

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Implantable Cardioverter Defibrillator (ICD) with Cardiac Resynchronization Therapy (CRT) and Left Ventricular (LV) Pacing Leads
Device Trade Name:	Tupos LV/ATx CRT-D Kronos LV-T CRT-D 505.U Programmer Software for the ICS 3000 A-K00.7.U Programmer Software for the EPR/TMS 1000 ^{PLUS} Corox OTW Steroid Lead
Applicant's Name and Address:	BIOTRONIK, Inc. 6024 Jean Road Lake Oswego, OR 97035
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P050023
Date of Notice of Approval to Applicant:	AUG 10 2006

II. INDICATIONS

Tupos LV/ATx and Kronos LV-T CRT-Ds

The Tupos LV/ATx and Kronos LV-T CRT-Ds are indicated for use in patients with all of the following conditions:

- Indicated for ICD therapy
- Receiving optimized and stable Congestive Heart Failure (CHF) drug therapy
- Symptomatic CHF (NYHA Class III/IV and LVEF \leq 35%); and
- Intraventricular conduction delay (QRS duration \geq 130 ms)

The Tupos LV/ATx is also indicated for patients who, in addition to an indication for a CRT-D device, have atrial tachyarrhythmias or are at risk of developing atrial tachyarrhythmias.

Corox OTW Steroid LV Leads

The Corox OTW Steroid leads are intended for implantation via the coronary veins to provide long term cardiac pacing when used in conjunction with a compatible pulse generator.

III. CONTRAINDICATIONS

Tupos LV/ATx and Kronos LV-T CRT-Ds

The Tupos LV/ATx and Kronos LV-T CRT-Ds are contraindicated for use in patients with the following conditions:

- Patients whose ventricular tachyarrhythmias may have transient or reversible causes such as:
 - Acute myocardial infarction
 - Digitalis intoxication
 - Drowning
 - Electrocutation
 - Electrolyte imbalance
 - Hypoxia
 - Sepsis
- Patients with incessant Ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Patients whose only disorder is bradyarrhythmias or atrial arrhythmias

Corox OTW Steroid LV Leads

The use of the Corox OTW Steroid lead is 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 0.65 mg of dexamethasone acetate (DXA)

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Tupos LV/ATx CRT-D, Kronos LV-T CRT-D and Corox OTW Steroid Lead technical manuals.

V. SYSTEM DESCRIPTION

The Tupos LV/ATx and Kronos LV-T System are implantable Cardioverter Defibrillators (ICDs) designed to provide cardiac resynchronization therapy (CRT) or biventricular pacing and standard ICD therapy. The systems consist of the pulse generators (Tupos and Kronos) commercially available leads and/or the Corox OTW Steroid Left Ventricular Lead and the 505.U and A-K00.7.U Programmer Software.

The Tupos and Kronos provide CRT in a “shared-ring” configuration with both the RV and LV outputs tied together and are only programmable to a single value for both outputs. These devices also provide therapy for ventricular tachyarrhythmias with a range of programmable antitachycardia pacing (ATP) and/or defibrillation therapy, which is identical to therapies provided by standard ICDs. Both devices provide biphasic shocks with programmable energies from 1.0 to 30 Joules. The devices also provide enhanced ventricular tachyarrhythmia discrimination through the Smart Detection™ algorithm. The SMART Detection™ algorithm is specifically designed to detect and treat ventricular tachycardias while withholding therapy for supraventricular tachyarrhythmias. In addition, the Tupos provides therapy for atrial

tachyarrhythmias (AT and AF) with a range of ATP, high frequency (HF) burst pacing, and/or defibrillation therapy.

The Tupos and Kronos also are designed to collect diagnostic data to aid the physician's assessment of a patient's condition and the performance of the implanted device. Unlike the Tupos, the Kronos can provide triggered ventricular pacing in response to ventricular sensed events (VVT pacing) and Home Monitoring. VVT triggered pacing ensures that biventricular pacing occurs when a RV signal is sensed. Home Monitoring allows the automatic transmission of diagnostic patient data from the device to the physician at any time. The device uses wireless communication technology to provide the physician with daily patient monitoring and trend analysis information between follow-up visits.

COROX OTW STEROID LEAD

BIOTRONIK's Corox OTW Steroid 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 unipolar (UP) IS-1 connector configuration. The lead can be positioned in the target vein using either the over-the-wire technique or a stylet.

The leads are constructed with multifilar conductors insulated with medical grade silicone and coated with polyurethane. The distal end of the lead is helix shaped at the lead tip, which facilitates attachment of the lead to the coronary vein.

The distal tip of the Corox OTW Steroid lead consists of a steroid-eluting collar, containing 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 Steroid lead features a tip electrode 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 Steroid leads are available in the following configurations: Corox OTW 75-UP Steroid (77 cm length) and Corox OTW 85-UP Steroid (87 cm length).

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Patients who require an ICD and also have heart failure are routinely treated with a legally marketed ICD 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-Ds. Alternative therapies for the treatment of life-threatening ventricular arrhythmias as deemed appropriate by the physician are based upon electrophysiology (EP) testing and other diagnostic evaluations. These include the use of antiarrhythmic medication, electrical ablation, cardiac surgery, pacemakers and other commercially available implantable cardioverter defibrillators or a combination thereof.

VII. MARKETING HISTORY

Tupos LV/ATx CRT-D

Tupos LV/ATx received CE certification (number I7020610275211) on June 28, 2002 and has been marketed outside of the United States since that time. The Tupos LV/ATx has been legally marketed outside the United States, with greater than 707 of systems sold as of June 6, 2005. In April 2003, BIOTRONIK announced a voluntary recall of 186 Tupos LV/ATx as part of a larger worldwide recall of the Tachos Family of ICDs. The recall involved a premature increase of

internal impedance in the high voltage (6V) battery due to a change in raw materials. This issue was resolved in future products with a return to the original raw material. No other adverse events associated with the use of this system have been reported to competent authorities outside the US as of May 2, 2006.

