-popliteal bypass graft occlusion, intracerebral hemorrhage, acute peritonitis and device embolization. In the Watchman group, procedure/device related deaths (n = 3) included those due to cardiac tamponade, stroke, and systemic embolism with device related thrombus.

Device- or Procedure-Related Serious Adverse Events

Table 15 provides a summary of CEC adjudicated device- or procedure-related serious adverse events from randomization until 548 days post procedure for attempted subjects and 548 days post randomization for subjects without an implant attempt. Events are categorized by system organ class (SOC).

Table 15: CEC Adjudicated Device- or Procedure-Related Serious Adverse Events at 548 days (ITT population)

	Amulet (N= 934) N of Subjects (N of Events)			Watchman (N= 944) N of Subjects (N of Events)		
System Organ Class (SOC)	**Related**	**Unrelated**	**Unknown**	**Related**	**Unrelated**	**Unknown**
Blood and lymphatic system disorders	**2 (2)**	**24 (29)**	**1 (1)**	**1 (1)**	**16 (19)**	**1 (1)**
Anemias	2 (2)	22 (27)	1 (1)	1 (1)	14 (16)	1 (1)
Aplastic Anemia/Hypoplastic Anemia	0	2 (2)	0	0	1 (1)	0
Iron-Deficiency Anemia	0	0	0	0	2 (2)	0
Cardiac disorders	**38 (41)**	**153 (232)**	**10 (10)**	**24 (24)**	**158 (221)**	**6 (6)**
Atrioventricular (AV) Block	0	1 (1)	0	0	0	0
Acute Pulmonary Edema	0	2 (2)	0	0	0	0
Angina Pectoris	0	1 (1)	0	0	5 (5)	0
Anterior Myocardial Infarction	0	2 (2)	0	0	0	0
Aortic Aneurysms	0	3 (3)	0	0	1 (1)	0
Aortic Dissection	0	1 (1)	0	0	0	0
Aortic Valve Regurgitation/Aortic Valve Insufficiency/Valvular Regurgitation Aortic Valve	0	1 (1)	0	0	1 (1)	0
Aortic Valve Stenosis	0	6 (6)	0	0	4 (4)	0
Asystole	0	0	0	1 (1)	0	0
Atrial Fibrillation	1 (1)	3 (3)	0	1 (1)	4 (4)	0
Atrial Flutter	0	4 (4)	0	0	1 (1)	0
Cardiac Arrest	0	15 (15)	0	0	18 (19)	2 (2)
Cardiac Perforation	1 (1)	0	0	1 (1)	0	0
Cardiac Thrombus	0	1 (1)	0	0	1 (1)	0
Cardiogenic Shock	0	2 (2)	0	0	0	0
Cardiomyopathy	0	1 (1)	0	0	1 (1)	0
Chest Pain	2 (2)	10 (12)	0	1 (1)	15 (16)	1 (1)
Congestive Heart Failure	4 (4)	79 (111)	1 (1)	1 (1)	79 (107)	0
Constrictive Pericarditis	0	1 (1)	0	0	0	0
Cor Pulmonale	0	0	0	0	0	1 (1)
Coronary Artery Disease	0	9 (9)	0	0	10 (11)	0
Coronary Artery Occlusion	0	1 (1)	0	0	0	0
Dyspnea	0	4 (4)	0	0	3 (3)	0
High Grade Block/Advanced AV Block	0	1 (1)	0	0	1 (1)	0
Inferior Myocardial Infarction	1 (1)	0	0	0	0	0

Mitral Valve Regurgitation/Mitral Insufficiency	1 (1)	8 (8)	0	0	5 (5)	0
Myocardial Infarction	1 (1)	9 (11)	0	0	13 (14)	0
Paroxysmal Atrial Fibrillation	0	0	0	0	1 (1)	0
Pericardial Effusion	10 (10)	1 (1)	5 (5)	5 (5)	1 (1)	0
Pericardial Tamponade	15 (15)	0	1 (1)	13 (13)	0	1 (1)
Pericarditis	4 (4)	2 (2)	2 (2)	0	1 (1)	1 (1)
Perivalvular Leak	0	0	0	0	1 (1)	0
Regular Narrow Complex Tachycardia/Supraventricular Tachycardias	0	1 (1)	0	0	0	0
Sick Sinus Syndrome	0	7 (7)	1 (1)	0	6 (6)	0
Sinus Bradycardia/Sinus Bradycardia (Cardiac Arrhythmia)	0	6 (6)	0	1 (1)	3 (3)	0
Sinus Node Dysfunction	0	1 (1)	0	0	0	0
Supravalvular Aortic Stenosis	0	1 (1)	0	0	0	0
Sustained Ventricular Tachycardia	0	1 (1)	0	0	2 (2)	0
Third Degree Heart Block (Complete Heart Block)	1 (1)	1 (1)	0	0	3 (3)	0
Tricuspid Regurgitation/Tricuspid Insufficiency/Valvular Regurgitation: Tricuspid Valve	0	2 (2)	0	0	2 (2)	0
Unstable Angina	0	3 (3)	0	0	5 (5)	0
Ventricular Fibrillation	0	0	0	0	1 (1)	0
Ventricular Tachycardia	0	3 (3)	0	0	1 (1)	0
Other	0	2 (2)	0	0	0	0
Eye disorders	**0**	**1 (1)**	**0**	**0**	**0**	**0**
Retinal Hemorrhage	0	1 (1)	0	0	0	0
Gastrointestinal disorders	**2 (2)**	**73 (99)**	**3 (3)**	**1 (1)**	**75 (98)**	**0**
Abdominal Pain	0	3 (3)	0	0	0	0
Acute Peritonitis	0	0	1 (1)	0	1 (1)	0
Bowel Obstruction	0	2 (2)	0	0	1 (1)	0
Colitis	0	1 (1)	0	0	0	0
Diarrhea	0	0	0	0	1 (1)	0
Diverticulitis	0	2 (2)	0	0	1 (1)	0
Dysphagia	0	2 (2)	0	0	0	0
Emesis/Vomiting	0	0	0	1 (1)	0	0
Gastroenteritis	1 (1)	1 (1)	0	0	0	0
Gastrointestinal Bleeding	0	65 (87)	2 (2)	0	72 (94)	0
Hemorrhoids/Piles	0	1 (1)	0	0	0	0
Nausea	1 (1)	0	0	0	0	0
General disorders	**2 (2)**	**15 (15)**	**0**	**3 (3)**	**21 (21)**	**1 (1)**
Chills/Rigors	0	0	0	1 (1)	0	0
Damage or Movement of Implantable Cardioverter Defibrillator (ICD) Leads Requiring Revisions	0	1 (1)	0	0	0	0
Drug Side Effect	0	1 (1)	0	0	0	0
Failure to Thrive	0	1 (1)	0	0	3 (3)	0
Fatigue/Generalized Fatigue	1 (1)	2 (2)	0	0	1 (1)	0
Fever	0	0	0	2 (2)	1 (1)	1 (1)
Multiple Organ Failure	0	3 (3)	0	0	4 (4)	0
Neck Pain	0	0	0	0	1 (1)	0
Non-Cardiac Chest Pain	1 (1)	2 (2)	0	0	3 (3)	0

