

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Implantable Pacemaker Pulse Generator with Cardiac Resynchronization Therapy (CRT) and Left Ventricular (LV) Pacing Leads

Device Trade Name: Stratos LV CRT-P
Stratos LV-T CRT-P
702.U Programmer Software for the ICS 3000
Corox OTW BP Lead
Corox OTW-S BP Lead

Applicant's Name and Address: BIOTRONIK, Inc.
6024 Jean Road
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Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P070008

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Expedited: Not Applicable

II. INDICATIONS

Stratos LV and Stratos LV-T CRT-Ps

The Stratos LV/LV-T pulse generators are indicated for patients who have moderate to severe heart failure (NYHA Class III/IV), including left ventricular dysfunction (EF \leq 35%) and QRS \geq 120 ms and remain symptomatic despite stable, optimal heart failure drug therapy.

Corox OTW(-S) BP Lead

The Corox OTW BP and Corox OTW-S BP left ventricular pacing leads are bipolar steroid-eluting leads, intended for permanent implantation in the left ventricle via the coronary veins to provide pacing and/or sensing when used in conjunction with a compatible IS-1 pulse generator.

III. CONTRAINDICATIONS

Stratos LV and Stratos LV-T CRT-Ps

Use of Stratos LV/LV-T pulse generators is contraindicated for the following patients:

- Unipolar pacing is contraindicated for patients with an implanted cardioverter-defibrillator (ICD) because it may cause unwanted delivery or inhibition of ICD therapy.
- Single chamber atrial pacing is contraindicated for patients with impaired AV nodal conduction.
- Dual chamber and single chamber atrial pacing is contraindicated for patients with chronic refractory atrial tachyarrhythmias.

Corox OTW(-S) BP Lead

The use of the Corox OTW BP and Corox OTW-S BP leads are contraindicated under the following circumstances:

- Coronary sinus anomalies
- Tissue in the coronary sinus area that has been damaged by an infarction
- Any anomalies of the venous system that preclude transvenous implantation of the lead
- Patient cannot tolerate a single systemic dose of up to 1.0 mg of dexamethasone acetate (DXA)

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Stratos LV/LV-T CRT-P and Corox OTW lead technical manuals.

V. SYSTEM DESCRIPTION

Stratos LV(-T) CRT-Ps

The Stratos LV and Stratos LV-T CRT-Ps are rate adaptive pacemakers designed to provide Cardiac Resynchronization Therapy (CRT). The Stratos CRT-Ps provide all standard bradycardia pacemaker therapy with the additional capabilities of biventricular pacing for CRT. Biventricular pacing in the Stratos CRT-Ps can be programmed to initially pace in either the right or left ventricular chambers with separately programmable outputs for both left and right channels. Sensing of cardiac signals only occurs in the right ventricular chamber.

The Stratos CRT-Ps can also provide single and dual chamber pacing in a variety of rate-adaptive and non-rate adaptive pacing modes. Pacing capability is supported by an extensive diagnostic set. For motion-based rate-adaptation, the Stratos CRT-Ps are equipped with an internal accelerometer. This sensor produces an electric signal during physical activity of the patient. If a rate-adaptive (R) mode is programmed, then the accelerometer sensor signal controls the stimulation rate.

The Stratos LV-T additionally also employs BIOTRONIK's Home Monitoring™ technology, which is an automatic, wireless, remote monitoring system for management of patients with implantable devices. With Home Monitoring, physicians can review data about the patient's cardiac status and CRT-P's functionality between regular follow-up visits, allowing the physician to optimize the therapy process. Stratos CRT-Ps are also designed to collect diagnostic data to aid the physician's assessment of a patient's condition and the performance of the implanted device.

The bipolar IS-1 connections are used for pacing and sensing (right atrial and ventricle) and the additional IS-1 connection is used for pacing in the left ventricle in either a bipolar or unipolar configuration depending on the left ventricular lead. The pulse amplitude and pulse width of each of the three channels is separately programmable.

Stratos CRT-Ps are designed to meet all indications for Cardiac Resynchronization Therapy in CHF patients as well as those for bradycardia therapy as exhibited in a wide variety of patients. The Stratos family is comprised of two CRT-Ps that are designed to handle a multitude of situations.

Stratos LV	Triple chamber, rate-adaptive, unipolar/bipolar pacing CRT-P
Stratos LV-T	Triple chamber, rate-adaptive, unipolar/bipolar pacing CRT-P with Home Monitoring

Corox OTW(-S) BP Leads

BIOTRONIK's Corox OTW (-S) BP leads are transvenous, steroid-eluting left ventricular pacing leads designed for use with a compatible cardiac resynchronization therapy (CRT) device that accepts leads with a bipolar (BP) IS-1 connector configurations. The leads can be positioned in the target vein using either the over-the-wire techniques or stylet driven methods.

The leads are constructed with multifilar conductors insulated with medical grade silicone and coated with polyurethane. There are two separate distal ends available with the Corox OTW leads, as described below. In addition to the bipolar leads that are helix shaped at the lead tip (Corox OTW BP), the Corox OTW-S BP has a bend in the distal tip that fixates by "wedging" across a vessel.

- Corox OTW BP left ventricular leads have distal ends that are helix shaped at the lead tip, which is designed to adhere to the coronary vein when the stylet or guide wire is removed. This system provides for flexible control and positioning of the lead during implantation while the stylet or guidewire is in place. Additionally, the helical shape of the distal end of the lead fixates the electrode within the vessel after the stylet or guide wire is removed. This fixation design is a clinically proven fixation mechanism for larger vessels.

- Corox OTW-S BP has a silicone thread attached to the lead body between the tip and ring electrodes, which fixates by “wedging” across a vessel. The distal end between the electrodes also exhibits a slight two dimensional bend, which facilitates the steering of the lead in the coronary venous system. This fixation option is designed for implantation in smaller coronary vessels.

The lead conductor of the Corox OTW(-S) BP consists of quadrafillar MP35N/DFT (25% Silver) arranged in a 2 x 2 coradial helix and insulated against each other by a layer of (blue or white) ethylene tetrafluoroethylene (ETFE) with a thickness of 50µm.

The Corox OTW Steroid lead features a tip and ring electrode, each with a fractal surface structure of iridium that provides a larger effective tissue interface. The electrode is comprised of a platinum/iridium alloy base.

The Corox OTW(-S) BP leads include a steroid-eluting collar at the ring electrode and at the distal tip of the lead to aid in decreasing the inflammation that often occurs after implantation of a pacing lead. Each steroid collar nominally contains 0.5 mg of dexamethasone acetate (DXA). Upon exposure to body fluids, the steroid elutes from the collar into the body tissue by diffusion.

The Corox OTW(-S)-BP leads are available in lengths of 77 or 87 cm, which are designated as Corox OTW(-S) 75-BP Steroid and Corox OTW(-S) 85-BP Steroid, respectively. The Corox OTW(-S)-BP lead fits through a 7 F lead introducer.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for patients who require a pacemaker and also have heart failure. 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. Patients who require a pacemaker and also have heart failure are routinely treated with legally marketed pulse generators and medications. Medications include both those to treat arrhythmias and medications to treat heart failure. Additional treatments for heart failure include, but are not limited to, exercise and nutrition programs, heart transplantation, and other legally marketed CRT-Ps.

VII. MARKETING HISTORY

Stratos LV(-T) CRT-Ps

The Stratos LV received CE certification on August 14, 2002 and re-certification on August 14, 2007.

The Stratos LV/LV-T have been distributed in the following countries: European Union and Switzerland, Argentina, Australia, Brazil, Canada, Chile, China, Columbia, Cuba, Egypt, Guatemala, Hong Kong, India, Indonesia, Iran, Iraq, Israel, Jordan, Lebanon, Macedonia, Mexico, Panama, Russian Federation, Saudi Arabia, Singapore, South Africa, Turkey, Ukraine, Uruguay, and Venezuela.

All reportable complaints for Stratos are associated with an OUS recall of the Stratos pulse generator: On July 24, 2006, 84 Stratos LV-T devices were recalled due to a lot of potentially defective low-voltage capacitors. All physicians were informed accordingly, and devices not yet implanted were returned to BIOTRONIK. Associated to this, eleven devices were returned for analysis. All devices proved to be fully functional. It is important to note the following key points regarding this recall:

- No patient injuries or deaths associated with this recall have been reported.
- The recall was initiated as a precautionary method and was not triggered by any field complaints.
- BIOTRONIK has initiated long-term testing for the capacitors under question. None of these low-voltage capacitors have failed during the testing.
- The recall has been terminated by the German competent authority.
- FDA has reviewed the details associated with this recall during a GMP inspection. No deviations were noted.

The Stratos LV/LV-T CRT-Ps have not been withdrawn from marketing in any country for any reason relating to the safety and effectiveness of the device.

Corox OTW(-S) BP Leads

BIOTRONIK received approval of the Corox OTW BP and Corox OTW-S BP left ventricular leads in Europe on July 17, 2006.

There have been three clinical events associated with these leads reported to date:

1. A lead was explanted due to high pacing impedances. Analysis of the lead demonstrated a lead fracture due to excessive mechanical stress as the result of the Subclavian Crush Syndrome (i.e., clavicular - first rib entrapment). The analysis did not show any sign of a material or manufacturing problem.
2. A lead was explanted due to an insulation defect. Analysis of the lead demonstrated a lead fracture due to excessive mechanical stress as the result of the Subclavian Crush Syndrome (i.e., clavicular - first rib entrapment). The analysis did not show any sign of a material or manufacturing problem.
3. A lead was explanted due to loss of capture. The analysis was based on the inspection of the quality documents accompanying this particular device, as the lead was not returned for analysis. There was no sign of any inconsistency during the manufacturing process which might be related to the clinical observation.

The Corox OTW(-S) BP has been distributed in the following countries: European Union and Switzerland, Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Croatia, Egypt, India, Iran, Israel, Lebanon, New Zealand, Panama, Russia, South Africa, Turkey, Uruguay, and Venezuela.

The Corox OTW(-S) BP lead has not been withdrawn from marketing in any country for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Stratos LV(-T) CRT-Ps

The following are possible adverse events that may occur relative to the implant procedure and chronic implant of the Stratos LV/LV-T CRT-Ps:

- Air embolism
- Allergic reactions to contrast media
- Arrhythmias
- Bleeding
- Body rejection phenomena
- Cardiac tamponade
- Chronic nerve damage
- Damage to heart valves
- Elevated pacing thresholds
- Extrusion
- Fluid accumulation
- Infection
- Keloid formation
- Lead dislodgment
- Lead fracture / insulation damage
- Lead-related thrombosis
- Local tissue reaction / fibrotic tissue formation
- Muscle or nerve stimulation
- Myocardial damage
- Myopotential sensing
- Pacemaker mediated tachycardia
- Pneumothorax
- Pocket erosion
- Hematoma
- Device migration
- Thromboembolism
- Undersensing of intrinsic signals
- Venous occlusion
- Venous or cardiac perforation

Corox OTW(-S) BP LV Leads

Potential complications resulting from the use of left ventricular leads include, but are not limited to: thrombosis, embolism, body rejection phenomena, cardiac tamponade, pneumothorax, muscle/nerve stimulation, valve damage, fibrillation, infection, skin erosion and ventricular ectopy. Lead perforation through the myocardium has been rarely observed. The table below summarizes some of the potential symptoms indicating a complication and possible corrective actions:

Table 1: Potential Complications and Corrective Actions

Symptom	Potential Complication	Potential Corrective Action
Loss of pacing or sensing	Lead dislodgement	Reposition lead
	Lead fracture	Replace lead
	Setscrew penetration of lead insulation	Replace lead
	Improper lead / pulse generator connection	Reconnect lead to pulse generator
Increase/decrease in threshold	Fibrotic tissue formation	Adjust pulse generator output; Replace/reposition lead

IX. SUMMARY OF PRE-CLINICAL STUDIES

A. NON-CLINICAL LABORATORY STUDIES - STRATOS LV/LV-T CRT-PS

The service times for the Stratos LV/LV-T devices from beginning of service (BOS) to elective replacement indication (ERI) is expected to be 51 months with a lead impedance of 500 ohms and 60 months with a lead impedance of 1000 ohms. All estimates assume a pacing rate of 60 ppm, pulse amplitude of 3.6 V at 0.4 ms. The Use Before Dating is 18 months after the battery is connected during the manufacturing process.

The Stratos LV/LV-T CRT-PS are a derivation of BIOTRONIK's legally marketed Philos DR (P950037/S12) and Protos (P950037/S28) pulse generators with biventricular pacing capabilities added to provide cardiac resynchronization therapy (CRT). Nearly all of the components used for the Stratos LV/LV-T are identical to those used for the Philos DR and Protos devices, including all blood / tissue contact materials; therefore, these components were validated with previously approved devices.

i. Finished Device Testing

The Stratos LV/LV-T CRT-PS finished devices have been subjected to validation testing according to the BIOTRONIK's validation plans. The Stratos LV/LV-T CRT-PS have passed all in vitro laboratory validation tests with acceptance based on Stratos LV/LV-T CRT-PS product specifications.