The Tupos LV/ATx has been distributed in the following countries: Argentina, Australia, Austria, Belgium, Brazil, Cyprus, Czech Republic, France, Germany, Great Britain, Hungary, Israel, Italy, Lebanon, Mexico, Netherland, Poland, Russia, Slovakia, Spain, Switzerland, Turkey, Uruguay, and Venezuela.

Kronos LV-T CRT-D

The Kronos LV-T received CE certification (I7 00 11 10275 168) on August 11, 2004 and has been marketed outside of the United States since that time. The Kronos LV-T has been legally marketed outside the United States, with greater than 1555 systems sold as of May 2, 2006. Two adverse events associated with the use of this system have been reported to competent authorities as of May 2, 2006. The adverse events included one case of intermittent oversensing at implant exhibited as a lack of pacing (5-7 second gaps in pacing) with no clear root cause identified and one case reported of a device in backup mode, after receipt this device was determined to be functioning completely within specification, but that it had been reset out of the backup mode on the date it was explanted. The stored error code indicated a temporary drop in supply voltage, resulting in backup mode. Further analysis was able to reproduce the failure when applying pressure to one of the internal integrated circuits, however a definitive root cause could not be determined.

The Kronos LV-T has been distributed in the following countries: Argentina, Australia, Austria, Belgium, China, Cyprus, Czech Republic, Egypt, France, Germany, Great Britain, Hungary, Israel, Italy, Lebanon, Mexico, Netherlands, Panama, Poland, Portugal, Spain, Switzerland, Uruguay, and Venezuela

Corox OTW Steroid LV Lead

BIOTRONIK received approval of the Corox OTW Steroid leads in Europe on 10-17-2003 (CE number I7 03 10 10275 005) by the Notified Body TÜV Product Service GmbH.

BIOTRONIK has distributed over 4277 Corox OTW Steroid leads outside the United States as of May 2, 2006. No adverse events or incidents associated with these leads have been reported to date.

The Corox OTW Steroid has been distributed in the following countries: Argentina, Australia, Austria, Belgium, Brazil, Chile, China, Cyprus, Czech Republic, Denmark, Egypt, Finland, France, Germany, Great Britain, Hungary, India, Iran, Israel, Italy, Latvia, Lebanon, Lithuania, Malta, Netherlands, Panama, Poland, Portugal, Romania, Russia, Slovakia, South Africa, Spain, Switzerland, Turkey, Uruguay, and Venezuela. The Corox OTW lead has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL AND OBSERVED EFFECTS OF THE DEVICE ON HEALTH

A. POTENTIAL ADVERSE EVENTS

Tupos LV/ATx and Kronos LV-T CRT-Ds

The following are possible adverse events that may occur relative to the implant procedure and chronic implant of the Tupos LV/ATx and Kronos LV-T CRT-Ds:

- Air embolism
- Allergic reactions to contrast media
- Arrhythmias
- Bleeding
- Body rejection phenomena
- Cardiac tamponade
- Chronic nerve damage
- Damage to heart valves
- Device migration
- Elevated pacing thresholds
- Extrusion
- Fluid accumulation
- Hematoma
- 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
- Thromboembolism
- Undersensing of intrinsic signals
- Venous occlusion
- Venous or cardiac perforation

In addition, patients implanted with the CRT-D system may have the following risks. These are the same risks relate with implantation of any CRT-D system:

- Acceleration of arrhythmias (speeding up heart rhythm caused by the CRT-D)
- Dependency
- Depression
- Fear of premature battery depletion (fear that battery will stop working before predicted time)
- Fear of shocking while awake
- Fear that shocking ability may be lost
- Anxiety about the CRT-D resulting from frequent shocks
- Imagined shock (phantom shock)
- Inappropriate detection of ventricular arrhythmias
- Inappropriate shocks
- Potential death due to inability to defibrillate or pace
- Shunting current or insulating myocardium during defibrillation with external or internal paddles

There may be other risks associated with this device that are currently unforeseeable.

Corox OTW Steroid 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

B. OBSERVED ADVERSE EVENTS

There were 3 clinical trials conducted that contributed to this analysis of adverse events: The OPTION CRT/ATx Study, the HOME-CARE Study, and the OVID Study. The adverse events associated with each of these are described below.

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.

Tupos LV/ATx CRT-Ds – Summary of Adverse Events in the OPTION CRT/ATx Study

The OPTION CRT/ATx study was a prospective, randomized, multi-center study 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. All patients enrolled into the clinical study were randomly assigned to either the study group or the control group at a 2 to 1 ratio. Patients in the study group were implanted with the Tupos LV/ATx. Patients in the control group were implanted with a legally marketed ICD that provides CRT.

Of the 278 adverse events reported in the Tupos LV/ATx study group, there have been 210 observations in 104 patients and 68 complications in 50 patients with a cumulative implant duration of 1240.4 months (101.9 patient-years). 37.6% of the enrolled study patients have experienced a complication. The rate of complications per patient-year is 0.67. 78.2% of the enrolled study patients have a reported observation. The rate of observations per patient-year is 2.06.