Weakness	0	3 (3)	0	0	2 (2)	0
Other	0	2 (2)	0	0	6 (6)	0
Hepatobiliary disorders	**0**	**3 (3)**	**0**	**0**	**2 (4)**	**0**
Ascites	0	0	0	0	1 (2)	0
Cholecystitis	0	0	0	0	1 (1)	0
Choledocholithiasis	0	1 (1)	0	0	0	0
Hepatic and Biliary Disorders	0	2 (2)	0	0	1 (1)	0
Infections and infestations	**6 (7)**	**29 (31)**	**2 (2)**	**4 (4)**	**23 (26)**	**1 (1)**
Acute Bacterial Endocarditis (ABE)	0	1 (1)	0	0	0	0
Bacteremia	0	1 (1)	0	0	1 (1)	0
Bacterial Infections	1 (1)	1 (1)	0	0	0	0
Bronchitis	0	0	0	1 (1)	0	0
Cellulitis	0	5 (5)	0	0	3 (3)	1 (1)
Chlamydial Pneumonia	0	1 (1)	0	0	0	0
Infected Cyst	0	0	0	0	1 (1)	0
Influenza	0	1 (1)	0	0	0	0
Pneumonia	0	11 (11)	0	2 (2)	4 (4)	0
Respiratory Syncytial Virus Infection (RSV)	1 (1)	0	0	0	0	0
Sepsis	1 (1)	7 (7)	1 (1)	0	11 (11)	0
Septicemia	1 (1)	0	0	0	0	0
Urinary Tract Infections	3 (3)	2 (2)	1 (1)	1 (1)	6 (6)	0
Other	0	1 (1)	0	0	0	0
Injury, poisoning and procedural complications	**11 (11)**	**16 (18)**	**0**	**17 (17)**	**28 (30)**	**0**
Air Embolus	2 (2)	0	0	2 (2)	0	0
Closed Head Injury	0	0	0	0	2 (2)	0
Contusion	0	0	0	0	1 (1)	0
Epidural Hematomas	0	1 (2)	0	0	0	0
Esophageal Laceration and Rupture	1 (1)	0	0	1 (1)	1 (1)	0
Fall	1 (1)	4 (4)	0	0	12 (12)	0
Hemothorax	1 (1)	2 (2)	0	0	0	0
Hip Fracture	0	0	0	0	1 (1)	0
Trauma	0	9 (10)	0	0	10 (11)	0
VASC Bleeding	1 (1)	0	0	3 (3)	0	0
VASC Hematoma	3 (3)	0	0	7 (7)	1 (1)	0
VASC Pseudoaneurysm	1 (1)	0	0	3 (3)	1 (1)	0
VASC Vessel Perforation	1 (1)	0	0	1 (1)	0	0
Investigations	**1 (1)**	**1 (1)**	**0**	**1 (1)**	**7 (7)**	**1 (1)**
Abnormal Coagulation Parameter	0	0	0	1 (1)	3 (3)	0
Abnormal Lab Value	1 (1)	0	0	0	4 (4)	0
EKG Abnormalities	0	1 (1)	0	0	0	0
Echo Finding	0	0	0	0	0	1 (1)
Metabolism and nutrition disorders	**2 (2)**	**4 (4)**	**0**	**1 (1)**	**4 (4)**	**0**
Dehydration	0	2 (2)	0	0	1 (1)	0
Diabetic Ketoacidosis	0	0	0	0	1 (1)	0
Edema	0	0	0	0	1 (1)	0
Hyperglycemia	0	1 (1)	0	0	0	0
Hyperkalemia	0	0	0	1 (1)	0	0