Table 2: Summary of Finished Device Validation Testing (Stratos LV / LV-T)

Test	Acceptance Criteria	Test Results (Pass/Fail)
Drop Test in Packaging	Testing was performed according to European Standards EN 45502-1 ¹ , Section 10.1	Pass
Transportation Test	Testing was performed according to European Standard EN 45502-2-1 ² , Sec. 10.1.	Pass
Humidity and Vacuum Storage	Protection from Temperature and Humidity Changes according to European Standard EN 45502-2-1 ² , Sect. 10.1.	Pass
Ultrasound Resistance	Exposure to Ultrasound according to European Standard EN 45502-1 ¹ , Sect. 22.1	Pass
Changes in Air Pressure	Exposure to Air Pressure Changes according to European Standard EN 45502-1 ¹ , Sect. 25.1	Pass
Temperature Cycle	Exposure to Temperature Changes according to European Standard EN 45502-2-1 ² , Sect.26.2.	Pass

¹ EN 45502-1: Active implantable medical devices. Part 1: General requirements for safety, labeling and information to be provided by the manufacturer

² EN 45502-2-1: Active implantable medical devices. Part 2-1: Particular requirements for active implantable medical devices intended to treat bradyarrhythmia (cardiac pacemakers)

Table 2: Summary of Finished Device Validation Testing (Stratos LV / LV-T)		
Test	Acceptance Criteria	Test Results (Pass/Fail)
Temperature Shock	The validation standard refers to the requirements from the norm DIN IEC 68-2-14: 6'87 ³ , Section 1 (Temperature Change) and MIL-STD 883D ⁴ , Method 1011.9 (Thermal Shock).	Pass
In Vitro 500 Hours	The pulse generator is required to function within specifications and with identical programming values before and after the 500 hour In Vitro Test.	Pass
Dimensional and Visual Inspection of the Header	Visual and dimensional inspection is performed according ISO 5841-3:12'92 ⁵ (IS- 1) for the header ports and internal BIOTRONIK specification for the other header characteristics (i.e., position of the antenna, wiring, lead drill holes, anchors, x-ray markers, and suture holes).	Pass
In Vitro 2000 Hours	The pulse generator is required to function within specifications and with identical programming values before and after the 2000 hour In Vitro Test.	Pass
Visual Inspection of the inner structure	The units were inspected to ensure proper arrangement of the subassembly and parts in terms of function and further processing.	Pass
Mechanical shock test	Exposure to Mechanical Shock according to European Standard EN45502-1 ¹ , Sect.23.7.	Pass
Vibration test	Exposure to Vibration according to European Standard EN45502-2-1 ² , Sect. 23.2	Pass
Header Shearing Test	The housing is mounted firmly and the header is stressed on its upper edge till it detaches from the housing. The test is passed if the mean shear value of five units $\geq 1.5 \text{ N/mm}^2$.	Pass
Pulse Generator Casting	The Stratos casting was inspected per EN 45502-1:1996 ¹ , Section 15.2.	Pass
Fixation Force of the Connector Block	The shear force of the connector block was determined by pulling the leads. Devices must withstand a force of >25 N when the torque is tightened to 6N / cm.	Pass
Corrosion Test In-Vitro	A housing with 4 anchors was stored for 2000h at 50°C in a 0.9% NaCl solution. The welding was visually inspected before and after the test.	Pass
T-Option: Home Monitoring Statistics Test (Functional Test with Implant)	For the Stratos LV-T device, selection, transmission and interrogation of Home Monitoring parameters from the programmer was confirmed. Using a patient simulator and a patient device, transmission and accuracy of patient-activated and periodic messages were confirmed.	Pass
Input Impedance	Testing performed according to European Standard EN 45502-2-1:1998 ² , Sect. 6.1.3	Pass
Noise Suppression	The sensing signal of the atrial and ventricular channels and the pacing signals of the triggered channels must appear sequentially in the IEGM (intracardiac electrogram) printout. The atrial and ventricular sensing signals must still be able to be differentiated from the noise signal.	Pass
Electric Neutrality of Pacemakers	Testing was performed according to European Standards EN 45502-2-1:1998 ² , Sect. 16.2.	Pass

³ DIN IEC 68-2-14: Environmental testing - Part 2: Tests. Test N: Change of temperature

⁴ MIL-STD 883D: Test Method Standard, Microcircuits

⁵ ISO 5841-3: Implants for surgery – Cardiac pacemaker. Part 3: Low-profile connectors (IS-1) for implantable pacemakers

Test	Acceptance Criteria	Test Results (Pass/Fail)
Longevity / Use Before Date	Calculation must be prepared for mean value data and -3-sigma data of battery discharge characteristics to achieve the total service life and use before date.	Pass
Defibrillation Protection	Testing according to European Standard, EN 45502-1:1997 ¹ , Sect. 20.2.	Pass

ii. Firmware

Embedded Software validation testing was designed to confirm the overall safety and functionality of the Stratos LV/LV-T CRT-Ps. The Stratos LV/LV-T embedded software successfully passed all test requirements. Validation testing was performed to verify that the Stratos LV/LV-T embedded software functioned as specified during and after exposure to a variety of external conditions and origins. The acceptance criteria for testing of the Stratos LV/LV-T firmware were based on internal BIOTRONIK specifications and all test data was acceptable.

Firmware Tests	Successfully Performed
Exposure to External / Internal Influences	<ul style="list-style-type: none"> • Demodulation of Product • High Rate Protection (Rate Limiting by Maximum Activity Rate (MAR) and Upper Tracking Rate (UTR)) • Influences on Device during RF Telemetry • Temperature Changes • Effect of Light
Elective Replacement Indication (ERI) and End of Service (EOS)	<ul style="list-style-type: none"> • Measurement of Current Consumption • ERI Onset • Service Life Calculations / Use Before Date • Enabling ERI Detection Independent of Implant Detection
Electrical Characteristics	<ul style="list-style-type: none"> • Electric Neutrality • Measurement of Input / Output Impedance • Input Filter Response • Sensing Input Amplifiers • Far-Field Sensing • Response to Reset • Crosstalk Sensitivity of Biventricular Sensing/Pacing • Pacing Impedance Measurements (Automatic Lead Check) • Repeatability of Output Current Analog Telemetry • Rate and AV Delay Limitation • Synchronization Behavior • AES Detection & Post AES Stimulation • Rate Management • VES Lock-In Protection • ICD Compatibility • CRC Check before Every Program Activation • Cyclic RAM Check • Secure ROM Behavior • Sensitivity within a Pacing Interval / Input Sensitivity as a Function of Time after Pace • Stress Tests: Rate Adaptive and Non-Rate Adaptive • Electric Neutrality / Electrostatic Discharge Susceptability • Impulse Parameters • Programming Responses

Firmware Tests	Successfully Performed	
Sensor Response Threshold	<ul style="list-style-type: none"> • Only Affected by Frequencies Between 2 and 10 Hz • Response During Patient Activity without exceeding Maximum Activity Rate • Appropriate Return to Baseline when Motion Removed • Automatic Gain 	
Pacing Characteristics	<ul style="list-style-type: none"> • Rate Hysteresis • Rate Repetitive Hysteresis • Rate Scan Hysteresis • AV Hysteresis • AV Repetitive Hysteresis • AV Scan Hysteresis • Refractory Period • Atrial Upper Rate • Biventricular Synchronization 	<ul style="list-style-type: none"> • Rate Fading • Night Mode • PMT Prevention and Termination • Mode Switching • Atrial Upper Rate • AF Classification • Common Mode Rejection
Battery Monitoring	<ul style="list-style-type: none"> • Internal Battery Impedance Measurement • Charge Accumulation • Battery Capacity 	
Programming Wand	<ul style="list-style-type: none"> • Programming and Interrogation Distances • Magnet Response at Various Distances • Response Under Magnet Application 	
Home Monitoring	<ul style="list-style-type: none"> • Service Distance • Transmission and Schedule of Trend Message • Transmission and Schedule of Event Message • Transmission and Schedule of Patient Message • Transmission Behavior in ERI Mode • Effectiveness of the Home Monitoring "Bug Fix" for Trend Errors 	

iii. Electronic Module Testing

Electronic Module validation testing was designed to confirm the overall functionality of the electronic circuits utilized in the Stratos LV/LV-T CRT-Ps. The Stratos LV/LV-T electronic module successfully passed all test requirements. Validation testing was performed to verify that the Stratos LV/LV-T electronic module functioned as specified during and after exposure to a variety of external conditions and origins. The acceptance criteria for testing of the Stratos LV/LV-T firmware were based on internal BIOTRONIK specifications and all test data was acceptable.

Test	Acceptance Criteria	Test Results (Pass/Fail)
Visual Inspection and Dimensions Before and After Life Test	The test was conducted over 1000 hours at 125°C and rated voltages were taken. Visual and dimensional inspection is performed according to internal BIOTRONIK specifications.	Pass
Final Acceptance Test (FAT) After Temperature Cycles	Testing performed according to military standards, MIL-STD-883E ⁶ M.1010.7 C.A and MIL-STD-883E M.1005.8.	Pass
Shear Test Initial	Testing performed according to military standard, MIL-STD-883 ⁶ , M2019.5.	Pass
Bond Pull Test	Testing performed according to military standard, MIL-STD-883E ⁶ M.2011.4D.	Pass

⁶ MIL-STD 883E: Test Method Standard, Microcircuits

Test	Acceptance Criteria	Test Results (Pass/Fail)
Mechanical Stability of Substrate During Point Load	The test specification was at orienting measurement, Fmax >50N.	Pass
Constant Acceleration (2000g)	Testing performed according to military standard, MIL-STD-883 ⁶ M2001.	Pass
Mechanical Shock Test	Testing performed according to European Standard, EN 45502-1 ¹ , Sect. 23.7.	Pass

iv. Electromagnetic Interference (EMI) Testing

BIOTRONIK has performed a comprehensive set of electromagnetic interference testing of the Stratos LV/LV-T CRT-Ps according to two separate industry standards, including the DIN VDE 0750, and EN 45502-2-1². All EMI susceptibility testing has successfully passed the criteria for medical implantable devices.

The purpose of testing to these standards was to assure that both European and U.S. concerns were satisfied for both conducted and radiated measurements over a wide frequency spectrum. Tests were performed at certified EMI laboratories CETECOM in Germany, as well as at BIOTRONIK facilities. All testing passed the requirements presented in standard EN 45502-2-1².

Test	Acceptance Criteria	Test Results (Pass/Fail)
Safety during EMI, Induced Electrical Currents in the Pacing Leads	Testing performed according to European Standard EN 45502-2-1: 2003, Sect. 27.2.	Pass
Safety during EMI, Non-modulated Electromagnetic Signals	Testing performed according to European Standard EN 45502-2-1: 2003, Sect. 27.3	Pass
Safety during EMI, Modulated Electromagnetic Signal	Testing performed according to European Standard. EN 45502-2-1: 2003, Sect. 27.4.	Pass
Immunity from EMV Signals in the Range of 16.6 Hz to 10 MHz	Testing according to European Standard, EN 45502-2-1:2003, Sect. 27.5.1; Sect. 27.5.2	Pass
Immunity from EMV Signals in the Range of 10 MHz to 450 MHz	Testing according to European Standard, EN 45502-2-1:2003, Sect. 27.5.3	Pass
Immunity from EMV Signals in the Range of 450 MHz to 3000 MHz	Testing according to European Standard, EN 45502-2-1:2003, Sect. 27.5.4	Pass
Immunity from Time-Variable Magnetic Fields	Testing according to European Standard, EN 45502-2-1:2003, Sect. 27.8	Pass
Radio Permit Test of the NF Telemetry	Testing according to European Standard, EN 300330 ⁷ (1995-05) and ETSI EN 300 220-3 ⁸ V 1.1.1 (2000-09).	Pass
Effect of Static Magnetic Field	Exposure to magnetic field strength of 1 mT. Testing performed according to European Standard EN 45502-2-1:1998 Sect. 27.5 & Sect. 27.6.	Pass
Demodulation Product	Testing performed according to internal BIOTRONIK procedures.	Pass

⁷ EN 300330: Electromagnetic compatibility and Radio spectrum Matters (ERM); Short Range Devices (SRD); Radio equipment in the frequency range 9 kHz to 25 MHz and inductive loop systems in the frequency range 9 kHz to 30 MHz

⁸ ETSI EN 300 220-3: Electromagnetic compatibility and Radio spectrum Matters (ERM); Short Range Devices (SRD); Radio equipment to be used in the 25 MHz to 1 000 MHz frequency range with power levels ranging up to 500 mW; Part 3: Harmonized EN covering essential requirements under article 3.2 of the R&TTE Directive

Test	Acceptance Criteria	Test Results (Pass/Fail)
Application of a Cautery Device on a Specimen in Physiologic Sodium Solution	Interrogation must be possible; there must be no changes in the characteristic parameters.	Pass
Programming Response During EMI Disturbances	Testing performed according to internal BIOTRONIK procedures to guarantee the programmability of pacemakers under the influence of EMU disturbances, as well as communication with the programmer via a minimum coverage range.	Pass
Radio Approval Measurement, EMC for Radio Equipment and Services, and Risk Control: Transmission Power vs. Tissue Damage	Testing according to European Standards, ETSI EN 301 839-2 ⁹ V 1.1.1 (2002-06), ETSI EN 301 489-27 ¹⁰ (2004-03), and EN 50371:2002 ¹¹ , Abs. 4.1.	Pass

B. NON-CLINICAL LABORATORY STUDIES – COROX OTW(-S) BP LEADS

The following tables summarize the validation testing (safety and performance) conducted on the components of BIOTRONIK's Corox OTW(-S) BP Leads, including performance testing, packaging, shelf life and biocompatibility tests. Validation has been performed according to the appropriate European, International and National standards, in addition to internal BIOTRONIK specifications. In the tables below, "Pass" denotes that the results satisfy the company's design specifications.

Test Performed	Test Results (Pass/Fail)
Biocompatibility and Sterilization	
Hemocompatibility (final product) according to ISO 10993-4 ¹²	Pass
Cell Toxicity (final product) according to ISO 10993-5: 1999 ¹³	Pass
Proof of Absence of Pyrogens with the Limulus Amoebocyte Lysate Test (LAL Test)	Pass
Proof of Bioburden on Medical Products / Determination of the Correction Factor according to DIN EN 1174-1: 1996 ¹⁴	Pass
Proof of Sterilization Success according to EN 550: 1994 ¹⁵	Pass
Residual Gas Analysis: Ethylene Oxide and Ethylene Chlorohydrin according to ISO 10993-7: 1995 ¹⁶	Pass
Final Product	
Electrical Continuity and DC Resistance according to FDA Lead Guidance*	Pass
Leakage Current according to FDA Lead Guidance*	Pass
Strength of Lead (bonds) (of Complete Lead, Weld and Crimp Connections) according to FDA Lead Guidance*	Pass
Leak Proof (Isotonic Saline at 37°C) according to FDA Lead Guidance*	Pass
Corrosion Resistance of Conductors according to FDA Lead Guidance*	Pass

⁹ ETSI EN 301 839-2: Electromagnetic compatibility and Radio spectrum Matters (ERM); Radio equipment in the frequency range 402 MHz to 405 MHz for Ultra Low Power Active Medical Implants and Accessories; Part 2: Harmonized EN covering essential requirements of article 3.2 of the R&TTE Directive

¹⁰ ETSI EN 301 489-27: Electromagnetic compatibility and Radio spectrum Matters (ERM); EMC standard for radio equipment and services; Part 27: Specific conditions for Ultra Low Power Active Medical Implants (ULP-AMI) and related peripheral devices (ULP-AMI-P)

¹¹ EN 50371: Generic standard to demonstrate the compliance of low power electronic and electrical apparatus with the basic restrictions related to human exposure to electromagnetic fields (10 MHz - 300 GHz). General public

¹² ISO 10993-4: Biological evaluation of medical devices. Part 4: Selection of tests for interactions with blood

¹³ ISO 10993-5: Biological evaluation of medical devices. Part 5: Tests for in-vitro cytotoxicity

¹⁴ DIN EN 1174-1: Sterilization of medical devices - Estimation of the population of micro-organisms on product - Part 1: Requirements

¹⁵ EN 550: Sterilization of medical devices - Validation and routine control of ethylene oxide sterilization

¹⁶ ISO 10993-7: Biological evaluation of medical devices. Part 7: Ethylene oxide sterilization residuals