Complications and observations for the Tupos LV/ATx study group are summarized in **Table 2** and **Table 3**. 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 2: Summary of Complications – Tupos LV/ATx

Category	Number of Patients	Percentage of Patients	Number of Complications	Complications per patient-year
Procedure Related				
Hematoma	4	3.01%	4	0.04
Pneumothorax	2	1.50%	2	0.02
Total	6	4.51%	6	0.06
Atrial Lead Related				
Dislodgement	3	2.26%	3	0.03
Total	3	2.26%	3	0.03
ICD Lead Related				
High threshold/ No capture	2	1.50%	2	0.02
Diaphragmatic/ Intercostal stimulation (RV)	1	0.75%	1	0.01
Total	3	2.26%	3	0.03
LV Lead Related				
High threshold/ Intermittent biventricular capture/ No capture	11	8.27%	12	0.12
Unable to implant lead via coronary sinus	11	8.27%	11	0.11
Dislodgement	4	3.01%	4	0.04
Diaphragmatic/ Intercostal stimulation	1	0.75%	2	0.02
Total	27	20.30%	29	0.28
Device Related				
Infection	3	2.26%	7	0.07
Device migration	4	3.01%	4	0.04
Elective replacement indicator	4	3.01%	4	0.04
Inductions and conversions	1	0.75%	1	0.01
Unable to interrogate device*	1	0.75%	1	0.01
Total	12	9.02%	17	0.17
Total Procedure, Lead and Device Related	43	32.33%	58	0.57
Other Medical Related				
Non-CHF Cardiac Symptoms	4	3.01%	4	0.04
Ventricular arrhythmias	2	1.50%	3	0.03
Other medical	2	1.50%	2	0.02
Atrial arrhythmia	1	0.75%	1	0.01
Total	9	6.77%	10	0.10
Total – All Patients and Categories	50	37.59%	68	0.67

Number of Patients = 133, Number of Patient-Years = 101.9

* 1 Unanticipated Adverse Device Effect (UADE) occurred with a Tupos LV/ATx CRT-D during the OPTION clinical study. The device was explanted after it was unable to be interrogated with the programmer software and no pacing output was evident. The analysis showed an appropriately depleted battery and no anomalies with the IC module. The battery depletion strongly suggests that the high voltage circuit was activated over a prolonged period due to a single-bit execution path failure. The current programmer software with Automatic Battery Management (ABM) would have prevented the battery from becoming completely depleted. There were no other instances of this failure mechanism in Tupos LV/ATx devices.

Table 3: Summary of Observations – Tupos LV/ATx

Category	Number of Patients with Observations	Percentage of Patients with Observations	Number of Observations	Observations per patient-year
Procedure Related				
Hematoma	10	7.52%	10	0.10
Cardiac arrest	2	1.50%	2	0.02
Unable to implant system	1	0.75%	1	0.01
Total	13	9.77%	13	0.13
Atrial Lead Related				
Dislodgement	1	0.75%	1	0.01
High threshold	1	0.75%	1	0.01
Total	2	1.50%	2	0.02
ICD Lead Related				
High threshold/No capture	1	0.75%	1	0.01
Total	1	0.75%	1	0.01
LV Lead Related				
High threshold/ Intermittent biventricular capture/ No capture	24	18.05%	24	0.24
Diaphragmatic / Intercostal stimulation	8	6.02%	8	0.08
Total	30	22.56%	32	0.31
Device Related				
Infection	1	0.75%	1	0.01
Inductions and conversions	6	4.51%	6	0.06
Inappropriate sensing	20	15.04%	20	0.20
Symptomatic with biventricular pacing	2	1.50%	2	0.02
Total	25	18.80%	29	0.28
Total Procedure, Lead and Device Related	61	45.86%	77	0.76
Other Medical Related				
Non-CHF Cardiac Symptoms	21	15.79%	21	0.21
Ventricular arrhythmias	11	8.27%	11	0.11
Other medical	26	19.55%	32	0.31
Atrial arrhythmia	14	10.53%	14	0.14
Dizziness	4	3.01%	4	0.04
Medication	5	3.76%	5	0.05
Worsening CHF	46	34.59%	46	0.45
Total	82	61.65%	133	1.31
Total – All Patients and Categories	104	78.20%	210	2.06

Number of Patients = 133 Number of Patient-Years = 101.9

There have been 4 patient deaths reported for the control group (out of 67 total control patients) and 10 patient deaths have been reported for the study group (out of 133 total study patients). None of the deaths were related to the implanted CRT-D system. One patient in the control group died prior to receiving a biventricular device implant. There is no significant difference between

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the number of deaths in the study group versus the control group ($p = 0.777$, Fisher's Exact Test, 2 sided). **Table 4** provides a summary of reported patient deaths and **Table 5** provides survival percentages by follow-up interval during the first 12 months of study participation.

Table 4: Summary of Patient Deaths

	Study Patients (N = 133)	Control Patients (N = 67)
Sudden Cardiac	1	1
Non-Sudden Cardiac	5	2
Non-Cardiac	4	1
All Causes	10	4

Figure 1 shows the associated Kaplan-Meier survival curves for the study and control groups. The significance level for the difference between the two study groups based on a Log Rank test was $p = 0.795$.

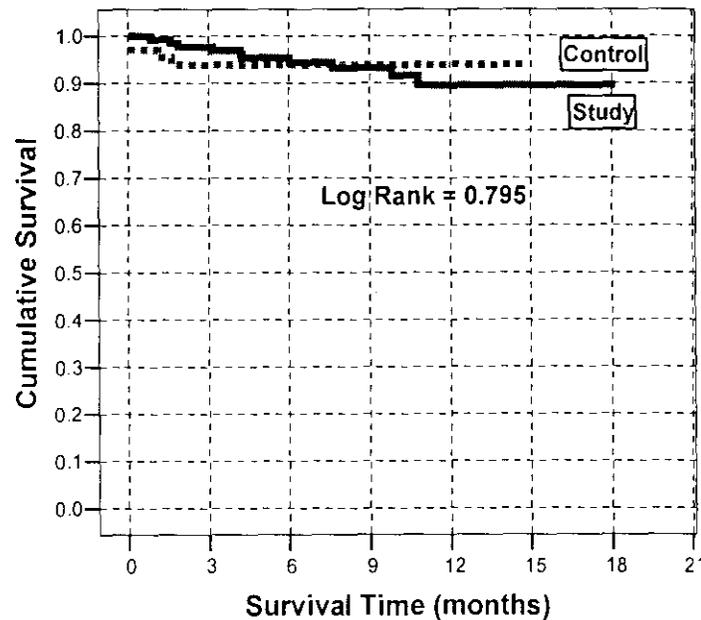


Figure 1: Kaplan-Meier Survival Curves

Table 5 Survival Table

	Study Group (n = 133)		Control Group (n = 66)	
	Number	%	Number	%
Enrollment	133	100.00%	67	100.00%
3-month	131	98.50%	63	94.03%
6-month	127	95.49%	63	94.03%
12-month	123	92.48%	63	94.03%

Kronos LV-T CRT-Ds – Summary of Adverse Events in the HOME-CARE Study

The HOME-CARE Observational study, conducted outside the US on the Kronos LV-T cardiac resynchronization defibrillator (CRT-D) in patients with congestive heart failure (CHF), involved 45 devices implanted with a cumulative implant duration of 202 months (mean implant duration of 4.5 months).