Hypervolemia	1 (1)	0	0	0	0	0
Hypoglycemia	0	0	0	0	1 (1)	0
Hyponatremia	0	1 (1)	0	0	0	0
Metabolic Acidosis	1 (1)	0	0	0	0	0
Musculoskeletal and connective tissue disorders	**0**	**1 (1)**	**0**	**0**	**0**	**0**
Spinal Stenosis	0	1 (1)	0	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**0**	**14 (15)**	**0**	**0**	**10 (10)**	**0**
Cancer	0	6 (6)	0	0	6 (6)	0
Colon Cancer	0	0	0	0	1 (1)	0
Leukemias	0	4 (4)	0	0	1 (1)	0
Lung Cancer	0	2 (2)	0	0	1 (1)	0
Pancreatic Cancer	0	1 (2)	0	0	1 (1)	0
Thyroid Cancer	0	1 (1)	0	0	0	0
Nervous system disorders	**7 (7)**	**37 (43)**	**27 (29)**	**8 (8)**	**47 (54)**	**26 (30)**
Acute Subdural Hematoma	0	1 (1)	0	0	1 (1)	0
Altered Sensorium	0	0	0	0	2 (2)	0
Ataxia	0	0	0	0	0	1 (1)
Bells Palsy	0	0	0	0	1 (1)	0
Blurred Vision	0	0	0	0	1 (1)	0
Cerebral Aneurysm	0	1 (1)	0	0	1 (1)	0
Concussion	0	0	0	0	1 (1)	0
Delirium	1 (1)	1 (1)	0	1 (1)	2 (2)	0
Dementia	0	0	0	0	2 (2)	0
Dizziness	0	3 (3)	0	0	2 (2)	0
Dysphasia	0	0	0	0	1 (1)	0
Encephalopathy	0	10 (10)	0	0	11 (11)	0
Hypertensive Encephalopathy	1 (1)	0	0	0	0	0
Intracerebral Hemorrhage	0	4 (4)	1 (1)	0	4 (4)	0
Ischemic Stroke	4 (4)	1 (1)	17 (17)	4 (4)	0	19 (21)
Microhemorrhage	0	0	0	0	1 (1)	0
Migraine	0	1 (1)	0	0	1 (1)	0
Neuralgic Facial Pain	0	1 (1)	0	0	0	0
New and Different Onset of Migraine Symptoms	1 (1)	0	0	0	0	0
Numbness	0	1 (1)	0	0	0	0
Parkinson's Disease	0	2 (2)	0	0	1 (1)	0
Radiculopathy	0	0	0	0	2 (2)	0
Seizure Disorder	0	2 (2)	0	0	0	0
Seizure/Convulsions/Epilepsy	0	6 (7)	0	0	6 (7)	0
Spells	0	3 (3)	1 (2)	0	6 (6)	0
Subarachnoid Hemorrhage	0	0	0	0	1 (1)	0
Subdural Hemorrhage	0	0	0	1 (1)	2 (2)	0
Transient Global Amnesia	0	1 (1)	0	0	0	0
Transient Ischemic Attack (TIA)	0	2 (2)	9 (9)	2 (2)	2 (2)	7 (8)
Vertigo	0	2 (2)	0	0	2 (2)	0
Product Issues	**8 (8)**	**0**	**0**	**9 (9)**	**0**	**0**
Device Embolization	6 (6)	0	0	2 (2)	0	0

Device Malposition or Malfunction	1 (1)	0	0	7 (7)	0	0
Thrombus on Device	1 (1)	0	0	0	0	0
Psychiatric disorders	**0**	**1 (1)**	**0**	**0**	**0**	**0**
Suicide Attempt	0	1 (1)	0	0	0	0
Renal and urinary disorders	**6 (6)**	**12 (15)**	**1 (1)**	**5 (6)**	**13 (14)**	**1 (1)**
Acute Kidney Injury	4 (4)	3 (4)	1 (1)	4 (4)	3 (3)	0
Chronic Renal Failure	0	0	0	0	1 (1)	0
Cystitis	0	0	0	0	1 (1)	0
Hematuria	1 (1)	7 (9)	0	1 (1)	7 (7)	0
Nephrolithiasis	0	1 (1)	0	0	0	0
Renal Infarct	0	0	0	0	0	1 (1)
Urinary Calculi	0	1 (1)	0	0	0	0
Urinary Retention	1 (1)	0	0	1 (1)	1 (2)	0
Reproductive system and breast disorders	**0**	**1 (1)**	**0**	**0**	**0**	**0**
Ovarian Cyst	0	1 (1)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	**7 (8)**	**21 (22)**	**1 (1)**	**2 (2)**	**36 (38)**	**1 (1)**
Asthma	1 (1)	0	0	0	0	0
Chronic Obstructive Pulmonary Disease (COPD)	0	1 (1)	0	0	7 (7)	0
Hypoxemia	0	1 (1)	0	0	1 (1)	0
Hypoxia	0	0	0	0	1 (1)	0
Idiopathic Interstitial Lung Diseases	0	1 (1)	0	0	1 (1)	0
Pleural Effusion	3 (4)	4 (4)	1 (1)	0	7 (8)	0
Pulmonary Embolism	2 (2)	7 (7)	0	0	5 (5)	1 (1)
Pulmonary Hypertension	0	0	0	0	1 (1)	0
Respiratory Failure	1 (1)	8 (8)	0	2 (2)	14 (14)	0
Skin and subcutaneous tissue disorders	**0**	**0**	**0**	**0**	**1 (1)**	**0**
Skin Ulcer	0	0	0	0	1 (1)	0
Surgical and medical procedures	**1 (1)**	**2 (2)**	**0**	**2 (2)**	**0**	**0**
Residual Shunt Requiring Closure	1 (1)	0	0	1 (1)	0	0
Surgical Closure of Atrial Septal Defect (ASD)	0	1 (1)	0	1 (1)	0	0
Other	0	1 (1)	0	0	0	0
Vascular disorders	**11 (11)**	**49 (63)**	**3 (3)**	**9 (9)**	**38 (44)**	**3 (3)**
Abdominal Bleeding	1 (1)	0	0	0	0	0
Arterial Hypertension/Hypertension	1 (1)	1 (1)	0	0	4 (4)	0
Bleeding	0	6 (6)	0	0	5 (6)	0
Blood Loss	1 (1)	1 (1)	0	0	1 (1)	0
Carotid Stenosis	0	4 (4)	0	0	0	0
Deep Vein/Venous Thrombosis	1 (1)	6 (6)	0	0	4 (4)	1 (1)
Epistaxis	0	11 (17)	0	0	3 (3)	0
Hematoma	1 (1)	1 (1)	0	1 (1)	6 (6)	1 (1)
Hemoptysis	0	2 (3)	0	2 (2)	1 (1)	0
Hypotension	2 (2)	3 (3)	1 (1)	4 (4)	3 (3)	0
Orthostatic Hypotension	0	1 (1)	0	0	0	0
Peripheral Arterial Occlusion	1 (1)	2 (2)	0	0	0	0
Peripheral Vascular Disease	0	5 (5)	0	0	1 (1)	0
Peripheral Venous Thrombus	0	1 (1)	0	0	1 (1)	0
Syncope	3 (3)	9 (10)	1 (1)	1 (1)	14 (14)	1 (1)