Table 6 Corox OTW(-S) BP Validation Testing	
Test Performed	Test Results (Pass/Fail)
Stylet Performance according to FDA Lead Guidance*	Pass
Fatigue Test (Bending Fatigue Test on Lead Body and on Connector) according to FDA Lead Guidance*	Pass
Connector Testing to ISO 5841-3 ⁵ (IS-1) (on Lead Body between Connector and Tip/Ring, at Connector Transition)	Pass
Anchoring Sleeve Performance according to FDA Lead Guidance*	Pass
Lead Tip Pressure (Compression Behavior: Determination of Pressure Exerted on Projected Area of Distal End) according to FDA Lead Guidance*	Pass
Labeling on Sales and Sterile Package according to EN 45502-1 ¹	Pass
Visual, Electrical & Dimensional Inspection of Complete Lead and Inspection of Markings according to EN 45502-1: 1998-07 and EN 45502-2-1: 2002-4 ²	Pass
Area Calculation of Tip Electrode according to Internal BIOTRONIK Specification; Leads were checked for conformance with the dimensions detailed in BIOTRONIK design specifications. The surface areas of the tip and ring electrodes were calculated from the design specifications to verify the electrodes had the specified surface area ($A = 5.0 \pm 0.2 \text{ mm}^2$ and 8.0 mm^2 , respectively)	Pass
Abrasion Resistance of Complete Lead according to Internal BIOTRONIK Specification; The number of shaft revolutions required to completely rub through the tubing must meet the following criteria: The lower limit of the 95% confidence interval of the population mean must be greater than 7500 revolutions. If the test was aborted before all specimens were completely rubbed through, then this statistic shall be calculated only with those specimens that were rubbed through. Each individual value must be ≥ 5000 revolutions.	Pass
X-Ray Visibility of Complete Lead according to DIN 13273-7: 1996-12 ¹⁷	Pass
Simulated Fixation of Distal End of Lead in Blood Vessel according to Internal BIOTRONIK Specification; Helix fixation at the distal end of the lead (immersed in NaCl solution at 37 °C) was inserted in a straight glass tube with inner diameter of 3.2 mm. The retention force when pulled axially out of the tube must be $\geq 0.05 \text{ N}$.	Pass
Steroid	
Test of Identification, Purity and Content of DXA in the Collar and Collar Subassemblies according to Internal BIOTRONIK Specification: Identity: the retention time of the DXA peak in the HPLC chromatograph must be comparable with the retention time of the standard substance peak. Purity: no peak more than 0.5% and the sum of all impurity peaks not more than 1% of main peak. Content of DXA must be $0.5 \text{ mg} \pm 30\%$ per collar.	Pass
Liberation of DXA from the Collar and Lead Assemblies –Determination of the Elution Rate according to Internal BIOTRONIK Specification; There must be more than 4 μg DXA released after two and more than 7 μg DXA released after 4 days for the collar and 4 – 8 μg DXA after two and 7 – 13 μg DXA after 4 days for the lead tip assemblies.	Pass
Accessories	
Use of Corox OTW(-S) BP with Implantation Tool ScoutPro 7F and 8F – Introduction and Retraction of the Lead according to Internal BIOTRONIK Specification; The lead was introduced to and retracted from the implantation tool five times. There must be no problem with handling and no damage to the lead, introducer or hemostatic valve. The friction force during advancement of the lead within the sheath must be less than 1 N (less than 2 N for the 7F).	Pass

¹⁷ DIN 13273-7: Catheters for medical use - Part 7: Determination of the x-ray attenuation of catheters; Requirements and testing

Table 6 Corox OTW(-S) BP Validation Testing	
Test Performed	Test Results (Pass/Fail)
Use of Corox OTW with Anchoring Sleeve EFH-16 (Straight Slitted) according to Internal BIOTRONIK Specification; A tensile load was applied at both ends of the thread until the thread breaks. No damage may occur to the lead or EFH at the maximum constriction force (which is equal to the tensile strength of the ligature). A normal manual force of 8 N was applied as knots are tied in the thread. The EFH may not shift at a tensile force up to 5 N.	Pass
Use of Corox OTW(-S) BP with Stylets S xx-K OTW and S xx-G OTW according to Internal BIOTRONIK Specification; The retention force of the stylet wire within connector pin (clamping function) was determined to verify that the insertion and extraction force is between 1.0 N and 5.0 N No damage may occur to the lead (including the distal seal) or the stylet. The stylet must maintain continuous movement. The stylet may not protrude from the distal end of the lead.	Pass
Use of Corox OTW(-S) BP with Torque Wrench for Guide Wire according to Internal BIOTRONIK Specification; The handling of the torque wrench was assessed. The torque wrench must easily tighten and loosen. The wrench must be threaded over 0.36 mm guidewire and tightened. The tightened wrench must not be moved on a 0.3 mm wire when a 2 N axial force is applied.	Pass
Use of Corox OTW(-S) BP with Cannula for Introducing Guide Wire into Introducer or Hemostatic Valve of Implantation Tool according to Internal BIOTRONIK Specification; The cannula was introduced into the hemostatic valve and introducer. The guidewire was inserted into the cannula and then removed. The testing was performed with four different samples. There must be no problem with handling and no damage to the lead, introducer or hemostatic valve.	Pass
Use of Corox OTW(-S) BP with Guide wire 0.36 mm: Handling, Insertion, Maneuverability, Friction Force according to Internal BIOTRONIK Specification; The maneuverability and handling of the guidewire were assessed after the guidewire was completely inserted into the lead from both ends. The friction forces were determined during advancement and retreat of the lead to verify that the forces were not greater than 0.5 N. No damage may occur to the lead or the guidewire. The guidewire must maintain continuous movement.	Pass

* Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions dated November 1, 2000

C. PROGRAMMER SOFTWARE

Validation of the programmer software presented in this PMA application was performed using automated or manual testing techniques. Testing was performed using BIOTRONIK's EVALUATOR™ automatic testing setup for evaluating the programmer screens and functional displays. All features and characteristics that could not be tested with the EVALUATOR system were tested manually (user). Results of the validation substantiate that the software used for interrogating and programming BIOTRONIK implants functions as designed.

D. BIOCOMPATIBILITY TESTING

All tissue-contacting materials of BIOTRONIK's CRT-Ps are currently utilized in BIOTRONIK products market-released in the US. Biocompatibility testing of all tissue-contacting materials utilized in BIOTRONIK's CRT-Ps has been successfully completed.

All tissue-contacting materials of BIOTRONIK's Corox OTW(-S) BP Left Ventricular Lead are currently utilized in BIOTRONIK products market-released in the US. Biocompatibility testing of all tissue-contacting materials utilized in BIOTRONIK's leads has been successfully completed.

The biocompatibility results demonstrated that the requirements of ISO 10993 were fulfilled and the Stratos LV/LV-T CRT-Ps and Corox OTW(-S) BP leads bear no additional biological risks.

E. SHELF LIFE

A 18-month expiration date, "Use Before Date" (UBD), has been established for the Stratos LV/LV-T CRT-Ps based on device longevity and internal battery characteristics. The use before date is assigned as the last date of the eighteenth month after battery connection is made during the manufacturing process.

A 24-month expiration date, "Use Before Date" (UBD), has been established for the Corox OTW(-S) BP Left Ventricular Lead based on sterility and long-term storage testing. The use before date is assigned as the last date of the twenty-fourth month after sterilization.

F. CONCLUSION CONCERNING NON-CLINICAL LABORATORY TESTING

BIOTRONIK conducted risk analyses on all new features and critical components and then conducted testing to evaluate these and other device characteristics. All test results were found to be acceptable to support reasonable safety to begin clinical trials.

X. SUMMARY OF CLINICAL STUDIES

The subsequent sections summarize the following four clinical studies that were used to support the safety and effectiveness of the Stratos LV/LV-T CRT-Ps and/or Corox OTW(-S) BP Left Ventricular Leads.

- The AVAIL CLS/CRT clinical study
- The OVID clinical study (OUS)
- The OPTION CRT/ATx clinical study
- The everesT clinical study (OUS)

Two of the studies, AVAIL CLS/CRT and OVID, collected significant safety data supporting use of the Stratos LV/LV-T CRT-P system. The third study, OPTION CRT/ATx, supports the effectiveness of cardiac resynchronization therapy (CRT). The OPTION CRT/ATx study was conducted on a device that delivers CRT but, in addition, also offers defibrillation therapy (CRT-D).

The everesT clinical investigation assessed the clinical safety and effectiveness of Corox OTW(-S) BP bipolar left ventricular leads.

A. STRATOS LV CLINICAL STUDY – AVAIL CLS/CRT

i. Study Design

The AVAIL CLS/CRT was a multi-center, prospective, randomized, blinded clinical study designed to support approval for cardiac resynchronization therapy for a Heart Failure (HF) patient population not requiring back up defibrillation and that are indicated for an ablate and pace procedures. All patients enrolled into the clinical study were randomly assigned to one of three groups using a 2:2:1 ratio for randomization.

- Patients assigned to Group 1 received biventricular pacing with CLS-based rate adaptive pacing using BIOTRONIK's Protos DR/CLS, which is a dual-chamber pulse generator with CLS-based rate adaptive pacing. During this study, the Protos DR/CLS devices were implanted with two ventricular leads: the right ventricular lead was connected to the ventricular port, and the left ventricular lead was connected to the atrial port. Protos DR/CLS was included in this study to evaluate biventricular pacing with a different type of rate adaptive sensor technology.
- Patients assigned to Group 2 received biventricular pacing with accelerometer-based rate adaptive pacing using the Stratos LV.
- Patients assigned to Group 3 (control group) received right ventricular pacing with accelerometer-based rate adaptive pacing using the Stratos LV. Therefore, 60% of the patients received a Stratos LV device.

Primarily, the study evaluated and compared the functional benefits of CRT between the three randomized groups using a composite endpoint consisting of a six-minute walk test (meters walked) and quality of life measurement (assessed using the Minnesota Living with Heart Failure Questionnaire). Relevant measurements were completed twice for each patient: once at the Baseline evaluation (prior to implant and ablation) and again at a six-month follow-up evaluation. The data collected during this clinical study was used to demonstrate superiority of CRT to RV only pacing. This study also evaluated the safety of both the Protos DR/CLS and Stratos LV devices through an analysis of the complication-free rate through six months. Secondly, the study also evaluated the superiority of CRT with CLS rate adaptation compared to CRT with accelerometer rate adaptation.

ii. Clinical Inclusion and Exclusion Criteria

a. Clinical Inclusion Criteria

To support the objectives of this investigation, patients were required to meet the following inclusion criteria prior to enrollment:

- Meet the indications for therapy
- Persistent (documented for more than 7 days), symptomatic AF with poorly controlled rapid ventricular rates or permanent, (documented for more than 30 days with failed cardioversion, or longstanding AF of 6 months or more) symptomatic AF with poorly controlled rapid ventricular rates.
- Eligible for AV nodal ablation and permanent pacemaker implantation
- NYHA Class II or III heart failure
- Age \geq 18 years
- Understand the nature of the procedure
- Ability to tolerate the surgical procedure required for implantation
- Give informed consent
- Able to complete all testing required by the clinical protocol
- Available for follow-up visits on a regular basis at the investigational site

b. Clinical Exclusion Criteria

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment included the following:

- Meet one or more of the contraindications
- Have a life expectancy of less than six months
- Expected to receive heart transplantation within six months
- Enrolled in another cardiovascular or pharmacological clinical investigation
- Patients with an ICD, or being considered for an ICD
- Patients with previously implanted biventricular pacing systems
- Patients with previously implanted single or dual chamber pacing system with $>50\%$ documented ventricular pacing
- Patients with previous AV node ablation
- Six-minute walk test distance greater than 450 meters
- Any condition preventing the patient from being able to perform required testing
- Presence of another life-threatening, underlying illness separate from their cardiac disorder
- Conditions that prohibit placement of any of the lead systems

iii. Follow-Up Schedule

At the enrollment screening, the physician evaluated the patient to verify that all inclusion/exclusion criteria have been met in accordance to the protocol and the patient has signed the informed consent. After successful enrollment, all patients were implanted with either a Stratos LV CRT-P or Protos DR/CLS device. Evaluations at the Four Week, Three and Six Month follow-ups included NYHA classification, medications, and percentage of ventricular pacing.

iv. Clinical Endpoints

a. Primary Endpoint: Complication-free Rate (Safety)

The safety of the Stratos LV was evaluated based on complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Stratos LV, the right ventricular, the left ventricular lead, lead ventricular lead adapters (if used) and the implant procedure. The target complication-free rate at six months is 85%.

b. Primary Endpoint: Six Minute Walk Test & QOL (Effectiveness)

The purpose of Primary Endpoint 1 was to evaluate the effectiveness of the CRT (Groups 1 and 2) compared to RV only (Group 3) pacing as measured by the average composite rate of improvement in six minute walk test and QOL.

v. Accountability of PMA Cohorts

After randomization and enrollment, 23 patients (8 in Group 1, 8 in Group 2 and 7 in Group 3) did not receive an implant. The reasons for patients not receiving an implant are outlined in **Figure 1**. Two additional patients in Group 1 had an unsuccessful first implant attempt (unable to implant the LV lead), but follow up data was not received.

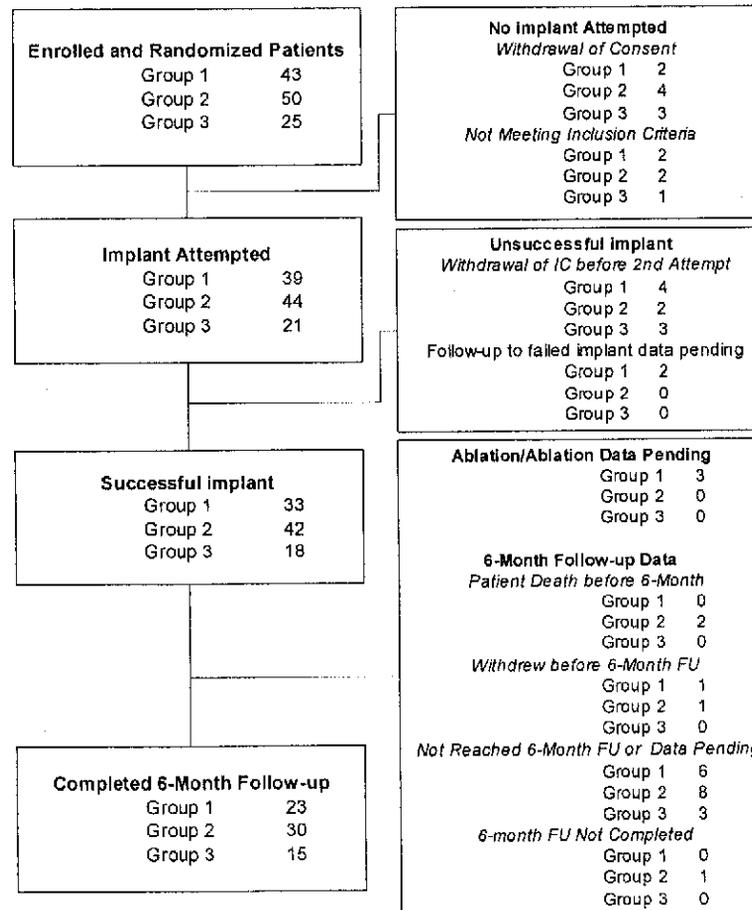


Figure 1: Patient Accountability

vi. Demographics and Baseline Parameters

Table 7 provides a summary of the patient demographics at enrollment. There were no statistical differences in enrollment demographics between the 3 groups.