Of the 31 adverse events reported, there were 26 observations in 23 patients and 5 complications in 3 patients with a cumulative implant duration of 202 months (16.8 patient-years). 6.7% of the enrolled patients experienced a complication with 2 patients experiencing 2 separate complications. The rate of complications per patient-year is 0.30. 51% of the enrolled study patients had a reported observation with 3 patients having more than 1 observation. The rate of observations per patient-year was 1.54. Complications and observations for the patient group are summarized in **Table 6** and **Table 7**, respectively.

Table 6: Summary of Complications – Kronos LV-T

Category	Number of Patients	% of Patients	Number	Per patient-year
Left Ventricular Lead Related				
Dislodgement	1	2.2%	1	0.06
No Capture	1	2.2%	1	0.06
Total	2	4.4%	2	0.12
ICD Lead Related				
Dislodgement	1	2.2%	1	0.06
Elevated Pacing Threshold	1	2.2%	1	0.06
Total	2	4.4%	2	0.12
Unrelated to CRT-D or Leads				
Hemathorax	1	2.2%	1	0.06
Total	1	2.2%	1	0.06
Overall Complication Totals	3	6.7%	5	0.30

Number of Patients = 45, Number of Patient-Years = 16.8

Table 7: Summary of Observations – Kronos LV-T

Category	Number of Patients	%of Patients	Number	per patient-year
Unsuccessful LV lead implant	8	17.8%	8	0.48
Elevated LV pacing threshold	5	11.1%	5	0.30
Phrenic nerve stimulation	3	6.7%	3	0.18
Elevated DFT measurement	2	4.4%	2	0.12
T-wave oversensing	2	4.4%	2	0.12
Worsening CHF	2	4.4%	2	0.12
Elevated RV pacing threshold	1	2.2%	1	0.06
Hepatitis	1	2.2%	1	0.06
Arrhythmias	1	2.2%	1	0.06
Cardiac Decompensation	1	2.2%	1	0.06
All Observations	23	51.1%	26	1.54

Number of Patients = 45, Number of Patient-Years = 16

Two patient deaths were reported during the HOME-CARE Observational Study. One death resulted from worsening heart failure and the second death resulted from cardiogenic shock due to ischemic cardiomyopathy. None of the deaths were related to the implanted CRT-D system. There were no device explants during the HOME-CARE Observational Study.

Corox OTW Steroid LV Leads – Summary of Adverse Events in the OVID Study

An outside the US clinical evaluation of the Corox OTW Steroid (OVID) involved a total of 132 patients meeting indications for biventricular pacing. The coronary sinus was accessed in all patients, and of these, 121 were successfully implanted with the Corox OTW Steroid LV lead. The cumulative implant duration was 1145 months with a mean duration of 9.6 months. Ninety-six (79%) of the patients have implant durations greater than 6 months.

Of the 44 adverse events reported, there were 28 observations and 16 complications in a total of 132 patients. **Table 8** and **Table 9** provide a summary by category of each type of adverse event (complications and observations).

Table 8: Summary of Complications

Category	# of Pts	Percentage of Patients	# of Complications	Complication per pt-year
Corox OTW Steroid Lead-Related				
Loss of capture	5	3.8%	5	0.05
Phrenic nerve stimulation	2	1.5%	2	0.02
Total LV Lead Related	7	5.3%	7	0.07
Atrial Lead Related				
Loss of capture	2	1.5%	2	0.02
Total Atrial Lead Related	2	1.5%	2	0.02
RV Lead Related				
Loss of capture	3	2.3%	3	0.03
Elevated Pacing thresholds	2	1.5%	2	0.02
Total RV Lead Related	5	3.8%	5	0.05
Medical				
Arrhythmias	1	0.8%	1	0.01
Pocket infection	1	0.8%	1	0.01
Total Medical	2	1.5%	2	0.02
Overall Complication Totals	13	9.8%	16	0.17

Number of Patients = 132; Number of Patient-Years = 94.1

Table 9: Summary of Observations

Category	# of Pts	Percentage of Patients	# of Observations	Observations per pt-year
Corox OTW Steroid Lead-Related				
Implant failure	11	8.3%	11	0.12
Phrenic nerve stimulation	4	3.0%	4	0.04
Total LV Lead-Related	15	11.4%	15	0.16
Atrial Lead Related				
Loss of capture	1	0.8%	1	0.01
Elevated Pacing thresholds	1	0.8%	1	0.01
Total Atrial Lead Related	2	1.5%	2	0.02
RV Lead Related				
Elevated Pacing thresholds	2	1.5%	2	0.02
Total RV Lead Related	2	1.5%	2	0.02
Medical				
Arrhythmias	2	1.5%	2	0.02
Pocket infection/ Pericardial Effusion	2	1.5%	2	0.02
Chest pain	1	0.8%	1	0.01
Shortness of breath, palpitations	1	0.8%	1	0.01
Total Medical	6	4.5%	6	0.06
Miscellaneous				
Malfunction of hemostatic valve	2	1.5%	2	0.02
Improper Lead preparation	1	0.8%	1	0.01
Total Miscellaneous	3	2.3%	3	0.03
Overall Observation Totals	26	19.7%	28	0.30

Number of Patients = 132; Number of Patient-Years = 94.1

There were a total of 12 patient deaths reported in the OVID study. The clinical investigators determined that no deaths were related to the Corox OTW Steroid LV lead.