Systemic Embolism	0	1 (1)	1 (1)	1 (1)	0	0
Vascular Ischemia	0	1 (1)	0	0	0	0
Total	**75 (109)**	**304 (596)**	**47 (50)**	**76 (88)**	**319 (591)**	**41 (45)**

Note: Relatedness refers to the Procedure or Device *thrombus on device was determined by the CEC
Note: Other includes AV node ablation, AV-shunt revision, Bradycardia, Death of Unknown Cause, Death of unknown cause, Gangrene, Pacemaker erosion, Pacemaker lead failure, Unknown cause of death

Pericardial effusion

A total of 50 Amulet subjects and 34 Watchman subjects experienced pericardial effusion events in the study. The majority of these events occurred within 2 days post procedure. Surgical or percutaneous drainage was required to treat 43 pericardial effusion events, and the rate was numerically higher in the Amulet group (3.2%) compared to the Watchman group (1.5%). **Table 16** presents these pericardial effusion events by treatment group and time of onset.

Table 16: Pericardial Effusion Requiring Percutaneous or Surgical Intervention (AT population)

	0-2 Days Post Procedure		**>2 Days Post Procedure**	
	Amulet (N=917)	**Watchman (N=916)**	**Amulet (N=917)**	**Watchman (N=916)**
Pericardial Effusion, requiring percutaneous or surgical intervention	12 (1.3%)	10 (1.1%)	17 (1.9%)	4 (0.4%)

Data is presented as number of subjects with events (%)

Of the 17 delayed pericardial effusion events in the Amulet group, two were related to other interventions (i.e., pacemaker implantation, TAVR). Ten of the remaining 15 cases were detected before or on the 45-day TEE (up to 57 days after implantation), and 6 of these subjects received oral anticoagulation and aspirin post implant. Further analysis showed the use of OAC on discharge was significantly associated with late pericardial effusion after adjusting for baseline patient characteristics. Overall, the rate of late pericardial effusion was 5.3% vs. 1.8% for subjects discharged with OAC vs. without OAC. There were 4 additional events within one year. In all Amulet late pericardial effusion cases, the events resolved without long-term sequalae and none resulted in death.

Device Embolization

Device embolization occurred in 6 of 915 (0.7%) Amulet subjects. Of these, 2 subjects required open-heart surgery for device removal. Except for one, all cases occurred on the day of or the day after the procedure. The device embolization rate in the Amulet group was numerically higher than that observed in the Watchman group but still being clinically acceptable. An analysis of the relationship between device embolization and operator experience showed 5 of 6 events occurred early in the implanter's experience and might be related to suboptimal device sizing.

Device-Related Thrombus

As shown in **Table 17**, the incidence of device-related thrombus at 18 months was 3.3%

for Amulet (30 subjects) and 4.5% for Watchman (40 subjects). Most device-related thrombus events were identified during regular scheduled follow-up. No Amulet subjects with device- related thrombus experienced an ischemic stroke or systemic embolism. Two (2) Watchman subjects with a device-related thrombus experienced an ischemic stroke and/or systemic embolism.

Table 17: Device-Related Thrombus at 18 Months (Successful Implant as Randomized)

	Amulet (N=903)	Watchman (N=885)
Device -Related Thrombus	3.3% (30/903)	4.5% (40/885)

2. Effectiveness Results

Primary Effectiveness Endpoint

The primary effectiveness endpoint is a composite of ischemic stroke and systemic embolism at 18 months. **Table 18** presents the primary effectiveness endpoint results. A total of 25 Amulet subjects and 24 Watchman subjects experienced at least one primary effectiveness endpoint event at 18 months following the procedure, and the Kaplan-Meier estimated primary composite endpoint rate was 2.8% for both groups (**Figure 10**). The 97.5% upper confidence limit of the difference was 1.55% and less than the prespecified noninferiority margin of 3.2%; therefore, the primary effectiveness endpoint was met.