Table 7: Patient Demographics at Enrollment

Characteristic	Group 1	Group 2	Group 3	P-value
Age at Enrollment (Years)	N=42	N=50	N=25	
Mean ± SE	73.7 ± 1.3	72.3 ± 1.2	71.5 ± 1.6	0.534*
Range	56 to 90	51 to 86	52 to 85	
Gender	N=42	N=50	N=25	
Male	18 (42.9%)	19 (38.0%)	13 (52.0%)	0.553**
Female	24 (57.1%)	31 (62.0%)	12 (48.0%)	
Six-Minute Walk Distance (meters)	N=42	N=50	N=25	
Mean ± SE	262.7 ± 15.1	283.6 ± 13.8	267.8 ± 22.9	0.395*
Range	78 to 420	37 to 438	23 to 420	
New York Heart Association Class	N=42	N=50	N=25	
Class II	23 (54.8%)	18 (36.0%)	10 (40.0%)	0.189**
Class III	19 (45.2%)	32 (64.0%)	15 (60.0%)	
Underlying Heart Disease	N=42	N=49	N=25	
Dilated Cardiomyopathy	8 (19.0%)	11 (22.4%)	1 (4.0%)	0.125**
Hypertrophic Cardiomyopathy	4 (9.5%)	1 (2.0%)	2 (8.0%)	0.216**
Valvular Heart Disease	12 (28.6%)	12 (24.5%)	5 (20.0%)	0.792**
Coronary Artery Disease	19 (45.2%)	28 (57.7%)	6 (24.0%)	0.031**
Hypertension	37 (88.1%)	37 (75.5%)	19 (76.0%)	0.348**
No underlying structural heart disease	3 (7.1%)	2 (4.1%)	7 (28.0%)	0.007**
Other Medical History	N=29	N=36	N=17	
Diabetes	13 (44.8%)	9 (25.0%)	4 (23.5%)	0.287**
Chronic Lung Disease	7 (24.1%)	16 (44.4%)	7 (41.2%)	0.211**
Thyroid Disease	12 (41.4%)	12 (33.3%)	5 (29.4%)	0.791**
Chronic Kidney Disease	4 (13.8%)	5 (13.9%)	1 (5.9%)	0.836**
Prior Ischemic Stroke or TIA	7 (24.1%)	10 (27.8%)	6 (35.3%)	0.726**
Prior Embolic Events (non-cerebrovascular)	1 (2.3%)	3 (6.0%)	2 (8.0%)	0.653**

*One-way ANOVA, ** Chi-Square test (2-sided)

Table 8 provides a summary of the AF medical history. **Table 9** provides a summary of cardiac medications patients were taking at the time of enrollment. Please note some categories may equal more than 100% as several categories allow more than one response. In some cases, complete demographic data was not provided for all patients. There were no statistical differences in AF medical history and cardiac medication at enrollment between the 3 groups.

Table 8: Atrial Fibrillation Demographics at Enrollment

Characteristic	Group 1	Group 2	Group 3	P-value*
Classification of Atrial Fibrillation	N=42	N=50	N=24	
Persistent AF	10 (23.8%)	17 (34%)	6 (25%)	0.537
Permanent AF	32 (76.2%)	33 (66%)	18 (75%)	
Classification of Symptoms Related to AF	N=42	N=49	N=25	
Palpitations	32 (76.2%)	34 (69.4%)	14 (56.0%)	0.236
Chest Pain	6 (14.3%)	7 (14.3%)	3 (12.0%)	1.000
Dyspnea or shortness of breath	36 (85.7%)	40 (81.6%)	19 (76.0%)	0.568
Fatigue	34 (81.0%)	45 (91.8%)	18 (72.0%)	0.149
Lightheadedness or syncope	17 (40.5%)	13 (26.5%)	9 (36.0%)	0.329
Other	9 (21.4%)	11 (22.4%)	10 (40.0%)	0.205
Previous AF Ablation	N=42	N=50	N=25	
No	37 (88.1%)	47 (94.0%)	21 (84.0%)	0.354
Yes	5 (11.9%)	3 (6.0%)	4 (16.0%)	

Characteristic	Group 1	Group 2	Group 3	P-value*
Past Medications for Rate or Rhythm Control	N=41	N=48	N=24	
Amiodarone	12 (29.3%)	10 (20.8%)	10 (41.7%)	0.192
Digoxin	17 (41.5%)	22 (45.8%)	13 (54.2%)	0.683
Diltiazem	17 (41.5%)	23 (47.9%)	12 (50.0%)	0.804
Disopyramide	0 (0.0%)	3 (6.3%)	0 (0.0%)	0.228
Dofetilide	4 (9.8%)	3 (6.3%)	2 (8.3%)	0.895
Flecainide	5 (12.2%)	5 (10.4%)	1 (4.2%)	0.656
Ibutilide	0 (0.0%)	0 (0.0%)	1 (4.2%)	0.215
Procainamide	0 (0.0%)	2 (4.2%)	0 (0.0%)	0.506
Propafenone	2 (4.9%)	4 (8.3%)	0 (0.0%)	0.423
Sotalol	9 (22.0%)	10 (20.8%)	2 (8.3%)	0.389
Verapamil	5 (12.2%)	8 (16.7%)	3 (12.5%)	0.829
Metoprolol	19 (46.3%)	28 (58.3%)	10(41.7%)	0.382
Propranolol	0 (0.0%)	0 (0.0%)	1 (4.2%)	0.215
Other Beta-Blockers	7 (17.1%)	15 (31.3%)	4 (16.7%)	0.248
Other Medications	5 (12.2%)	5 (10.4%)	1 (4.2%)	0.656
Rate Control Medication, Reasons for Discontinuation	N=17	N=20	N=12	
Ineffective	10 (58.8%)	13 (65.0%)	9 (75.0%)	0.558
Not tolerated	8 (47.1%)	7 (35.0%)	3 (25.0%)	0.760
Other	1 (5.9%)	2 (10.0%)	0 (0.0%)	0.800
Rhythm Control Medication, Reasons for Discontinuation	N=22	N=25	N=13	
Ineffective	17 (77.3%)	20 (80.0%)	8 (61.5%)	0.759
Not tolerated	6 (27.3%)	7 (28.0%)	6 (46.2%)	0.530
Other	1 (4.5%)	1 (4.0%)	2 (15.4%)	0.430
Cardioversion History	N=42	N=49	N=25	
Successful prior electrical cardioversion	13 (31.0%)	16 (32.7%)	10 (40.0%)	0.760
Transthoracic	13 (100.0%)	15 (93.8%)	10 (100.0%)	0.808
Transvenous	0 (0.0%)	1 (6.3%)	0 (0.0%)	
Unsuccessful prior electrical cardioversion	15 (35.7%)	14 (28.6%)	7 (28.0%)	0.680
Transthoracic	15 (100.0%)	14 (93.3%)	7 (100.0%)	0.741
Transvenous	0 (0.0%)	2 (13.3%)	0 (0.0%)	
No electrical cardioversion attempted	17 (40.5%)	20 (40.8%)	9 (36.0%)	0.936
Successful prior pharmacological cardioversion	5 (11.9%)	3 (6.1%)	3 (12.0%)	0.547
Unsuccessful prior pharmacological cardioversion	8 (19.0%)	11 (22.4%)	7 (28.0%)	0.678
No pharmacological cardioversion attempted	23 (54.8%)	29 (59.2%)	15 (60.0%)	0.915

*Chi-Square test (2-sided)

Table 9: Current Cardiac Medications at Enrollment

Drug Category	Group 1 N=42	Group 2 N=50	Group 3 N=25	P-value*
Anti-Arrhythmics	12 (28.6%)	10 (20.4%)	4 (16.0%)	0.480
Rate Control Medications	32 (76.2%)	43 (87.8%)	20(80.0%)	0.462
Anti-thrombic Agents	17 (40.5%)	19(38.8%)	11 (44.0%)	0.863
Anti-Coagulants	36 (85.7%)	40 (81.6%)	22 (88.0%)	0.686
ACE Inhibitors	16 (38.1%)	16 (32.7%)	8 (32.0%)	0.848
Angiotensin-Receptor Blockers	10 (23.8%)	7 (14.3%)	4 (16.0%)	0.491
Diuretics	30 (71.4%)	34 (69.4%)	13 (52.0%)	0.255
Inotropes	1 (2.4%)	2 (4.1%)	0 (0.0%)	0.803
Nitrates	3 (7.1%)	6 (12.2%)	2 (8.0%)	0.714
Beta-Blockers for CHF	6 (14.3%)	9 (18.4%)	4 (16.0%)	0.947
Other	23 (54.8%)	26 (53.1%)	14 (56.0%)	0.941

*Chi-Square test (2-sided)

vii. Safety and Effectiveness Results

A total of 118 patients were enrolled in the AVAIL CLS/CRT clinical study at 20 sites:

There were 43 Group 1, 50 Group 2, and 25 Group 3 patients in this prospective, multi-center, randomized clinical study. For Group 1, there were 33 successful implants (76.7%) of the Protos DR/CLS system. For Groups 2 and 3, there were 44 and 21 successful implants (88.0% and 84.0%), respectively, of the Stratos LV CRT-P system.

- The study was designed to enroll 265 patients. However, the study was evaluated early due to slow patient enrollment. There were no safety issues involved in the early evaluation decision. Due to the lack of patient data, the AVAIL CLS/CRT study alone was insufficient to support CRT pacing effectiveness or an ablate and pace indication.
- The cumulative enrollment duration was 416.7 months with a mean duration of 9.7 months for Group 1, 522.4 months with a mean duration of 10.4 months for Group 2, and 261.1 months with a mean duration of 10.4 months for Group 3. 73 (61.9%) of the study patients had enrollment durations greater than 6 months.
- There were 158 adverse events (115 observations in 68 patients and 43 complications in 34 patients). There were no unanticipated adverse device effects reported.
- The overall protocol violation non-compliance rate is 0.4% in Group 1, 0.5% in Group 2, and 0.4% in Group 3. The overall follow-up compliance rate is 99.8% in all groups.
- There were 3 patient deaths reported, two in Group 2 and one in Group 3. The clinical investigators and clinical events committee determined that none of these deaths were related to the study devices.
- Both the CRT pacing and the RV pacing only groups showed improvements in the primary composite endpoint of quality of life and six-minute walk distance between the baseline evaluation and the six-month follow-up. In addition, there was a trend towards improvement between the combined CRT pacing groups compared to the RV pacing only group at six months.

a. Primary Endpoint: Complication-free Rate (Safety)

The safety of the Stratos LV was evaluated based on complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Stratos LV, the right ventricular, the left ventricular lead, lead ventricular lead adapters (if used) and the implant procedure. The target complication-free rate at six months is 85%.

13 complications in these categories were seen in 11 patients with cumulative enrollment duration of 783.5 months (64.4 patient-years). 14.7% of the patients had a reported complication in these categories. The rate of complications per patient-year is 0.20. Details of the Stratos LV complications in the AVAIL CLS/CRT study are listed in [Table 10](#).

Table 10: AVAIL CLS/CRT Complication-Free Rate at Six Months – Stratos LV				
Category	Number of Patients	% of Patients	Number of Complications	Complication per patient-year
Device-Related				
Pocket Infection/Pain	1	1.3%	2	0.03
Total Device-Related	1	1.3%	2	0.03
LV Lead Related				
High Threshold/No Capture	1	1.3%	1	0.02
Diaphragmatic Stimulation	1	1.3%	1	0.02
Dislodgement	2	2.7%	2	0.03
Total LV Lead-Related	4	5.3%	4	0.06
RV Lead Related				
High Threshold/No Capture	4	5.3%	4	0.06
Total RV Lead-Related	4	5.3%	4	0.06
Procedure				
Pneumothorax	1	1.3%	1	0.02

Table 10: AVAIL CLS/CRT Complication-Free Rate at Six Months – Stratos LV				
Category	Number of Patients	% of Patients	Number of Complications	Complication per patient-year
User error	1	1.3%	1	0.02
Hematoma	1	1.3%	1	0.02
Total Procedure	3	4.0%	3	0.05
Total Lead and Procedure Related	11	14.7%	13	0.20
Other Medical				
Worsening CHF	2	2.7%	2	0.03
Repeat Ablation	3	4.0%	3	0.05
Non-CHF cardiac symptoms	3	4.0%	3	0.05
Other Medical	3	4.0%	3	0.05
Total Other Medical	10	13.3%	11	0.17
Total—All Patients and Categories	19	25.3%	24	0.37

Number of Patients = 75 Number of Patient-Years = 64.4

The freedom from Stratos LV system-related and procedure-related complications was 85.33% with a one sided lower 95% confidence bound of 76.89%. Therefore, the procedure, lead and device related complication-free rate at 6 months met the pre-specified acceptance criterion of equivalence (non-inferiority) within 10% of 85% ($p = 0.0196$).

b. Observed Adverse Events

Adverse events are classified as either observations or complications. Observations are defined as clinical events that do not require additional invasive intervention to resolve. Complications are defined as clinical events that require additional invasive intervention to resolve.

Of the 104 adverse events reported in the Stratos LV study groups, there have been 76 observations in 45 patients and 28 complications in 20 patients with a cumulative enrollment duration of 64.4 patient-years. 26.7% of the enrolled Stratos LV patients have experienced a complication. The rate of complications per patient-year is 0.43. 60.0% of the enrolled study patients have a reported observation. The rate of observations per patient-year is 1.18.

Complications and observations for the Stratos LV study groups are summarized in [Table 11](#) and [Table 12](#). The total number of patients may not equal the sum of the number of patients listed in each category, as an individual patient may have experienced more than one complication or observation.