IX. SUMMARY OF PRE-CLINICAL STUDIES

A. NON-CLINICAL LABORATORY STUDIES - TUPOS LV/ATX CRT-DS

Based on the design of the Tupos LV/ATx and the results of BIOTRONIK's clinical testing, the effective pacing voltage (at the lead tip) will be slightly lower for the Tupos LV/ATx when compared to commercially available CRT-Ds. However, there is no clinically significant difference (<0.5V) in the pacing thresholds between the Tupos LV/ATx CRT-D and other commercially available CRT-Ds. The results of the non-clinical testing showing the different programmed voltage levels is detailed in Table 10.

Table 10 Effective Pacing Voltage Summary (Tupos LV/ATx)

Programmed Pacing Amplitude in Volts	Effective Pacing Amplitude (Tupos LV/ATx)	Effective Pacing Amplitude at 600 ohms in True Triple Chamber Configuration (current commercially available CRT-Ds)
2.0	1.4	1.8
2.5	1.8	2.2
3.0	2.2	2.6
3.5	2.5	3.1
4.0	2.9	3.5

The service times for the Tupos LV/ATx from beginning of service (BOS) to elective replacement indication (ERI) are listed in **Table 11**. All estimates assume pacing rate of 50 ppm, atrial pulse amplitude of 2.4 V at 0.5 ms and a biventricular pulse amplitude of 4.0 V at 0.5 ms and 500 ohm pacing impedance for both the atrial and ventricles with periodic capacitor reformations and active use of the Automated Battery Management (ABM) functionality. The use before dating is 9 months after the battery is connected during the manufacturing process. It is assumed that the shocks are equally spaced throughout the life of the CRT-D. The estimates associated with 0% pacing support assume the CRT-D is sensing an intrinsic sinus rhythm at a rate of 70 bpm. These estimates are based on actual current consumption measurement made during testing of the electronic modules for the Tupos LV/ATx CRT-D.

Table 11: Longevity Estimates

100% DDD Pacing Support	Shocks per Year	Longevity in Years
100 %	12	2.9
	8	3.0
	4	3.2
	0	3.4
50 %	12	3.2
	8	3.4
	4	3.6
	0	3.9
0 %	12	3.5
	8	3.8
	4	4.1
	0	4.4

The Tupos LV/ATx CRT-D is a derivation of BIOTRONIK’s legally marketed Tachos ATx ICD (P000009/S4) with biventricular pacing capabilities added to provide cardiac resynchronization therapy (CRT). Nearly all of the components used for the Tupos LV/ATx are identical to those used for the Tachos ATx ICD. Because many of the performance requirements and pass / fail criteria for the Tachos ATx ICD and Tupos LV/ATx are identical, the successfully completed validation testing of the Tupos LV/ATx CRT-D was also supported by testing of the Tachos ATx ICD.

Table 12 Tupos LV/ATx Qualification Summary			
Component	Comparison to Tachos ATx ICD	Qualification Basis	Qualification Result
Header	The header is formed from HYSOL EE 0079/HD 0070 epoxy, a liquid, two-component, unfilled epoxy system. The epoxy is used to form the lead connector ports of the CRT-D's header to facilitate placement and consistent connections between the CRT-D and leads.	Finished device qualification testing of Tachos to Tupos LV/ATx including dimensional and visual inspection, temperature shock and header shear testing. Similar to Tachos ATx with additional LV connector port (IS-1 Standard).	Specifications met, qualification testing passed.
Batteries (2)	One battery, lithium-iodine type (pacemaker battery), for supplying power to the control hybrid portion of the Tupos LV/ATx electronic module, and the second battery, Lithium Manganese Dioxide (high voltage battery), supplies power to the portion of the electronic module that generates the high energy defibrillation and cardioversion shocks.	Previously qualified for the Tachos ICD Family due to identical ICD batteries as the Tupos LV/ATx. Qualification tests included humidity storage, pressure resistance, mechanical shock, mechanical loading of pins, temperature shock and vibration tests, charge voltage as a function of temperature, high temperature storage and rapid battery discharge tests.	Specifications met, qualification testing passed.
High Energy Shock Capacitors (2)	The capacitors are aluminum electrolytic construction having a triple anode foil configuration housed in a cylindrical shape providing high energy density and lightweight construction. The electrical interface is comprised of two lugs that form a solid mechanical connection with very low impedance and minimal energy loss.	Previously qualified for the Tachos ICD Family as they are identical to the Tupos LV/ATx shock capacitors. Qualification tests included solderability after aging, thermal stability when soldering, long-term voltage, outgassing response, capacitance and dissipation factor, leakage current, mechanical characterization, cyclic charge-discharge testing, formation response, temperature storage, helium overpressure storage, electrolytic recombination, leakage current for excess voltage. Mechanical testing included vibration tests, temperature cycle, vacuum load and humidity storage.	Specifications met, qualification testing passed.

Table 12 Tupos LV/ATx Qualification Summary

Component	Comparison to Tachos ATx ICD	Qualification Basis	Qualification Result
Feedthrough	Ceramic feedthroughs are used to connect the internal circuitry of the CRT-Ds to the connector ports located in the header of each CRT-D. Identical to Tachos ATx ICD feedthroughs.	Qualification testing including temperature shock, helium leak and insulation testing as well as dimensional inspections and pin tensile strength test same as for earlier versions of BIOTRONIK ICDs., e.g., Tachos and Belos.	Specifications met, qualification testing passed.
Electronic Module	<p>The Tupos LV/ATx CRT-D uses the identical layout as the legally marketed Tachos ATx ICD with activation of biventricular pacing circuitry through a simple jumper. The control logic for Cardiac Resynchronization Therapy is in the Tachos ATx ICD although inactive.</p> <p>The entire electronic module is fabricated on a single hybrid substrate. The hybrid substrate consists of four (4) layers of laminated rigid and flexible polyamide materials in a symmetrical stack. The hybrid substrate utilizes wide copper traces (for minimum resistance) for shock delivery and battery current paths that provide maximum power delivery.</p>	Qualified for the Tachos ATx ICD, which has an electronic module that is identical to the Tupos LV/ATx. Qualification tests included physical dimensions, mechanical stress (temperature cycle), element shear, outgassed materials, constant acceleration, 250 and 1000 shock dump test, spacer insertion test, folding test, visual and electrical inspection, mechanical shock, vibration / variable frequency, 184 hour, 150c, life test as well as visual inspection and physical dimension changes.	Specifications met, qualification testing passed.