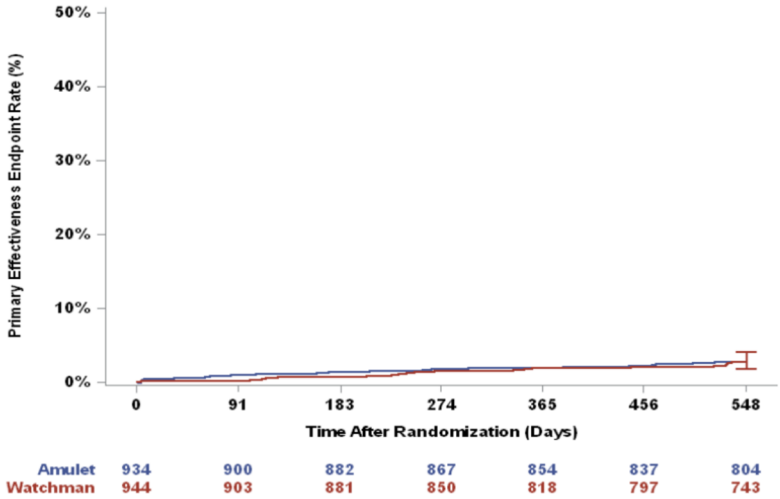
Ischemic stroke and systemic embolism occurred in 44 subjects (22 Amulet and 23 Watchman) and 5 subjects (3 Amulet and 2 Watchman), respectively. One Watchman subject experienced both an ischemic stroke and a systemic embolism.

Table 18: Primary Effectiveness Endpoint (ITT Population)

	Amulet (N=934)	Watchman (N=944)	97.5% Upper Confidence Limit	P-value (NIM: 3.2%)	Result
Primary Effectiveness Endpoint	2.8% (n=25)	2.8% (n=24)	1.55%	<.0001	Pass

Kaplan-Meier method was used to estimate the event rate (number of subjects with events).

Figure 10: Kaplan-Meier curve Primary Effectiveness Endpoint



Mechanism of Action Primary Endpoint

The third primary endpoint is device closure rate on the 45-day TEE. The analysis included 801 Amulet subjects and 792 Watchman subjects who received the device as randomized and who had 45-day closure status determined by the imaging core lab.

Table 19 presents the results for the third primary endpoint. Device closure (defined as residual jet around the device ≤ 5 mm) was observed in 98.9% of Amulet subjects and 96.8% of Watchman subjects (difference = 2.03%). The 97.5% lower confidence bound for the difference in proportions between the two groups was 0.41% which was greater than the predefined non-inferiority margin of -3%, and the primary mechanism of action endpoint was met (p<0.0001). No residual jet around the device was observed in 63% of Amulet subjects and 46% of Watchman subjects.

Table19. Mechanism of Action Primary Endpoint

	Amulet (N=903)	Watchman (N=885)	97.5% Lower Confidence Bound (LC B)	P-value (Non-inferiority margin: -3%)	Result
Primary Mechanism of Action Endpoint	98.9% (792/801)	96.8% (767/792)	0.41%	<0.0001	Pass

Residual jet around the device ≤ 5 mm at the 45-day visit documented by transesophageal echocardiogram defined by Doppler flow. The lower confidence bound was calculated by the Farrington Manning method

3. Secondary Endpoints

Since all three primary endpoints of non-inferiority were met, the five secondary endpoints were tested using the Hochberg procedure. **Table 20** summarizes the results of the secondary endpoint analysis. The following endpoints were met:
(1) superiority of mechanism of action endpoint, and
(2) non-inferiority of the composite of stroke, systemic embolism, cardiovascular/ unexplained death at 18 months.

Table 20: Summary of Secondary Endpoint Results

Secondary Endpoint	Amulet	Watchman	Difference	P-value	Significance Level Cutoff	Result
A. Superiority Test of Primary Effectiveness Endpoint	2.8% (0.6%)	2.8% (0.6%)	0.00%	0.5017	0.025	Based on the Hochberg procedure the following endpoints were met: D, E
B. Superiority Test of Primary Safety Endpoint	14.5% (1.2%)	14.7% (1.2%)	-0.14%	0.4660	0.0125	
C. Major Bleeding at 18 Months (Superiority)	11.6% (1.1%)	12.3% (1.1%)	-0.71%	0.3229	0.0083	
D. Superiority Test of Primary Mechanism of Action Endpoint	98.9% (792/801)	96.8% (767/792)	2.03%	0.0025	0.0063	
E. Stroke/Systemic Embolism/CV or unexplained death at 18 Months (Non-Inferiority)	5.6% (0.8%)	7.7% (0.9%)	-2.12%	<0.0001		

4. Subgroup Analyses

Subgroup analyses were conducted to assess the consistency of primary outcomes across the following patient characteristics: age, gender, race, ethnicity, stroke risk, bleeding risk, device size, and AF pattern via an interaction test between treatment group and subgroup stratum in a logistic regression model. No significant interaction effects were observed (interaction p-value > 0.15 for all subgroups).

5. Pediatric Extrapolation

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

F. 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 330 investigators of which none were full-time or part-time employees of the sponsor and 14 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: 12
- Proprietary interest in the product tested held by the investigator: none
- 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.

XI. SUMMARY OF SUPPLEMENTARY CLINICAL DATA

The applicant also submitted additional data from a post-market registry to supplement the pivotal study dataset. Data from the Amplatzer Amulet Observational Post Market Study was considered in the benefit-risk assessment of the PMA.