Table 11: Summary of Complications – Stratos LV				
Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
Device-Related				
Pocket Infection or Pain	2	2.7%	3	0.05
Total	2	2.7%	3	0.05
LV Lead-Related				
High Threshold/No Capture	1	1.3%	1	0.02
Diaphragmatic Stimulation	1	1.3%	1	0.02
Dislodgement	2	2.7%	2	0.03
Total	4	5.3%	4	0.06
RV Lead Related				
High Threshold/No Capture	4	5.3%	4	0.06
Total	4	5.3%	4	0.06

Table 11: Summary of Complications – Stratos LV				
Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
Procedure				
Pneumothorax	1	1.3%	1	0.02
User error	1	1.3%	1	0.02
Hematoma	1	1.3%	1	0.02
Total	3	4.0%	3	0.05
Total Lead and Procedure Related	11	14.7%	14	0.22
Other Medical				
Worsening CHF	2	2.7%	2	0.03
Non-CHF cardiac symptoms	5	6.7%	5	0.08
Repeated ablation	3	4.0%	3	0.05
Lead addition	1	1.3%	1	0.02
Other medical	3	4.0%	3	0.05
Total	12	16.0%	14	0.22
Total—All Patients and Categories	20	26.7%	28	0.43

Number of Patients = 75, Number of Patient-Years = 64.4

Table 12: Summary of Observations – Stratos LV				
Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
LV Lead-Related				
High Threshold/No Capture	1	1.3%	1	0.02
Diaphragmatic Stimulation	13	17.3%	13	0.20
Total LV	14	18.7%	14	0.22
Device Related				
Pocket Infection or pain	5	6.7%	5	0.08
Total	5	6.7%	5	0.08
Procedure				
Pneumothorax	1	1.3%	1	0.02
Atrial edema	1	1.3%	1	0.02
User error	1	1.3%	1	0.02
Total	3	4.0%	3	0.05
Total Lead, Device and Procedure Related	19	25.3%	22	0.34
Other Medical				
Dizziness	3	4.0%	3	0.05
Other Medical	24	32.0%	34	0.53
Worsening CHF	8	10.7%	8	0.12
Ventricular arrhythmias	2	2.7%	2	0.03
Shortness of Breath	5	6.7%	5	0.08
Stroke/TIA	1	1.3%	1	0.02

Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
Non-CHF cardiac symptoms	1	1.3%	1	0.02
Total	35	46.7%	54	0.84
Total—All Patients and Categories	45	60.0%	76	1.18

Number of Patients = 75 Number of Patient-Years = 64.4

There have been 3 patient deaths reported for the Stratos LV groups (out of 75 Stratos LV patients). None of the deaths were related to the implanted CRT-P system. **Table 13** provides a summary of reported patient deaths.

Table 13: Summary of Patient Deaths

	Stratos LV Patients (N = 75)
Sudden Cardiac	1
Non-Cardiac	2
All Causes	3

c. Primary Endpoint: Six Minute Walk Test & QOL (Effectiveness)

The purpose of Primary Endpoint 1 was to evaluate the effectiveness of the CRT (Groups 1 and 2) compared to RV only (Group 3) pacing as measured by the average composite rate of improvement in six minute walk test and QOL.

- Stratos LV Effectiveness (Group 2 compared to Group 3): The average composite rate for Group 2 (N=30) was 48.1% with a standard error of 12.3%. The average composite rate for Group 3 (N=15) was 33.0% with a standard error of 12.3%. The difference in the mean composite rate between Group 2 and Group 3 is 15.1%. The p value for superiority is 0.442.
- Protos DR/CLS Effectiveness (Group 1 compared to Group 3): The average composite rate for the Group 1 (N=23) is 36.8% with a standard error of 7.9%. The average composite rate for Group 3 (N=15) is 33.0% with a standard error of 12.3%. The difference in the mean composite rate between Group 1 and Group 3 is 3.8%. The p value for superiority is 0.788.

Table 14 presents the average composite rate of improvement in six minute walk test distance and QOL score, the average 6-minute walk test distance and the average QOL score at Baseline and at the Six-Month follow-up, as well as the average difference in 6-minute walk test distance and QOL score between Baseline and the Six-Month follow-up for the CRT (Groups 1 and 2) and RV only (Group 3) for those patients with six minute walk test data and complete QOL data at both Baseline and the Six-Month follow-up.

Category	CRT (Group 1 & 2) (N = 53) Mean ± SE	RV only Group 3 (N = 15) Mean ± SE	p value * (student's t-test, 2-sided)
Distance Walked at Baseline	262.8 ± 13.7	288.5 ± 22.4	0.369 *
Distance Walked at Six-Months	312.8 ± 14.6	345.8 ± 30.0	0.303 *
Δ Distance Walked (meters)	50.0 ± 12.2	57.2 ± 26.7	0.790 *
Δ Distance Walked (%)	39.0% ± 13.1%	25.7% ± 15.0%	0.610 *
QOL Score at Baseline	58.5 ± 2.9	49.3 ± 5.5	0.137 *
QOL Score at Six-Months	30.1 ± 3.2	27.7 ± 6.5	0.731 *
Δ in QOL Score	28.4 ± 3.4	21.6 ± 7.7	0.367 *

Category	CRT (Group 1 & 2) (N = 53) Mean ± SE	RV only Group 3 (N = 15) Mean ± SE	p value * (student's t-test, 2-sided)
Δ in QOL Score (%)	47.4% ± 5.1%	40.4% ± 11.1%	0.537 *
Composite Rate	43.2% ± 7.7%	33.0% ± 12.3%	0.525 *

* p value is provided for informational purposes to show trends only; clinical significance is not indicated by p values for analyses that were not prespecified.

d. Primary Effectiveness Endpoint Analysis and Conclusions

The primary effectiveness endpoint evaluated CRT effectiveness (Groups 1 and 2) compared to RV only effectiveness (Group 3), as measured by the composite rate of the six minute walk test and QOL improvement from Baseline to the Six-Month follow-up (**Table 14**). For this analysis, both six minute walk test and QOL were equally weighted at 50%. Due to the small number of patients with data available for the analysis of the primary endpoint, the results lack power to demonstrate that biventricular pacing with either the Protos DR/CLS or Stratos LV device is statistically different from RV only pacing with the Stratos LV device in patients undergoing an “ablate and pace” procedure.

e. Multi-site Poolability and Gender Analysis

The AVAIL CLS/CRT clinical report included data from multiple centers with centralized coordination, data processing, and reporting at BIOTRONIK. All of the clinical centers followed the requirements of an identical clinical protocol, and all of the clinical centers used the same methods to collect and report the clinical data, including New York Heart Association evaluation, six-minute walk test, Minnesota Living with Heart Failure questionnaire, and echocardiographic measurements. In order to justify pooling of the data from multiple centers, several analyses were completed. All of the centers were divided into two groups (Small and Large sites) based on implant volume. Comparisons were then made between the patient populations based on the results of the safety and effectiveness endpoints. Additionally, analyses were performed on the data collected in the AVAIL clinical investigation in order to compare results between males and females. The first type of analysis compared enrollment by patient gender in each of the study groups. The second type of analysis compared effectiveness and safety outcomes in each gender.

The results of these analyses demonstrated poolability of the data between sites. There were no significant differences in the primary safety or effectiveness endpoints between high and low volume implant centers.

The gender distribution in this clinical investigation was consistent within the study groups and included a representative proportion of enrolled female participants (57.2% versus 42.7% male). There were no significant differences in the primary safety or effectiveness endpoints between the male and female population.

B. STRATOS LV CLINICAL STUDY – OVID STUDY

The OVID clinical study collected significant safety data supporting the Stratos LV/LV-T CRT-P System.

i. Study Design

BIOTRONIK conducted the Corox Over-the-Wire Lead Evaluation (OVID) prospective registry outside the United States (OUS) of the Corox OTW Steroid LV lead in a multi-center trial with legally marketed CRT-D and CRT-P pulse generators that provide biventricular pacing therapy. Data from this registry is presented in the following sections to support the safety of the Stratos LV CRT-P.

The multi-center investigation was designed to validate the safety of the Corox OTW Steroid LV lead through a comparison of successfully implanted LV leads against a pre-defined success rate threshold, when no anatomical restrictions prevent access to the coronary sinus. The evaluation of safety is based on the analysis of the incidence of adverse events, defined as any complications or observations judged by the investigator to be in probable relationship with Corox OTW Steroid LV lead system. Additionally, the effectiveness of the leads was evaluated using lead parameter data, including sensing amplitudes, pacing thresholds, and impedance values.

In the OVID study, enrolled patients could be implanted with any legally marketed CRT-P or CRT-D device. There were 121 patients enrolled in the OVID clinical study, and 89 patients were implanted with a Stratos LV device.

ii. Clinical Inclusion and Exclusion Criteria

a. Clinical Inclusion Criteria

To support the objectives of this investigation, patients were required to meet the following inclusion criteria prior to enrollment:

- Meet the indications for bi-ventricular pacing
- Age \geq 18 years
- Receiving optimal drug therapy for Congestive Heart Failure treatment
- Give informed consent

b. Clinical Exclusion Criteria

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment included the following requirements:

- Myocardial infarction or unstable angina pectoris
- Acute myocarditis
- Life expectancy \leq 6 months
- Planned cardiac surgical procedures or interventional measures within the next 6 months
- Pregnancy

iii. Follow-Up Schedule

All patients were implanted with the Corox OTW/Steroid LV lead system and a CRT-P or CRT-D pulse generator capable of providing bi-ventricular pacing for the treatment of CHF. The specific study procedures were performed at:

- Pre-operative Visit
- Implantation
- Pre-discharge follow-up
- One-month follow-up
- Three-month follow-up
- Six-month follow-up
- Twelve-month follow-up

iv. Clinical Endpoints

The safety of the Stratos LV was evaluated based on complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Stratos LV device, the atrial lead, the right ventricular lead the left ventricular lead and the implant procedure. The target complication-free rate at six months was 85%.

v. Accountability of PMA Cohorts

During the OVID study, 84 patients were implanted with the Stratos LV CRT-P and Corox OTW/Steroid LV lead system. Additionally, 5 other patients were implanted with a Stratos LV CRT-P device following an unsuccessful Corox OTW/Steroid LV lead implant attempt. Of these 5 patients, three were not implanted with any LV pacing lead, one was implanted with a non-study LV pacing lead and one was implanted with a BIOTRONIK Elox P 60 BP placed in the RV outflow tract for bi-focal ventricular pacing. These 5 patients were excluded from the OVID study at 1 month post-implant, because the primary endpoint of the OVID study was the evaluation of the safety and effectiveness of the Corox OTW/Steroid lead.

vi. Demographics and Baseline Parameters

Table 15 provides a summary of the patient demographics and medical history for the 89 enrolled patients implanted with a Stratos LV. The typical patient implanted with a Stratos LV CRT-P was a 68 year old male with NYHA Class III heart failure, Left Bundle Branch Block (LBBB), a mean QRS duration of 160 ms, and non-ischemic cardiomyopathy.

Table 15: Patient Demographics

Characteristic	Results
Age at Implant (Years)	n=88
Mean ± SD	68 ± 10
Range	34 to 84
Gender	n=89
Male	66 (74%)
Female	23 (26%)
QRS-width (ms)	n=70
Mean ± SD	160 ± 23
Range	110 to 210
Etiology of Heart Failure	n=87
Ischemic	32 (37%)
Non-Ischemic	55 (63%)
New York Heart Association (NYHA) Classification	n=87
Class III	73 (84%)
Class IV	14 (16%)
Atrial Tachyarrhythmias	N=87
None	48 (55%)
Atrial flutter	5 (5.7%)
Paroxysmal atrial fibrillation	19 (22%)
Persistent atrial fibrillation	10 (11.5%)
Other	5 (5.7%)
Ventricular Tachyarrhythmias	N=87
None	80 (92%)
Ventricular fibrillation	-
Sustained or non-sustained VT	5 (5.7%) ¹⁾
Other VT	2 (2.3%) ²⁾
Existing/chronic leads prior to Corox OTW/Steroid	n=88
None	73 (83%)
Yes, due to previous pacemaker therapy	15 (17%)

¹⁾ non-sustained VT (n=4); no further information available (n=1); ²⁾ VES (n=2)

vii. Safety and Effectiveness Results

- The cumulative implant duration was 760 months with a mean duration of 9.2 months. Sixty-five (77%) of the patients had implant durations greater than 6 months.
- The implant success rate for the Stratos LV CRT-P was 100% (89 out of 89). The implant success of the Stratos LV CRT-P in combination with the Corox OTW/Steroid LV lead was 94.4% (84 out of 89).
- The mean LV pacing threshold at implant was 0.9 and at 6-months was 0.9 volts.
- The mean R-wave at implant was 15.7 mV.
- The mean LV lead impedance at implant was 729 ohms and at 6-months was 603 ohms.
- There were 29 adverse events (18 observations in 17 patients and 11 complications in 10 patients). There were no unanticipated adverse device effects reported.

- There were 10 patient deaths reported in the OVID study. The clinical investigators have determined that no deaths were related to the Stratos LV CRT-P system.
- The overall follow-up compliance rate for the OVID study is 93%.

a. Primary Endpoint—Complication-free Rate (Safety)

The safety of the Stratos LV was evaluated based on complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Stratos LV device, the atrial lead, the right ventricular lead the left ventricular lead and the implant procedure. The target complication-free rate at six months was 85%.

Ten (10) complications in these categories were seen in 10 patients with cumulative implant duration of 760 months (63.3 patient-years). 11.2% of the patients had a reported complication in these categories. The rate of complications per patient-year was 0.16. Details of the Stratos LV complications in the AVAIL CLS/CRT study are listed in **Table 16**.

Table 16: OVID Complication-Free Rate at Six Months – Stratos LV				
Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
Corox OTW/Steroid Lead-Related				
Loss of capture	2	2.2%	2	0.03
Phrenic nerve stimulation	1	1.1%	1	0.02
Total	3	3.3%	3	0.05
Atrial Lead Related				
Loss of capture	1	1.1%	1	0.02
Total	1	1.1%	1	0.02
RV Lead Related				
Loss of capture	3	3.3%	3	0.05
Elevated Pacing thresholds	2	2.2%	2	0.03
Total	5	5.6%	5	0.08
Device Related				
Pocket infection	1	1.1%	1	0.02
Total	1	1.1%	1	0.02
Total System Related	10	11.2%	10	0.16
Other Medical				
Arrhythmias	1	1.1%	1	0.02
Total	1	1.1%	1	0.02
Overall Complication Totals	10	11.2%	11	0.17

Number of Patients = 89, Number of Patient-Years = 63.3

The freedom from Stratos LV system-related and procedure-related complications was 88.76% with a one sided lower 95% confidence bound of 81.69%. Therefore, the null hypothesis was rejected, and it was concluded that the complication-free rate at 6 months is equivalent to 85% within 10% ($p = 0.0014$).

b. Observed Adverse Events

Adverse events are classified as either observations or complications. Observations are defined as clinical events that do not require additional invasive intervention to resolve. Complications are defined as clinical events that require additional invasive intervention to resolve.

Of the 29 adverse events reported, there were 18 observations and 11 complications in a total of 89 patients. **Table 17** and **Table 18** provide a summary by category of each type of adverse event (complications and observations).