Component	Comparison to Tachos ATx ICD	Qualification Basis	Qualification Result
Firmware	The CRT-Ds require embedded software to provide basic instructions for operating the device microcontroller. This software is contained in the RAM memory within the CRT-D and is not accessible by the user.	Qualified for the Tachos ATx ICD because of identical firmware when compared to the Tupos LV/ATx. Qualification testing included Defibrillation Strength, Demodulation of Product, ESD Resistance, Electrical Neutrality, High Rate Protection, Testing of the Input Protection against High Voltages generated during Shock, Rate Limit by UTR, Input Impedance, Input Filter Characteristics, Pace Pulses as a Function of Load and Pacing Parameters, Shock Output as a Function of Load, Programmed Shock Energy, Battery Voltage and Temperature, Parameters as a Function of Temperature, Attack and Decay Times, Motion Sensor tests, Switch-On Behavior, Expanded Test for the Influence of Interference caused by HF Surgical Devices, Operation Voltage Measurement, Battery Management, Magnet Distances, IEGM Transmission and Signal Noise, and numerous tests for crosstalk.	Specifications met, qualification testing passed.

Finished Device Testing – Tupos LV/ATx CRT-D

The Tupos LV/ATx finished device has been subjected to validation testing according to the Biotronik’s validation plans. The Tupos LV/ATx CRT-Ds have passed all in vitro laboratory validation tests with acceptance based on Tupos LV/ATx product specifications.

Test Performed	Acceptance Criteria	Sample Size	Test Results (Pass/Fail)
Visual Inspection	Visual inspection is performed according to European Standards EN 45502-1:1998 and EN 45502-2-1:1998	1	Pass

Table 13 Tupos LV/ATx Finished Device Validation Testing

Test Performed	Acceptance Criteria	Sample Size	Test Results (Pass/Fail)
Transportation / Drop Test	This test was performed according to DIN IEC 68 T.2-55, Procedure A in conjunction with the Drop Test according to European Standards DIN EN 45502-1: 1998-07, Section 10.1; and EN 60068-2-32: 3/95.	6	Pass
Humidity and Vacuum Storage	Protection from Temperature and Humidity Changes according to European Standard DIN EN 45502-1: 1998-07, Section 10.2,	3	Pass
Wipe Test, Abrasion Test, and Bonding Strength of the Blister Label	The wipe test, abrasion test, and bonding strength test are verified per European Standard EN 45502-1:1998, Section 10.3	5	Pass
Sterilization Process	Three devices were inoculated under the dummy plug with 100 µL Bacillus subtilis spore suspension in the connector opening and on the surface. The products were dried under the laminar flow and sealed in double PETG blisters. Then they were sterilized with the half-cycle method (sterilization time of 60 min.) and tested for growth of Bacillus subtilis, no bacillus subtilis is allowed on the samples under test.	3	Pass
Protection of the Patient or the User from Injury Caused by External Physical Properties or by Heat	The ICD casting was inspected per European Standards EN 45502-1:1998 Section 15.2 and prEN 45502-2-2:1998, Sec. 17.1.	4	Pass
Ultrasonic Resistance	Exposure to Ultrasound according to European Standard pr EN 45502-1, 1996 D, Section 22.1	1	Pass
Vibration Test	Exposure to Vibration according to European Standard EN 45502-2-2, Sec. 23.2.	5	Pass
Mechanical Shock Test	Exposure to Mechanical Shock according to European Standard prEN 45502-2-2 03.98 Section 23.7	5	Pass
Protection from Damage caused by Air Pressure or Temperature Changes	Exposure to Air Pressure and Temperature Changes according to European Standard EN 45502-1 Sec. 25.1 and Sec. 26.2.	6	Pass

Table 13 Tupos LV/ATx Finished Device Validation Testing

Test Performed	Acceptance Criteria	Sample Size	Test Results (Pass/Fail)
EtO Residual Gas Analysis	Residual Gas Analysis of Ethylene Oxide, Ethylene Chlorohydrine, Ethylene Glycol according to ISO 10993-7	5	Pass
Microbial Impermeability of the Sealed Seam	Neither colonies of Staphylococcus aureus nor colonies of Bacillus subtilis shall grow on any of the 40 tested Rodak plates. With this, it is guaranteed that the PETG blister material is adequately impermeable. In principle, the test method is based on contaminating the test material on one side with microorganisms for a defined period of time. Afterwards, it is tested whether the microorganisms have penetrated through the test material to the underside. No penetrations are allowed.	2	Pass
Microbiology: Bio-Burden and Pyrogen Test	The endotoxin limit for medical devices is indicated in EU/ml. The warning limit is 5 EU/Device and the intervention limit is 20 EU/Device. No gelation may occur in a 40 ml extract solution and a lysate sensitivity of 0.125 EU/ml. The final cleaning procedure must be tested if the limits are exceeded. The microbe load must be less than the specified maximum values (20 EU/Device). The pyrogenicity must be 0% after EtO sterilization.	3	Pass
Dimensional and Visual Inspection of the Header/ Feedthroughs	The validation standard refers to ISO 11318: 05'92 (DF-1) and ISO 5841-3:12'92 (IS- 1) for the header ports and internal BIOTRONIK specification for the other header characteristics.	3	Pass
Temperature Shock	The validation standard refers to the requirements from the norm DIN IEC 68-2-14: 6'87, Section 1 (Temperature Change) and MIL-STD 883D, Method 1011.9 (Thermal Shock).	5	Pass
Header Shear Test	The housing is mounted firmly and the header is stressed on its upper edge till it breaks. The test is passed if the mean shear value of five units > to 1.5 N/mm ² .	5	Pass
Visual Inspection of the Inner Construction	The units were inspected to ensure proper arrangement of the subassembly and parts in terms of function and further processing.	2	Pass