The Amplatzer Amulet Post Market Observation Study was a prospective, non-randomized, open-label, post-market study assessing the safety and effectiveness of the Amulet occluder over 2-years during commercial use outside of the US. The study enrolled Non-Valvular Atrial Fibrillation (NVAF) patients ≥ 18 years of age. After LAA closure with the Amulet device, patients were followed at discharge, 1-3 month, 6 months (by phone), one year, and 2 years (by phone). A TTE was performed prior to discharge, and TEEs were required at 1-3 months post-implant and with a diagnosis of a stroke or TIA.

The study utilized an independent clinical events committee (CEC) to adjudicate all major adverse events for relatedness to the procedure, device, or delivery system, and an independent core laboratory to review echocardiograms. Centralized data monitoring occurred throughout the study.

There were 4 study objectives:

1. Assessment of acute (0 – 7 days post-procedure) serious adverse events
2. Assessment of late (> 7 days post-procedure) serious adverse events
3. Assessment of ischemic stroke, systemic embolism, and cardiovascular death through 2 years
4. Assessment of bleeding events through 2 years

Between 6/1/2015 and 9/19/2016, the study enrolled 1088 subjects at 61 sites in Western Europe, Australia, Chile, Hong Kong, and Israel. Of these, 1078 (99.1%) subjects had a successful implant procedure. **Table 21** presents the follow-up visit compliance.

Table 21: Follow-up Visit Compliance

Study Visit	Completed Visits	Expected Visits	Follow-Up Compliance
Discharge	1074	1075	99.9%
1-3 Month	1018	1058	96.2%
6 Month	1009	1034	97.6%
12 Month	950	987	96.3%
24 Month	864	917	94.2%

The mean age of the enrolled subjects was 75.2 ± 8.5 years, and 35.5% were female. The mean CHA_2DS_2-VASc score was 4.2 ± 1.6, and 27.5% of subjects had prior history of stroke. The mean HAS-BLED score was 3.3 ± 1.1, and 71.7% had prior history of major bleed. Indications for LAA occlusion include 6.6% and 34.1% of subjects with absolute and relative

contraindications to OAC, respectively.

Technical success, defined as successful implantation of the Amulet device in the LAA, was achieved in 1078 of 1088 (99.1%). Most subjects were discharged from the index hospitalization on antiplatelet therapy (Dual Antiplatelet Therapy (DAPT) or Single Antiplatelet Therapy (SAPT)), and 11.2% of subjects were discharged on oral anticoagulation.

Adverse Events

There were 98 serious adverse events in 83 subjects within 7 days after the index procedure. The CEC adjudicated 73 events (in 63 subjects) as procedure- or device-related (**Table 22**).

Table 22: CEC Adjudicated Acute Serious Adverse Events within 7 Days of the Index Procedure

Event	Subjects % (n/N)	Events N	Related to Procedure	Related to Device	Related to Delivery System	Unrelated
AV Block	0.1% (1/1088)	1	1	0	0	0
Acute Bronchitis	0.1% (1/1088)	1	0	0	0	1
Acute Pulmonary Edema	0.2% (2/1088)	2	1	0	0	1
Acute Renal Failure	0.1% (1/1088)	1	1	0	0	0
Air Embolus	0.1% (1/1088)	1	1	0	1	0
Alcohol Intoxication	0.1% (1/1088)	1	0	0	0	1
Anemias	0.3% (3/1088)	3	3	0	0	0
Aphasia	0.1% (1/1088)	1	1	0	0	0
Arterial Hypertension/Hypertension	0.1% (1/1088)	1	1	0	0	0
Atrial Fibrillation	0.5% (5/1088)	5	1	0	0	4
Bleeding	0.1% (1/1088)	1	1	0	0	0
Cardiac Arrest	0.1% (1/1088)	1	0	0	0	1
Cardiac Decompensation	0.1% (1/1088)	1	1	0	0	0
Cardiac Perforation	0.1% (1/1088)	1	1	1	0	0
Chronic Obstructive Pulmonary Disease (COPD)	0.1% (1/1088)	1	1	0	0	0
Chronic Subdural Hematoma	0.1% (1/1088)	1	1	0	0	0
Confusion	0.1% (1/1088)	1	1	0	0	0
Congestive Heart Failure	0.1% (1/1088)	1	0	0	0	1
Decompensated Heart Failure	0.2% (2/1088)	2	1	0	0	1
Delirium	0.1% (1/1088)	1	1	0	0	0
Device Embolization	0.2% (2/1088)	2	2	2	0	0
Dyspnea	0.1% (1/1088)	1	0	0	0	1
Epistaxis	0.1% (1/1088)	1	1	0	0	0
Fall	0.1% (1/1088)	1	1	0	0	0
Fever	0.2% (2/1088)	2	1	0	0	1
Gastrointestinal Bleeding	0.5% (5/1088)	5	3	0	0	2
Gout	0.2% (2/1088)	2	0	0	0	2
Hematoma	0.1% (1/1088)	1	1	0	1	0
Hematuria	0.1% (1/1088)	1	1	0	0	0
Hemoperitoneum	0.1% (1/1088)	1	1	0	1	0
Hemoptysis	0.1% (1/1088)	1	0	0	0	1
Hypotension	0.1% (1/1088)	1	1	0	0	0
Hypoventilation	0.1% (1/1088)	1	1	0	0	0
Ischemic Stroke	0.4% (4/1088)	4	4	1	0	0
Pericardial Effusion	0.6% (6/1088)	6	6	2	1	0
Pericardial Tamponade	0.9% (10/1088)	10	9	7	6	1
Pleural Effusion	0.2% (2/1088)	2	2	0	0	0
Pneumonia	0.3% (3/1088)	3	1	0	0	2