Table 17: Summary of Complications at Six Months				
Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
Corox OTW/Steroid Lead-Related				
Loss of capture	2	2.2%	2	0.03
Phrenic nerve stimulation	1	1.1%	1	0.02
Total	3	3.3%	3	0.05
Atrial Lead Related				
Loss of capture	1	1.1%	1	0.02
Total	1	1.1%	1	0.02
RV Lead Related				
Loss of capture	3	3.3%	3	0.05
Elevated Pacing thresholds	2	2.2%	2	0.03
Total	5	5.6%	5	0.08
Device Related				
Pocket infection	1	1.1%	1	0.02
Total	1	1.1%	1	0.02
Total System Related	10	11.2%	10	0.16
Other Medical				
Arrhythmias	1	1.1%	1	0.02
Total	1	1.1%	1	0.02
Overall Complication Totals	10	11.2%	11	0.17

Number of Patients = 89; Number of Patient-Years = 63.3

Table 18: Summary of Observations at Six Months				
Category	Number of Patients	% of Patients	Number of Observations	Observations per patient-year
Corox OTW/Steroid Lead-Related				
Implant failure	5	5.6%	5	0.08
Phrenic nerve stimulation	4	4.5%	4	0.06
Total	9	10.1%	9	0.14
Atrial Lead Related				
Loss of capture	1	1.1%	1	0.02
Total Atrial Lead Related	1	1.1%	1	0.02
RV Lead Related				
Elevated Pacing thresholds	2	2.2%	2	0.03
Total RV Lead Related	2	2.2%	2	0.03
Device Related				
Pocket infection/ Pericardial Effusion	1	1.1%	1	0.02
Total Device Related	1	1.1%	1	0.02
Total System Related	12	13.5%	13	0.21
Medical				
Arrhythmias	2	2.2%	2	0.03
Shortness of breath, palpitations	1	1.1%	1	0.02
Total Medical	3	3.3%	3	0.05
Miscellaneous				
Malfunction of hemostatic valve	1	1.1%	1	0.02

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Category	Number of Patients	% of Patients	Number of Observations	Observations per patient-year
Improper Lead preparation	1	1.1%	1	0.02
Total Miscellaneous	2	2.2%	2	0.04
Overall Observation Totals	17	19.1%	18	0.28

Number of Patients = 89; Number of Patient-Years = 63.3

There were a total of 10 patient deaths reported in the OVID study for patients with the Stratos LV device. The clinical investigators determined that no deaths were related to the Stratos LV device system.

C. AVAIL AND OVID COMBINED PRIMARY ENDPOINT—COMPLICATION-FREE RATE (SAFETY)

The results from for the AVAIL CLS/CRT and OVID studies were pooled to evaluate the safety of the Stratos LV device. The safety of the Stratos LV was evaluated based on complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Stratos LV, the atrial lead, the right ventricular lead, the left ventricular lead and the implant procedure. The target complication-free rate at six months was 85%.

Twenty-three (23) complications in these categories were seen in 21 patients with cumulative implant duration of 127.7 years. 12.8% of the patients had a reported complication in these categories. The rate of complications per patient-year was 0.18. Details of the Stratos LV complications in the AVAIL CLS/CRT and OVID studies are listed in **Table 19**.

Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
LV Lead-Related				
High Threshold/No Capture	3	1.8%	3	0.02
Diaphragmatic Stimulation	2	1.2%	2	0.02
Dislodgement	1	1.2%	2	0.01
Total	7	4.3%	7	0.06
RV Lead Related				
High Threshold/No Capture	9	5.5%	9	0.07
Total	9	5.5%	9	0.07
Atrial Lead Related				
No Capture	1	0.6%	1	0.01
Total	1	0.6%	1	0.01
Device Related				
Pocket Infection	2	1.2%	3	0.02
Total	2	1.2%	3	0.02
Procedure				
Pneumothorax	1	0.6%	1	0.01
User error	1	0.6%	1	0.01
Hematoma	1	0.6%	1	0.01
Total	3	1.8%	3	0.02
Total Lead, Device and Procedure Related	21	12.8%	23	0.18
Other Medical				
Arrhythmias	1	0.6%	1	0.01
Repeated ablation	3	1.8%	3	0.02
Worsening CHF	2	1.2%	2	0.02

Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
Other Medical	3	1.8%	3	0.02
Non-CHF cardiac symptoms	3	1.8%	3	0.02
Total	11	6.7%	12	0.09
Total—All Patients and Categories	29	17.7%	35	0.27

Number of Patients = 164 Number of Patient-Years = 127.7

The freedom from Stratos LV system-related and procedure-related complications was 87.2% with a one sided lower 95% confidence bound of 82.09%. Therefore, the null hypothesis was rejected, and it was concluded that the complication-free rate at 6 months is equivalent to 85% within 10% and the primary safety endpoint was met ($p = 0.0002$).

* p value is provided for informational purposes to show trends only; clinical significance is not indicated by p values for analyses that were not prespecified.

D. TUPOS LV/ATX CLINICAL IDE STUDY – OPTION CRT/ATX

The CRT functionality of the Stratos CRT-P devices is based on the FDA approved Tupos LVT/ATx (P050023). Therefore, the data from the OPTION CRT/ATx study support the effectiveness of CRT. The Option CRT/ATx study was conducted on the Tupos LVT/ATx, a device that delivers CRT but, in addition, also offers defibrillation therapy (CRT-D).

i. Study Design

The purpose of the prospective, randomized, multi-center OPTION CRT/ATx study was to demonstrate the safety and effectiveness of the investigational Tupos LV/ATx Cardiac Resynchronization Therapy Defibrillator (CRT-D) in patients with congestive heart failure (CHF) and atrial tachyarrhythmias. Patients in the study group were implanted with a BIOTRONIK Tupos LV/ATx. Patients in the control group were implanted with any legally marketed CRT-D. Patients in both the study and control groups were implanted with a legally marketed left ventricular lead.

Primarily, the study evaluates and compares the functional benefits of CRT between the two randomized groups using a composite endpoint consisting of a six-minute walk test (meters walked) and quality of life measurement (assessed using the Minnesota Living with Heart Failure Questionnaire). Relevant measurements were completed twice for each patient: once at the Baseline evaluation (two-week post implant follow-up) and again at a six-month follow-up evaluation. The data collected during this clinical study was used to demonstrate equivalent treatment of CHF in both the study and control groups. This study also evaluated other outcomes including: the percentage of time CRT is delivered, and other measures of CHF status, including NYHA classification, peak oxygen consumption during metabolic exercise testing, and the rate of hospitalization for CHF.

ii. Clinical Inclusion and Exclusion Criteria

a. Clinical Inclusion Criteria

To support the objectives of this investigation, patients were required to meet the following inclusion criteria prior to enrollment:

- Stable, symptomatic CHF status
- NYHA Class III or IV congestive heart failure
- Left ventricular ejection fraction $\leq 35\%$ (measured within six-months prior to enrollment)
- Intraventricular conduction delay (QRS duration greater than or equal to 130 ms)
- For patients with an existing ICD, optimal and stable CHF drug regimen including ACE-inhibitors and beta-blockers unless contraindicated (stable is defined as changes in dosages less than 50% during the last 30 days)

- Indicated for ICD therapy
- History or significant risk of atrial tachyarrhythmias
- Willing to receive possibly uncomfortable atrial shock therapy for the treatment of atrial tachyarrhythmias
- Able to understand the nature of the study and give informed consent
- Ability to tolerate the surgical procedure required for implantation
- Ability to complete all required testing including the six-minute walk test and cardiopulmonary exercise testing
- Available for follow-up visits on a regular basis at the investigational site
- Age greater than or equal to 18 years

b. Clinical Exclusion Criteria

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment included the following:

- Previously implanted CRT device
- ACC/AHA/NASPE indication for bradycardia pacing (sinus node dysfunction)
- Six-minute walk test distance greater than 450 meters
- Chronic atrial tachyarrhythmias refractory to cardioversion shock therapy
- Receiving intermittent, unstable intravenous inotropic drug therapy (patients on stable doses of positive inotropic outpatient therapy for at least one-month are permitted)
- Enrolled in another cardiovascular or pharmacological clinical investigation
- Expected to receive a heart transplant within 6 months
- Life expectancy less than 6 months
- Presence of another life-threatening, underlying illness separate from their cardiac disorder
- Acute myocardial infarction, unstable angina or cardiac revascularization within the last 30 days prior to enrollment
- Conditions that prohibit placement of any of the lead systems

iii. Follow-Up Schedule

After successful enrollment, all patients were randomly assigned to either the study group or the control group. The specific procedures of this study were:

- Pre-enrollment screening
- Randomization
- System implantation
- Pre-discharge follow-up
- Baseline evaluation / CRT activation
- One-Month follow-up
- Three-Month follow-up
- Six-Month follow-up
- Subsequent routine follow-ups (every three months)

iv. Clinical Endpoints

a. Primary Endpoint 1: Six Minute Walk Test & QOL (Effectiveness)

The purpose of Primary Endpoint 1 is to evaluate the effectiveness of the Tupos LV/ATx system in providing CRT as measured by the average composite rate of improvement in six minute walk test and QOL.

b. Secondary Endpoint Results

1. The purpose of this secondary endpoint is to evaluate improvement in functional capacity as measured by the six minute walk test. The six minute walk test is a well-accepted measure of functional capacity and exercise tolerance. Also, this test more closely mimics the patient's day-to-day activities than maximal exercise testing.
2. The purpose of this secondary endpoint is to evaluate the improvement in the patient's NYHA classification.

v. Accountability of PMA Cohorts

After randomization and enrollment, 7 patients (4 in the study group and 3 in the control group) did not receive an implant. The reasons for patients not receiving an implant are outlined in **Figure 2**.

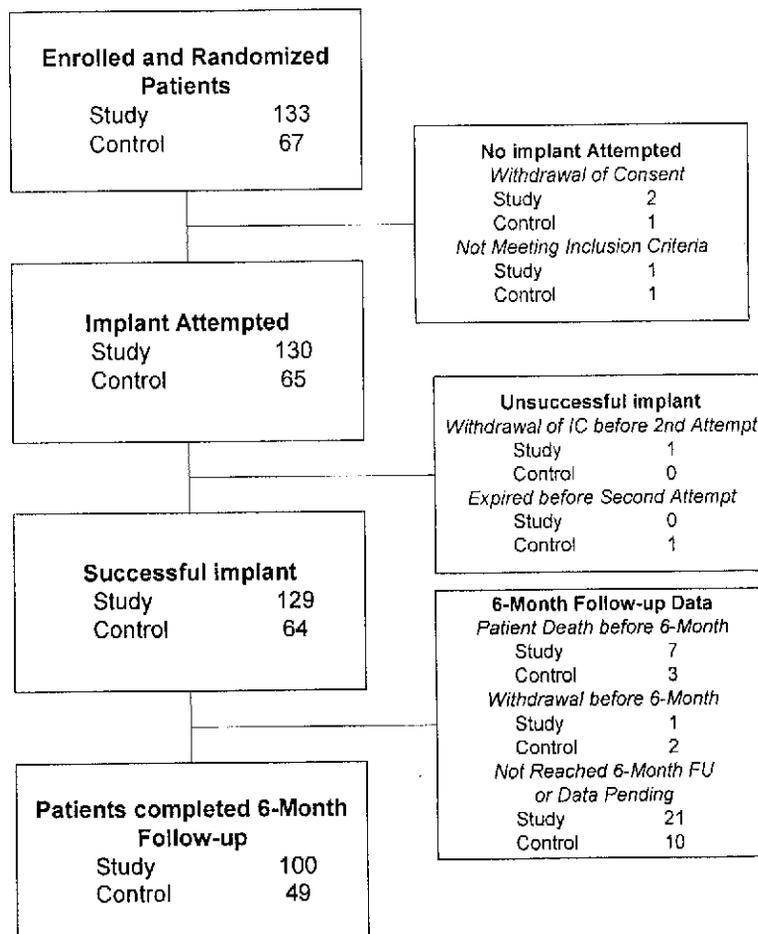


Figure 2: Patient Accountability

vi. Demographics and Baseline Parameters

Table 20 provides a summary of the pre-enrollment demographics of enrolled patients.

Table 20: Patient Demographics at Pre-Enrollment

Characteristic	Study N=133	Control N=67	P-value
Age at Enrollment (Years)			
Mean ± SE	69.5 ± 0.9	69.1 ± 1.2	0.781*
Range	43 to 88	38 to 84	
Gender			
Male	93 (69.9%)	51 (76.1%)	0.407**
Female	40 (30.1%)	16 (23.9%)	

Characteristic	Study N=133	Control N=67	P-value
Underlying Heart Disease			
Ischemic Cardiomyopathy	100 (75.2%)	54 (80.6%)	0.294***
Nonischemic Cardiomyopathy	34 (25.6%)	15 (22.4%)	
Type of Bundle Branch Block			
Left Bundle Branch Block	91 (68.4%)	49 (73.1%)	0.877***
Right Bundle Branch Block	26 (19.5%)	10 (14.9%)	
Other	19 (14.3%)	11 (16.4%)	
New York Heart Association Class			
Class III	121 (91.0%)	60 (89.6%)	0.800**
Class IV	12 (9.0%)	7 (10.4%)	
Intrinsic QRS Duration (ms)			
Mean ± SE	161.9 ± 2.0	156.1 ± 2.3	0.073*
Range	130 to 252	130 to 200	
Left Ventricular Ejection Fraction (%)			
Mean ± SE	22.1 ± 0.6	23.3 ± 0.8	0.255*
Range	5 to 35	10 to 35	
Six Minute Walk Distance (meters)			
Mean ± SE	254.8 ± 8.9	250.5 ± 11.9	0.775*
Range	20 to 451	27 to 447	
Quality of Life Questionnaire Score			
Mean ± SE	54.3 ± 2.1	52.5 ± 3.1	0.638*
Range	0 to 105	0 to 102	

*Student's t-test (2-sided) for means, **Fisher's Exact Test (2-sided) for 2 possible answers, ***Chi-Square test (2-sided) for more than 2 possible answers

Table 21 provides a summary of cardiac medications patients were taking at the time of enrollment. Some categories may be more than 100% as several categories allow more than one response.

Table 21: Cardiac Medications at Pre-Enrollment

Drug Category	Study (N=133)	Control (N=67)	P-value
Specific CHF Medications			
ACE inhibitors	89 (66.9%)	45 (67.2%)	1.000**
Angiotensin receptor blockers	21 (15.8%)	16 (23.9%)	0.180**
Beta blockers	111 (83.5%)	55 (82.1%)	0.843**
Cardiac glycosides (Digoxin)	60 (45.1%)	35 (52.2%)	0.370**
Diuretic	114 (85.7%)	57 (85.1%)	1.000**
Inotropes	1 (0.8%)	3 (4.5%)	0.110**
Anti-arrhythmics	34 (25.6%)	19 (28.4%)	0.735**
Nitrates	36 (27.1%)	14 (20.9%)	0.390**

*Student's t-test (2-sided) for means, **Fisher's Exact Test (2-sided) for 2 possible answers, ***Chi-Square test (2-sided) for more than 2 possible answers

vii. Safety and Effectiveness Results

A total of 200 patients were enrolled in the OPTION CRT/ATx clinical study at 25 sites:

There were 133 study patients and 67 active control patients in this prospective, multi-center, randomized clinical study. For the study group, there were 129 successful implants (91.4%) of the Tupos LV/ATx CRT-D system. For the active control group, there were 64 successful implants (92.2%) of the legally marketed CRT-D systems.

- There were 192 endocardial and 19 epicardial leads implanted in 193 patients. Investigators were allowed to choose among any legally marketed LV lead according to their familiarity with the lead and patient anatomy. The Tupos LV/ATx CRT-D was implanted with 7 endocardial and 4 epicardial lead models from 6 different manufacturers. There were no adverse events reported attributable to lead-generator incompatibility.