Test Performed	Acceptance Criteria	Sample Size	Test Results (Pass/Fail)
In-Vitro Test 2000 Hours	The ICD is required to function within all electrical and mechanical specifications and with identical programming values before and after the 2000 hour In Vitro Test.	3	Pass
Life-Time Calculation / Use Before Time	The individual service periods of both batteries (LI 12100 & LIS3482) are calculated to achieve the total service life. The longevity is calculated based on measurement of twenty-five electronic circuits to estimate the total service life. The service life calculation is required according to prEN 45502-2-2: 1998, Par. 28.19, the average period of longevity must be determined for numerous patient use scenarios.	25	Specification met, results accepted.

B. NON-CLINICAL LABORATORY STUDIES - KRONOS LV-T CRT-Ds

The Kronos LV-T CRT-D is a derivation of BIOTRONIK’s legally marketed Belos DR ICD (P000009/S05) with biventricular pacing capabilities added to provide cardiac resynchronization therapy (CRT). Nearly all of the components used for the Kronos LV-T are identical to those used for the Belos DR ICD. Because many of the performance requirements and pass / fail criteria for the Belos DR ICD and Kronos LV-T are identical, the successfully completed validation testing of the Kronos LV-T CRT-D was also supported by testing of the Belos DR ICD.

Component	Comparison to Belos DR ICD	Qualification Basis	Qualification Result
Header	The header is formed from HYSOL EE 0079/HD 0070 epoxy, a liquid, two-component, unfilled epoxy system. The epoxy is used to form the lead connector ports of the CRT-D’s header to facilitate placement and consistent connections between the CRT-D and leads.	Finished device qualification testing of Kronos LV-T including dimensional and visual inspection, temperature shock and header shear testing. Similar to Belos DR-T with additional LV connector port (IS-1 Standard).	Specifications met, qualification testing passed.

Table 14 Kronos LV-T Qualification Summary

Component	Comparison to Belos DR ICD	Qualification Basis	Qualification Result
Battery	One, Lithium Manganese Dioxide battery supplies power to the electronic module for all system functions.	Previously qualified for the Belos ICD Family due to the battery being identical to Kronos LV-T battery. Qualification testing included pressure resistance, vacuum stability, mechanical shock, vibration test, high temperature test, temperature shock, high and low temperature storage, accelerated pulse testing, load stress dependent on temperature, rapid discharge, short circuit test, charging test, high energy discharge, thin pin impression, stamp impression, destruction test, verification of safe weld seam.	Specifications met, qualification testing passed.
High Energy Shock Capacitors (2)	The capacitors are aluminum electrolytic construction having a four layer anode foil configuration housed in a cylindrical shape providing high energy density and lightweight construction. The electrical interface is comprised of two lugs that form a solid mechanical connection with very low impedance and minimal energy loss.	Previously qualified for the Belos ICD Family due to the capacitors being identical to Kronos LV-T CRT-D capacitors. Qualification testing included capacity and dissipation factor, leakage current, cyclic charge-discharge test, mechanical characterization, vibration and temperature cycle testing, humidity storage, leakage current, vacuum load, soldering after conditioning, thermal stability when soldering, outgassing, electrolytic recombination, formation response, response during long-term helium pressurized and temperature storage.	Specifications met, qualification testing passed.

Table 14 Kronos LV-T Qualification Summary			
Component	Comparison to Belos DR ICD	Qualification Basis	Qualification Result
Feedthrough	Ceramic feedthroughs are used to connect the internal circuitry of the CRT-Ds to the connector ports located in the header of each CRT-D.	Qualification testing including temperature shock, helium leak and insulation testing as well as dimensional inspections and pin tensile strength test same as for earlier versions of BIOTRONIK ICDs, e.g., Tachos and Belos.	Specifications met, qualification testing passed.
Electronic Module	<p>The Kronos LV-T CRT-D uses the identical layout as the legally marketed Belos DR ICD with activated of biventricular pacing circuitry.</p> <p>The entire electronic module is fabricated on a single hybrid substrate. The hybrid substrate consists of four (4) layers of laminated rigid and flexible polyamide materials in a symmetrical stack. The hybrid substrate utilizes wide copper traces (for minimum resistance) for shock delivery and battery current paths</p>	Qualified for the Belos DR-T ICD, which has an electronic module that is identical to the Kronos LV-T. Qualification tests included temperature cycling, physical dimension tests, element shear test, constant acceleration, 250 shock dumps and 1000 shock testing, numerous mechanical tests after high temperature storage, transportation and drop tests in the circuit packaging, 184 hour, 150c, life test, visual inspection and physical dimensions / shrinkage changes.	Specifications met, qualification testing passed.

Finished Device Testing – Kronos LV-T CRT-D

The Kronos LV-T finished device has been subjected to thorough validation testing according to the validation plans. The Kronos LV-T CRT-Ds have passed all in vitro laboratory validation tests with acceptance based on Kronos LV-T product specifications.