Pneumonia Caused By Gram-Negative Bacilli	0.1% (1/1088)	1	0	0	0	1
Pulmonary Edema	0.1% (1/1088)	1	1	0	0	0
Pulmonary Embolism	0.1% (1/1088)	1	1	0	1	0
Respiratory Failure	0.1% (1/1088)	1	1	0	0	0
Seizure/Convulsions/Epilepsy	0.1% (1/1088)	1	1	0	0	0
Shock	0.1% (1/1088)	1	1	0	0	0
Skin Cancer	0.1% (1/1088)	1	0	0	0	1
Status Epilepticus	0.1% (1/1088)	1	0	0	0	1
TEE-Related Event	0.1% (1/1088)	1	1	0	0	0
Thrombus on Device	0.1% (1/1088)	1	1	1	0	0
Trauma	0.1% (1/1088)	1	0	0	0	1
Urinary Retention	0.2% (2/1088)	2	1	0	0	1
VASC AV Fistula	0.2% (2/1088)	2	2	0	2	0
VASC Bleeding	0.3% (3/1088)	3	3	0	3	0
VASC Hematoma	0.4% (4/1088)	4	4	0	3	0
VASC Pseudoaneurysm	0.2% (2/1088)	2	2	0	1	0
Other[1]	0.1% (1/1088)	1	1	0	1	0
Total	**7.6% (83/1088)**	**98**	**73**	**14**	**21**	**25**

In the Amplatzer Amulet Observational Post Market Study , late events were defined as those with an onset date > 7 days post-procedure. A total of 1097 late SAEs occurred in 504 subjects. **Table 23** presents the late serious adverse events (SAEs) that were adjudicated by CEC as procedure or device related.

Table 23: Number of CEC Adjudicated Procedure or Device Related Late SAEs

Event Description	Related to Procedure	Related to Device
Anemias	1	0
Bacterial infections	1	0
Deep vein thrombosis	1	0
Gastrointestinal Bleeding	1	0
Ischemic stroke	0	2
Pericardial effusion	1	2
Pericardial tamponade	0	1
Pleural effusion	1	0
Thrombus on device	0	18
VASC AV Fistula	2	0
VASC Pseudoaneurysm	1	0
Other (device infection)	0	1
Total	9	24

Overall, procedure related complications, defined as adverse events adjudicated by the CEC as procedure related and requiring either invasive surgical or percutaneous intervention, occurred in 24 subjects (**Table 24**).

Table 24: Procedure Related Complications

Event Description	Amulet Observational Study (N=1088)
Pericardial Effusion 0-2 days post procedure	11
Pericardial Effusion >2 days post procedure	1
Device Embolization	2
Vascular Access-Related Complications	5
Air Embolus	1
Cardiac Perforation	1
Hematoma	1
Pleural Effusion	2
Total Number of Subjects	**24 (2.2%)**

The observed device embolization rate in the Amplatzer Amulet Observational Post Market Study was 0.18%. In total, 21 subjects experienced 22 pericardial effusion events (**Table 25**). Of these, 16 subjects required percutaneous or surgical drainage, including 4 of 5 subjects who experienced pericardial effusion beyond 48 hours (on Postoperative Day (POD) 4, 17, 23, 34, 207).

Table 25: Pericardial Effusion/Cardiac Perforation in the Amulet Observational Study

	Amulet Observational Study (N=1088)
Total Subjects	1.9% (21/1088)
By Timeframe	
0-2 Days	1.5% (16/1088)
> 2 Days	0.5% (5/1088)
By intervention*	
No intervention	0.6% (6/1088)
Surgical/Percutaneous Intervention	1.5% (16/1088)

*One subject experienced two events: one that required surgical/percutaneous intervention.

Incidences of Ischemic stroke, Systemic embolism, Cardiovascular Death, and Major Bleed

There were 42 ischemic stroke events in 39 subjects as adjudicated by the CEC, corresponding to an annualized rate of 2.2% per year. No clinical events were adjudicated by the CEC as systemic embolism.

A total of 161 subjects died. Of these, the CEC adjudicated 55 deaths as due to cardiovascular causes and 35 deaths as due to unknown causes.

The CEC adjudicated 140 bleeding events in 110 subjects as major bleeds (defined as BARC Type 3 or greater), corresponding to an annualized rate of 7.2%/year. A total of 32 major bleeding events were adjudicated as related to the Amulet occluder or implant procedure. The rate of procedural complications observed in the Amulet Observational Study is lower than the rate in the Amulet group of the IDE trial, and consistent with the rate observed in the Watchman group of the

IDE trial. Data from the Amulet Observational Study provide additional insights into Amulet occluder safety in a 'real-world' post market setting from outside the US.

XII. PANEL MEETING RECOMMENDATIONS 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.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint, a composite of ischemic stroke and systemic embolism at 18 months was 2.8% for both groups. The 97.5% upper confidence bound was 1.55% which was within the predefined non-inferiority margin of 3.2% ($p<0.0001$), indicating non-inferiority of effectiveness of Amulet to Watchman. Examination of the two individual components included in the primary effectiveness endpoint revealed similar ischemic stroke rates in both groups (Amulet group: 2.5% vs. Watchman group: 2.7%). Consistent with prior studies, systemic embolism occurred at low rates in both groups (0.3% Amulet, 0.2% Watchman). The primary mechanism of action endpoint of device closure at 45 days was observed in 98.9% of Amulet subjects and 96.8% of Watchman subjects. The 97.5% lower confidence bound was 0.41% which was greater than the predefined non-inferiority margin of -3% ($p<0.0001$). Therefore, device closure with the Amulet device was non-inferior to the Watchman device.