- The cumulative implant duration is 1240.4 months with a mean duration of 9.6 months for the study group. The cumulative implant duration is 596.5 months with a mean duration of 9.3 months for the control group.
- The overall protocol compliance rate is 79.2% in the study group and 85.9% in the control group. The overall follow-up compliance rate is 99.4% in the study group and 98.3% in the control group.
- There have been 10 patient deaths reported in the study group and 4 patient deaths reported in the control group. The clinical investigators have determined that no deaths were related to the study device.

a. Primary Endpoint 1: Six Minute Walk Test & QOL (Effectiveness)

The purpose of Primary Endpoint 1 is to evaluate the effectiveness of the Tupos LV/ATx system in providing CRT as measured by the average composite rate of improvement in six minute walk test and QOL.

Table 22 presents the average composite rate of improvement in six minute walk test distance and QOL score, the average 6-minute walk test distance and the average QOL score at Baseline and at the Six-Month follow-up, as well as the average difference in 6-minute walk test distance and QOL score between Baseline and the Six-Month follow-up for the Study and Control Groups for those patients with six minute walk test data and complete QOL data at both Baseline and the Six-Month follow-up.

Table 22: Composite of Six Minute Walk Test and QOL (Effectiveness)			
Category	Study Group (N = 74) Mean ± SE	Control Group (N = 38) Mean ± SE	P-value*
Distance Walked at Baseline	310.51 ± 10.89	288.76 ± 15.37	0.249
Distance Walked at Six-Months	340.77 ± 12.32	301.84 ± 17.02	0.067
Δ Distance Walked	30.26 ± 10.40 17.27% ± 5.59%	13.08 ± 13.05 8.71% ± 5.26%	0.322 0.326
QOL Score at Baseline	44.39 ± 2.78	45.53 ± 4.13	0.817
QOL Score at Six-Months	28.68 ± 2.66	33.95 ± 4.35	0.279
Δ in QOL Score**	15.72 ± 2.83 19.08% ± 12.21%	11.58 ± 3.45 -13.42% ± 34.54%	0.376 0.281
Composite Rate***	18.18% ± 7.07%	-2.36% ± 17.73%	0.030

*The calculated p-values are associated with a Student's t-test (2-sided) of the equality of means in the two groups, except for the p-value of the composite rate, which is associated with a test of equivalence (non-inferiority).

**Δ in QOL Score is calculated as the average of the individual differences between Baseline and Six-Months for each patient. Negative values for mean Δ QOL in percent are possible when positive mean values for absolute changes in QOL are recorded. In some cases, small, negative changes in absolute QOL scores resulted in relatively large percentage changes.

***The Composite Rate $(= (\Delta \text{ Distance Walked (\%)} + \Delta \text{ QOL Score (\%)}) / 2)$ is calculated for each patient and then averaged to obtain the Composite Rates. For all calculations, a positive number represents improvement from Baseline to Six-Months.

b. Primary Effectiveness Endpoint Analysis and Conclusions

A composite rate of six minute walk test and QOL improvement from Baseline to the Six-Month follow-up is evaluated as a measure of CRT effectiveness. For this analysis both six minute walk test and QOL are equally weighted at 50%.

The mean difference in the composite rate between study and control group was 20.53% with an associated one-sided, 95% confidence bound of (-6.10%). The p-value for non-inferiority within 10% is 0.030. The analysis of the composite rate in six minute walk test distance and QOL score demonstrates that the study group is non-inferior to the control group and that the primary effectiveness endpoint was met (p=0.030).

c. Secondary Endpoint Results

- The purpose of this secondary endpoint is to evaluate improvement in functional capacity as measured by the six minute walk test. The six minute walk test is a well-accepted measure of functional capacity and exercise tolerance. Also, this test more closely mimics the patient's day-to-day activities than maximal exercise testing.

Table 23 summarizes the six minute walk test distance at Baseline and the Six-Month follow-up for patients in the study group and the control group.

Distance (meters)	Study	Control
Baseline		
N	127	61
Mean ± SE	283.14 ± 9.27	269.43 ± 13.77
Range	23 to 511	29 to 507
Median	302.00	244.00
Six-Month		
N	93	44
Mean ± SE	329.73 ± 10.82	310.70 ± 15.49
Range	78 to 596	91 to 489
Median	335.00	313.00

* Student's t-test, 2-sided

There are no clinically relevant differences in the six minute walk test results between the study and the control group.

- The purpose of this secondary endpoint is to evaluate the improvement in the patient's NYHA classification. **Table 24** summarizes the average improvement in NYHA from Baseline to Six-Months for 140 patients that were able to complete both NYHA classification evaluations.

Change in NYHA class	Study (N=97)		Control (N=43)	
	Number of Patients	Percentage of Total Patients	Number of Patients	Percentage of Total Patients
Improved 2 classes	10	10.3%	2	4.7%
Improved 1 class	47	48.5%	20	46.5%
Total improved	57	58.8%	23	51.2%
No change	39	40.2%	20	46.5%
Worsened 1 class	1	1.0%	1	2.3%

The study and the control group have similar NYHA classes and similar rates of improvement in NYHA class from Baseline to the Six-Month follow-up.

d. Multi-site Poolability and Gender Analysis

The OPTION CRT/ATx clinical report includes data from multiple centers with centralized coordination, data processing, and reporting at BIOTRONIK. All of the clinical centers followed the requirements of an identical clinical protocol, and all of the clinical centers used the same methods to collect and report the clinical data. In order to justify pooling of the data from multiple centers, several analyses were completed. All of the centers were divided into two groups based on implant volume. Comparisons were then made between the patient populations based on the results of each of the endpoints. Additionally, analyses were performed on the data collected in the OPTION CRT/ATx clinical investigation in order to compare results between males and females. The first type of analysis compared enrollment by patient gender in each of the study and control groups. The second type of analysis compared effectiveness outcomes in each gender.

The results of these analyses demonstrate poolability of the data between sites. There were no significant differences in the second primary endpoint or any of the secondary endpoints between high and low volume implant centers.

The gender distribution in this clinical investigation is consistent within the study groups and includes a representative proportion of enrolled female participants (28.0% versus 72.0% male). There were no significant differences in any of the primary or secondary endpoints between the male and female population.

E. COROX OTW(-S) BP LV LEAD CLINICAL STUDY – EVEREST

The clinical investigation everesT: "Evaluation of the new BIOTRONIK Resynchronization + ICD System" was used to support the safety and effectiveness of the Corox OTW BP leads.

i. Study Design

The clinical investigation everesT was designed to assess the clinical safety and effectiveness of the FDA approved Lumax HF-T 300 and Lumax HF-T 340 CRT-D (P050023/S1), as well as the clinical safety and effectiveness of the Corox OTW BP Steroid and Corox OTW-S BP Steroid polyurethane coated bipolar LV leads. The everesT Study was a multi-center trial conducted Outside the United States (OUS) with legally marked pulse generators and leads to provide biventricular pacing therapy.

While the everesT investigation was designed to study both Lumax devices and Corox OTW(-S) BP Steroid LV leads, for purposes of this section, only everesT results from the Corox OTW(-S) BP Steroid LV leads are presented.

ii. Clinical Inclusion and Exclusion Criteria

a. Clinical Inclusion Criteria

To support the objectives of this investigation, patients were required to meet the following inclusion criteria prior to enrolment:

- Patient is willing and able to comply with the protocol and has provided written informed consent
- Indication for cardiac resynchronization therapy (CRT)
- Indication for implantation of an ICD
- Stable residence anticipated for 6 months after enrollment

b. Clinical Exclusion Criteria

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment included the following:

- Planned cardiac surgical procedures within 6 months after enrollment
- Life expectancy < 6 months
- Pregnant and breast-feeding women
- Age < 18 years or otherwise missing complete contractual capability
- Participation in another clinical study

- Corox BP not yet available on the market
- Any failed LV implant attempt or LV lead implanted prior to enrollment

iii. Follow-Up Schedule

Follow-ups were required for all patients participating in this clinical investigation. Follow-up dates were calculated from initial implantation (day 0). The total follow-up period after implant was 6 months per patient. Study specific procedures were performed at:

- Pre-Hospital Discharge Follow-Up (at the latest five days after implantation)
- One-Month Follow-Up (± 1 week)
- Three-Month Follow-Up (± 2 weeks)
- Six-Month Follow-Up (± 4 weeks)
- Interim Follow-Up (if necessary as long as the patient was enrolled)

iv. Clinical Endpoints

a. Primary Endpoint: Safety of Corox OTW(-S) BP Steroid

The goal was to demonstrate that the Corox BP lead related complication rate is significantly higher than the borderline value of 0.80.

b. Primary Endpoint: Effectiveness of Corox OTW(-S) BP Steroid

The goal was to demonstrate that the probability for successful Corox BP implantation (if the coronary sinus (CS) was found) is significantly higher than the borderline value of 0.75.

v. Accountability of PMA Cohorts

During the everesT clinical study, a total of 148 patients were enrolled and implanted with a Lumax HF-T device. There were 131 patients successfully implanted with a Corox BP LV lead. Additionally, there were 17 patients who underwent a Corox BP implant attempt but the procedure was unsuccessful due to anatomy, pacing thresholds, or lead instability. These patients were subsequently implanted with another LV lead and are included in the Corox-relevant sections of this report.

Figure 3 provides a graphical presentation of the patient's accountability.

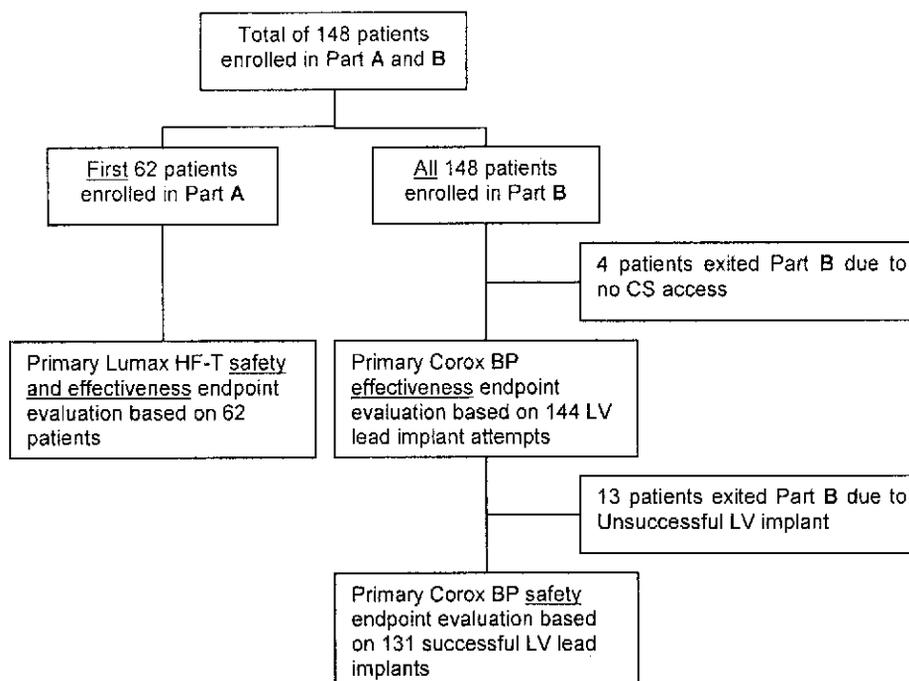


Figure 3: Patient Accountability Flow Chart

vi. Demographics and Baseline Parameters

Table 25 provides a summary of the patient demographics and medical history for the 148 enrolled patients. The typical patient enrolled in the everesT study was a 67 year old male with NYHA Class III heart failure, a mean QRS duration of 162 ms, no AF, and ischemic cardiomyopathy. Note that the percentages in some characteristics may add up to more than 100% because multiple answers per patients were possible.

Table 25: Patient Demographics

Characteristic	Patients
Enrollment in Study Parts	n=148
A only	n=0
B only	n=86
A+B	n=62
Age at Implant (years)	n=148
Mean ± SD	67 ± 9
Range	33 to 84
Gender	n=148
male	121 (82%)
female	27 (18%)
NYHA Class	n=148
I	0 (0%)
II	27 (18%)
III	114 (77%)
IV	7 (5%)
QRS Duration (ms)	n=140
Mean ± SD	162 ± 43
Range	86 to 380

Characteristic	Patients
Atrial Rhythm	n=146
No AF	88 (60%)
Paroxysmal AF	18 (12%)
Persistent AF	25 (17%)
Permanent AF	15 (10%)
Left Ventricular Ejection Fraction	n=143
Mean \pm SD	26 \pm 7
Range	10 to 44
Ischemic disease	N=93 (63%)
Cardiomyopathy	N=97 (66%)
Co-Morbidities	n=148
Diabetes mellitus	56 (38%)
Renal insufficiency	55 (37%)
Chronic pulmonary disease	33 (22%)
ICD Indication	n=147
Survived cardiac arrest	15 (10%)
VT with or without hemodynamic instability	24 (16%)
Non-sustained VT post MI and LVEF \leq 40%	15 (10%)
Syncope and LVEF \leq 40%	14 (10%)
Positive family history	1 (1%)
Primary prophylactic indication	95 (65%)
Other	4 (3%)
Cardiovascular Medication	n=148
ACE Inhibitors / ARBs	127 (86%)
β -blockers	126 (85%)
Amiodarone	32 (22%)
Calcium antagonists	17 (11%)
Digitalis	56 (38%)
Sotalol	12 (8%)
Other antiarrhythmics	3 (2%)
Anticoagulants	84 (57%)
Platelet aggregation inhibitors	62 (42%)
Lipid lowering drugs	85 (57%)
Nitrates	17 (11%)
Spironolactones	76 (%)
Other diuretics	115 (78%)
Other	15 (10%)

vii. Safety and Effectiveness Results

Data from a total of 148 patients are included in this clinical summary to support the Corox OTW-BP LV lead.

- The cumulative enrollment duration was 683.4 months with a mean duration of 4.6 months. 34/148 (23%) of patients had implant durations greater than 6 months.
- The implant success rate for the Corox OTW(-S) BP Steroid LV leads was 91% (131/144)
- The mean bipolar LV pacing threshold was 1.2 V at implant and at 0.8 V at 6-months
- The mean bipolar LV signal amplitude was 7.8 mV at both implant and 6-months
- The mean bipolar LV lead impedance was 839 ohms at implant and 886 ohms at 6-months
- Of the total 46 adverse events reported (e.g. device, lead, procedural, etc), there were 20 complications in 19 patients and 26 observations in 24 patients over cumulative enrollment duration of 57.1 patient-years

- There were 4 patient deaths reported in the everesT study. The clinical investigators have determined that no deaths were related to the Lumax HF-T 300/340 devices or the Corox OTW(-S) BP Steroid LV leads.
- The overall follow-up compliance rate for the everesT study was 96%

a. Primary Endpoint: Safety of Corox OTW(-S) BP Steroid

Objective: The goal was to demonstrate that the Corox BP lead related complication rate is significantly higher than the borderline value of 0.80.