The totality of clinical evidence provides a reasonable assurance that the Amulet device is effective for reducing the risk of thrombus embolization from the LAA in select patients with non-valvular atrial fibrillation.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in clinical studies conducted to support PMA approval as described above. The results from the nonclinical laboratory and animal studies performed on the Amulet device demonstrate that this device is suitable for long- term implant. The potential risks associated with the device include procedure- related complications such as pericardial effusion, cardiac tamponade and procedure-related major bleeding complications.

The primary safety endpoint of the Amulet IDE Trial, a composite of procedure- related complications, all-cause death and major bleeding at 12 months, revealed comparable event rates of 14.5% and 14.7% for the Amulet and Watchman groups, respectively. The 97.5% upper confidence bound was 3.13% which was less than the predefined non-inferiority margin of 5.8% ($p=0.0002$), indicating the primary safety endpoint was met.

However, there was a notable difference in the distribution of primary safety endpoint events. Procedure-related complications occurred more frequently in the Amulet group (4.5% vs. 2.5%). The numerical difference in complication rate was driven mainly by higher rates of device embolization and procedure-related delayed pericardial effusion/tamponade in the Amulet group. The causes for these differences are not well understood. Post-hoc subgroup analyses suggested a learning curve and post-implant anticoagulation therapy may be responsible. Data from a large OUS post-market observational study suggest that these complication rates may be lowered with operator experience and the preferential use of antiplatelet drugs post-implant.

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 LAA. The latter may be important for certain patient populations. Non-valvular AF patients with elevated stroke risk treated with transcatheter LAA occlusion using the Amulet device gain similar magnitude of risk reduction in LAA-associated thromboembolic events as those treated with the Watchman device. Based on the Amulet IDE Trial results, a significant portion of patients undergoing LAA closure with the Amulet 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 and real-world data as described above. The probable risks of the Amulet device include procedure-related serious adverse events (such as pericardial effusion, cardiac tamponade and procedure related major bleeding complications) and device-related thrombus. The results of the Amulet IDE Trial show that patients treated with the Amulet device may be more likely to experience device embolization and delayed pericardial effusion/tamponade than the Watchman device. While a significant pericardial effusion can be effectively treated with percutaneous or surgical pericardial drainage, they can lead to serious complications when not recognized and intervened in a timely fashion.

Additional factors to be considered in determining probable risks and benefits for the Amulet device included:

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.

2. Risk mitigation
   Several strategies may lower the probability of a harmful event occurring. The risk mitigation strategies include:

- Descriptions of known and probable benefits and risks in physician labeling including appropriate Contraindications, Warnings, Precautions, and Instructions for Use incorporating recommendation for post-implant anti-thrombotic therapy and testing for post-implant pericardial effusion.
- Limit to users with a minimum set of qualifications who have completed a required training program

3. Post-market Actions
   In addition to rigorous long-term postmarket surveillance of the US commercial use of the Amulet Left Atrial Appendage Occluder, confirmatory clinical data will be collected from large scale and high-quality clinical surveillance to confirm that the risk mitigation strategies are effective and to refine our understanding of the observed delayed pericardial effusion complications.

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 Amulet device outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the Amulet device when used to reduce the risk of thrombus embolization from the 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 have appropriate rationale to seek a non-pharmacologic alternative to oral anticoagulation.

XIV. CDRH DECISION

CDRH issued an approval order on August 14, 2021. The final clinical conditions of approval cited in the approval order are described below.

1. **Continued Follow-up of the Amulet IDE Cohorts:**
   The study objective is to characterize the safety and effectiveness of the Amulet LAA closure device through 5 years post-procedure. This study should be conducted per the latest version of the Amulet IDE protocol. The study will consist of all IDE patients who are currently enrolled and alive. Safety and effectiveness endpoints include: all-cause death, ischemic stroke, systemic embolism, major bleeding (Type 3 or greater per Bleeding Academic Research Consortium), procedure and device related complications, pericardial effusion requiring intervention, and device-related thrombus. All available patients in the Amulet IDE trial will be followed at 24 months, 3, 4, 5 years post-implant intervals.

2. **Amulet 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 Amulet Left Atrial Appendage Occluder. The surveillance will be carried out to characterize clinical outcomes and to assess the real-world use of the commercial Amulet device. 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 but not limited to: implant success rate, procedural safety, pericardial effusion, effective closure of the orifice of the left atrial appendage, and stroke [including ischemic or hemorrhagic]). The rate of pericardial effusion events requiring intervention, the composite of ischemic stroke and systemic embolism, the composite of procedure-related complications, all-cause death, and major bleeding, and the rate of effective device closure will be compared to pre-specified performance goals.

The applicant's as-submitted manufacturing information was reviewed and was found to be in compliance with the device Quality System (QS) regulation (21 CFR 820). It has been determined an inspection at the applicant's manufacturing facilities is not necessary at this time.

XV. APPROVAL SPECIFICATIONS

Directions for Use: See final approved device labeling (Instructions for Use).

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the final labeling (Instructions for Use).

Post-Approval requirements and restrictions: See approval order