Results: Out of 131 study patients with a successful Corox BP implant, a total of 2 Corox BP LV lead related complications were seen in 2 patients within 90 days post implant. At 3 months post implant, 1.5% of the study patients with a successful Corox BP implant experienced an LV lead related complication.

Table 26: Summary of Corox BP Complications ≤ 90 days				
Category	Number of Patients	Percentage of Patients (n = 131)	Number of Complications	Complication per patient-year
Corox OTW BP Steroid (helix) n = 97				
High Threshold, Loss of capture	1	0.75%	1	0.03
Dislodgement	1	0.75%	1	0.03
Corox OTW-S BP Steroid (straight) n = 34				
N/A	0	0%	0	0
Total n = 131				
Total Corox BP Complications	2	1.5%	2	0.06

Number of Patients = 131 Number of Patient-Years = 31.8

The Corox BP is offered with two different types of fixation mechanisms: a three dimensional pre-shaped helical tip to achieve a stable position in larger veins (Corox OTW BP Steroid), or a straight tip for placement in smaller veins, 'wedge position' (Corox OTW-S BP Steroid). Out of 97 patients implanted with the Corox OTW BP Steroid there were 2 LV lead related complications seen in 2 patients within 90 days post implant. None of the 34 patients implanted with the Corox OTW-S BP Steroid experienced a LV lead related complication within 90 days post implant.

The observed total overall Corox BP related complication-free rate at 3 months was 98.5% based on 129 patients without LV lead related complications within the group of 131 patients with a successful Corox BP implant.

Conclusions: The 95% lower bound criterion was found to be 94.6%. This is higher than the pre-determined borderline value of 80%, therefore the respective null hypothesis is rejected and the primary Corox BP LV lead safely endpoint is met.

b. Observed Adverse Events

Adverse events are classified as either observations or complications. Observations are defined as clinical events that do not require additional invasive intervention to resolve. Complications are defined as clinical events that require additional invasive intervention to resolve.

Of the 46 adverse events reported, there have been 20 complications in 19 patients and 26 observations in 24 patients over cumulative enrollment duration of 57.1 patient-years. A total of 12.8% of study patients experienced a complication. The rate of complications per patient-year was 0.35. A total of 16.2% of study patients have a reported observation. The rate of observations per patient-year was 0.46.

Table 27 and **Table 28** provide a summary by category of each type of adverse event (complications and observations) for all 148 patients enrolled in the everesT study.

Table 27: Summary of Complications				
Category	Number of Patients	Percentage of Patients	Number of Complications	Complications per patient-year
Corox BP LV Lead				
Unable to implant LV lead after CS access	2	1.5%	2	0.04
Dislodgement	2	1.5%	2	0.04
High threshold / Loss of capture	1	0.8%	1	0.02
Total LV Lead Related	5	3.4%	5	0.09
RV Lead				
High DFT	1	0.7%	1	0.02
High threshold / Loss of capture	1	0.7%	1	0.02
Sensing / Detection issues	1	0.7%	1	0.02
Total RV Lead Related	2	1.4%	3	0.05
Atrial Lead				
Dislodgement	1	0.7%	1	0.02
Total Atrial Lead Related	1	0.7%	1	0.02
Lumax HF-T CRT-D				
Pocket infection	2	1.4%	2	0.04
Total Device Related	2	1.4%	2	0.04
Procedure				
Hematoma	3	2.0%	3	0.05
Pocket revision	2	1.5%	2	0.04
Pneumothorax	1	0.7%	1	0.02
Total Procedure Related	6	4.0%	6	0.11
Medical				
Atrial tachyarrhythmia	2	1.4%	2	0.04
Ventricular tachyarrhythmia	1	0.7%	1	0.02
Total Medical Related	3	0.7%	3	0.05
Overall Complication Totals	19	12.8%	20	0.35

Number of Patients = 148, Number of Patient-Years = 57.1

Table 28: Summary of Observations				
Category	Number of Patients	Percentage of Patients	Number of Observations	Observations per patient-year
Corox BP LV Lead				
Phrenic nerve stimulation	4	2.7%	4	0.07
High threshold / Loss of capture	2	1.4%	2	0.04
Total LV Lead Related	6	4.1%	6	0.11
RV Lead				
High threshold / Loss of capture	1	0.7%	1	0.02
Total RV Lead Related	1	0.7%	1	0.02
Atrial Lead				
Dislodgement	1	0.7%	1	0.02
Total Atrial Lead Related	1	0.7%	1	0.02
Lumax HF-T CRT-D				
Sensing / Detection issues	5	3.4%	5	0.09
Total Device Related	5	3.4%	5	0.09

Table 28: Summary of Observations				
Category	Number of Patients	Percentage of Patients	Number of Observations	Observations per patient-year
Procedure				
Hematoma	2	1.4%	2	0.04
Dissection of coronary sinus	1	0.7%	1	0.02
Total Procedure Related	3	2.0%	3	0.05
Other Medical				
Stroke	2	1.4%	2	0.04
Worsening CHF	2	1.4%	2	0.04
RA thrombus	2	1.4%	2	0.04
Atrial tachyarrhythmia	1	0.7%	1	0.02
Cardiogenic shock	1	0.7%	1	0.02
Other Medical	2	1.4%	2	0.02
Total Medical	10	6.8%	10	0.18
Overall Observation Totals	24	16.2%	26	0.46

Number of Patients = 148, Number of Patient-Years = 57.1

During the everesT trial 4 patient deaths were reported. None of the deaths were related to the devices under investigation.

c. Primary Endpoint: Effectiveness of Corox OTW(-S) BP Steroid

Objective: The goal was to demonstrate that the probability for successful Corox BP implantation (if the CS was found) is significantly higher than the borderline value of 0.75.

Results: Out of the 148 study patients, CS access was attained in 144 (97%) patients. Of the attempted Corox BP LV lead implants, 131 (91%) were successful. Of the 106 attempted Corox OTW BP Steroid LV lead implants, 97 (91.5%) were successful. Of the 38 attempted Corox OTW-S BP Steroid LV lead implants 34 (89.5%) were successful. A two-sided Pearson's asymptotic chi-square test results in a p-value of 0.71 and therefore there is no significant difference for the two models related to implant success. The Corox BP implant success rate of 91% compares well to the 91.7% implant success rate of the market released BIOTRONIK Corox OTW/Steroid Unipolar LV lead (P050023). Additionally, studies with other manufacturer's LV leads report an implant success rate in the range of 85.6 to 94.4%.

Table 29 lists the reasons for the 13 unsuccessful Corox BP LV lead implantations. Note that the percentages for the reasons may add up to more than 100% because multiple answers could be given for implant failure. **Table 30** lists the final outcome for each Corox BP implant failure.

Table 29: Reasons for Corox BP Implant Failure	
Reason	N
Inability to find stable position	6 (46%)
Anatomical difficulties	5 (38%)
Inability to advance the lead	4 (31%)
Lead dislodged while removing guide catheter	4 (31%)
High threshold	3 (23%)
Dissection of coronary sinus	1 (8%)
Phrenic nerve stimulation	1 (8%)
No reason given	1 (8%)
Total Corox BP Implant Failures	13

Final Outcome	n
Implantation of Corox OTW Unipolar lead	4 (31%)
Patient received epicardial lead	2 (15%)
Implantation of Corox LV-H lead (not FDA approved)	1 (8%)
Patient received Medtronic LV lead	1 (8%)
Patient was exited from the study by the physician	1 (8%)
Patient withdrew consent	1 (8%)
Information pending	3 (23%)
Total	13

Table 31 provides the individual implant success rates for Corox OTW BP Steroid and Corox OTW-S BP Steroid leads. There are two types of fixation mechanisms available for the Corox OTW BP LV lead: helical and straight. In order to reveal if the implant success rate was directly related to fixation type, the implant success rate for both mechanisms is presented.

Lead Type	Successful	Unsuccessful	% Successful
Corox OTW BP Steroid (helix)	97	9	91.5%
Corox OTW-S BP Steroid (straight)	34	4	89.5%
Total LV Implant Results	131	13	91.0%

Conclusions: The 95% lower bound criterion was found to be 85.1%. This is higher than the pre-determined borderline value of 75%, therefore the respective null hypothesis is rejected and the primary Corox BP effectiveness endpoint is met. There is no significant difference ($p = 0.71$) in complication rates between the Corox OTW BP Steroid and the Corox OTW-S BP Steroid leads.

d. Additional Data of Interest: Corox BP LV Lead Measurements

Investigators were required to use the implanted pulse generator to obtain ventricular lead measurements including pacing thresholds, lead impedance, and signal amplitude at implant and all routine follow-ups. Unless indicated, all measurements were made in a bipolar configuration at 0.5 millisecond pulse width. Intra-operative data were measured with the external pacing system analyzer or through the CRT pulse generator.

Table 32 provides a summary of lead measurements.

Table 32: Corox BP LV Lead Measurements at different follow-ups					
Pacing threshold @ 0.5 ms (V)					
	Imp.	PHD	1M-FU	3M-FU	6M-FU
n	121	128	108	99	15
Mean ± SD	1.2 ± 0.9	1.5 ± 1.3	1.3 ± 1.2	1.2 ± 1.1	0.8 ± 0.6
Min	0.2	0.3	0.3	0.4	0.4
Median	0.9	1.0	0.9	0.7	0.6
Max	4.5	7.5	7.5	5.2	2.7
Pacing impedance @ 0.5 ms (Ohm)					
	Imp.	PHD	1M-FU	3M-FU	6M-FU
n	115	121	103	94	15
Mean ± SD	839 ± 262	732 ± 219	806 ± 245	788 ± 202	886 ± 194
Min	362	305	374	346	646
Median	795	686	756	755	850
Max	1720	1748	1652	1379	1407
Bipolar Signal Amplitude (mV)					
	Imp.	PHD	1M-FU	3M-FU	6M-FU
n	105	122	95	83	11
Mean ± SD	7.8 ± 3.9	7.5 ± 4.0	8.3 ± 3.9	8.2 ± 4.0	7.8 ± 2.8
Min	2.1	0.9	1.0	0.7	4.4
Median	7.2	6.7	7.3	7.2	7.1
Max	22.0	22.0	22.0	21.7	12.9

XI. PANEL RECOMMENDATION AND FDA'S POST-PANEL ACTION

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

XII. CONCLUSIONS DRAWN FROM PRE-CLINICAL AND CLINICAL STUDIES

Enrollment into the AVAIL CLS/CRT study was not completed prior to PMA submission for FDA approval of the Stratos LV device. Low patient enrollment into the study did not allow for sufficient data to support a CRT indication for patients with a prior AV node ablation. Rather, data from the AVAIL CLS/CRT study were combined with the OPTION CRT/ATx clinical study and OVID clinical study to support the safety and effectiveness claim for indications for use for moderate to severe heart failure. Therefore, the AVAIL study results are presented as they assist in establishing that the Stratos LV/LV-T is reasonably safe for use.

Safety Conclusion (Stratos LV/LV-T)

The AVAIL CLS/CRT and Corox (OVID) clinical studies demonstrated the safety of the Stratos LV CRT-P in NYHA Class II/III and Class III/IV heart failure patients.

Effectiveness Conclusion (Stratos LV/LV-T)

The OPTION CRT/ATx clinical study completed and reviewed under P050023 provided a reasonable assurance that bi-ventricular pacing is effective in NYHA class III/IV heart failure patients with a prolonged QRS and a left ventricular ejection fraction <35%. The addition of ICD back-up therapy does not affect the biventricular pacing performance of the device.

Safety and Effectiveness Conclusion (Corox OTW (-S) BP)

The everest clinical study demonstrates the safety and effectiveness of the Corox OTW (-S) BP Steroid LV Leads in NYHA class III/IV heart failure patients with a prolonged QRS and a left ventricular ejection fraction <35%.

Overall Conclusion

Stratos LV is a CRT-P device approved outside the U.S., based on the FDA-approved Tupos LV/ATx CRT-D device (P050023, approved August 10, 2006). The Stratos is a modification of the Tupos primarily due to lacking defibrillation functionality and having added, separately programmable ventricular pacing outputs, added diagnostics, home monitoring and changes to hardware, including batteries and feedthrough available on prior approved Philos pacemakers (P950037).

The AVAIL CLS/CRT study (G040150) was intended to fully support safety and effectiveness of Stratos LV but was not completed. However, the data were used to support safety. The AVAIL study compared delivery of CRT and RV pacing in chronic atrial fibrillation among 118 of 265 planned enrollees indicated for resynchronization therapy. Fifty-five (55) Stratos LV devices were shown to have reasonable safety and good protocol compliance in 6 months of use. Types and frequency of adverse events in AVAIL was comparable to that of other CRT trials without unanticipated adverse events or device-related deaths. BIOTRONIK submitted findings of an OUS registry, OVID, which showed safe delivery of CRT by 89 Stratos devices.

FDA noted effectiveness of Stratos LV in effectiveness data that previously supported approval of Tupos LV/ATx (OPTION trial). This trial showed comparable effectiveness of CRT delivered by Tupos (and, by extension, Stratos) compared to market-approved CRT devices in terms of similar 6 month improvements in six minute walk and quality of life scores. In summary, the data submitted for Stratos LV are sufficient to support market approval of this CRT-P, showing reasonable safety and effectiveness.

The clinical study results as well as the pre-clinical validation and biocompatibility testing support the safety and effectiveness of the Stratos LV/LV-T CRT-Ps and Corox OTW (-S) BP left ventricular leads.

XIII. CDRH DECISION

CDRH issued an approval order for P070008 on May 12, 2008. The final conditions of approval cited in the approval order are described below:

As a condition of approval, Biotronik has agreed to the following regarding the post-approval study for the BIOTRONIK Corox BP leads:

1. a prospective study design to characterize chronic lead performance following device implant, as well as a robust process to retrospectively collect implant data for each study subject;
2. a post-approval study duration of at least 5 years;
3. a sample size that results in a 2-sided 95% upper confidence bound of no more than 1.0% for individual adverse event rates, assuming an expected rate of 0.4%, using the exact binomial method;
4. a total enrollment which accounts for estimated attrition, and an enrollment plan which attempts to fully enroll the study within 12 to 24 months;
5. a primary safety endpoint as complication-free rate greater than 95% at 5 years, with any clinical adverse events omitted from the primary endpoint collected and reported as secondary data;
6. a rigorous process to monitor the status of all study subjects, to actively follow-up missed visits, and to document the reason for all subject dropouts;
7. inclusion of a trend analysis process in the protocol to provide a robust early warning mechanism to identify, characterize, and report adverse events, failure modes, and failure rates;
8. post-approval study status reporting at least every 6 months and a mechanism for providing non-scheduled trend analysis reports for new information;
9. inclusion of a full list of complications, failure modes, and definition of terms within the study protocol; and
10. collection of secondary data including implant data, demographic information, all cause adverse events, electrical performance, returned product analyses, extraction experience, and other parameters of interest.

The applicant's manufacturing facility was inspected and found to be in compliance with the device quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for Use:

See device labeling

Hazards to Health from Use of the Device:

See Indications, Contraindications, Warnings, Precautions and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions:

See approval order