Table 15 Kronos LV-T Finished Device Validation Testing			
Test Performed	Acceptance Criteria	Sample Size	Test Results (Pass/Fail)
Visual Inspection	Visual inspection is performed according to European Standards EN 45502-1:1998 and EN 45502-2-1:1998	1	Pass

Table 15 Kronos LV-T Finished Device Validation Testing			
Test Performed	Acceptance Criteria	Sample Size	Test Results (Pass/Fail)
Transportation / Drop Test	This test was performed according to DIN IEC 68 T.2-55, Procedure A in conjunction with the Drop Test according to European Standards DIN EN 45502-1: 1998-07, Section 10.1; and EN 60068-2-32: 3/95.	5	Pass
Humidity and Vacuum Storage	Protection from Temperature and Humidity Changes according to European Standard DIN EN 45502-1: 1998-07, Section 10.2,	1	Pass
Wipe Test, Abrasion Test, and Bonding Strength of the Blister Label	The wipe test, abrasion test, and bonding strength test are verified per European Standard EN 45502-1:1998, Section 10.3	5	Pass
Sterilization Process	Three devices were inoculated under the dummy plug with 100 µL Bacillus subtilis spore suspension in the connector opening and on the surface. The products were dried under the laminar flow and sealed in double PETG blisters. Then they were sterilized with the half-cycle method (sterilization time of 60 min.) and tested for growth of Bacillus subtilis. No bacillus subtilis is allowed on the samples under test.	3	Pass
Protection of the Patient or the User from Injury Caused by External Physical Properties or by Heat	The ICD casting was inspected per European Standards EN 45502-1:1998 Section 15.2 and prEN 45502-2-2:1998, Sec. 17.1.	2	Pass
Ultrasonic Resistance	Exposure to Ultrasound according to European Standard pr EN 45502-1, 1996 D, Section 22.1	1	Pass
Vibration Test	Exposure to Vibration according to European Standard EN 45502-2-2, Sec. 23.2.	4	Pass
Mechanical Shock Test	Exposure to Mechanical Shock according to European Standard prEN 45502-2-2 03.98 Section 23.7	4	Pass

Table 15 Kronos LV-T Finished Device Validation Testing			
Test Performed	Acceptance Criteria	Sample Size	Test Results (Pass/Fail)
Protection from Damage caused by Air Pressure or Temperature Changes	Exposure to Air Pressure and Temperature Changes according to European Standard EN 45502-1 Sec. 25.1 and Sec. 26.2.	6	Pass
EtO Residual Gas Analysis	Residual Gas Analysis of Ethylene Oxide, Ethylene Chlorohydrine, Ethylene Glycol according to ISO 10993-7	4	Pass
Microbial Impermeability of the Sealed Seam	Neither colonies of Staphylococcus aureus nor colonies of Bacillus subtilis shall grow on any of the 40 tested Rodak plates. With this, it is guaranteed that the PETG blister material is adequately impermeable.	3	Pass
Microbiology: Bio-Burden and Pyrogen Test	The endotoxin limit for medical devices is indicated in EU/ml. The warning limit is 5 EU/Device and the intervention limit is 20 EU/Device. No gelation may occur in a 40 ml extract solution and a lysate sensitivity of 0.125 EU/ml. The final cleaning procedure must be tested if the limits are exceeded. The microbe load must be less than the specified maximum values (20 EU/Device). The pyrogenicity must be 0% after EtO sterilization.	1	Pass
Dimensional and Visual Inspection of the Header/ Feedthroughs	The validation standard refers to ISO 11318: 05'92 (DF-1) and ISO 5841-3:12'92 (IS- 1) for the header ports and internal BIOTRONIK specification for the other header characteristics.	3	Pass
Temperature Shock	The validation standard refers to the requirements from the norm DIN IEC 68-2-14: 6'87, Section 1 (Temperature Change) and MIL-STD 883D, Method 1011.9 (Thermal Shock).	1	Pass
Header Shear Test	The housing is mounted firmly and the header is stressed on its upper edge till it breaks. The test is passed if the mean shear value of five units > to 1.5 N/mm ² .	3	Pass
In-Vitro Test 2000 Hours	The ICD is required to function within specifications and with identical programming values before and after the 2000 hour In Vitro Test.	5	Pass

Table 15 Kronos LV-T Finished Device Validation Testing			
Test Performed	Acceptance Criteria	Sample Size	Test Results (Pass/Fail)
Life-Time Calculation / Use Before Time	The individual service periods are calculated based on measurement of twenty electronic circuits to estimate the total service life. The service life calculation is required according to prEN 45502-2-2: 1998, Par. 28.19, the average period of longevity must be determined for numerous patient use scenarios.	20	Specification met, results accepted.

Firmware

Embedded Software validation testing was designed to confirm the overall safety and functionality of the Kronos LV-T CRT-Ds. The Kronos LV-T embedded software successfully passed all test requirements. Validation testing was performed to verify that the Kronos 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 Kronos LV-T firmware were based on internal BIOTRONIK specifications and all test data was acceptable.

Table 16 Kronos LV-T Firmware Validation Testing	
Firmware Tests	Successfully Performed
Exposure to External Influences+	<ul style="list-style-type: none"> • Defibrillation Stability, • Demodulation of Product, • Electrostatic Discharge Susceptibility • Effect of HF Electrosurgery • Temperature Changes
Exposure to Internal Influences	<ul style="list-style-type: none"> • Test of the Input Protection against High Voltages Emitted during a Shock, • High Rate Protection • Timing Based on Age of Crystal • High Voltage Strength of Inner Assembly • Risk of HV Switch or Capacitor Failure • Risk of HV Generation • Influences on Device during RF Telemetry
Elective Replacement Indication (ERI) and End of Service (EOS)	<ul style="list-style-type: none"> • Long-term 100% BiV Pacing • Measurement of Current Consumption • EOS Behavior with Low Battery Voltage • Service Life Calculations / Use Before Date

Table 16 Kronos LV-T Firmware Validation Testing

Firmware Tests	Successfully Performed
Electrical Characteristics	<ul style="list-style-type: none"> • Electric Neutrality • Measurement of Input Impedance • Common Mode Rejection Ratio (CMRR) • Input Filter Response, • Battery Voltage • Switch-On Response • Latch-up Stability • Response to Reset • Non-Rate Adaptive Pacing Mode Appropriateness • VF Detection • VF Redetection • Emergency Shocks • Crosstalk of Feedthroughs • Brady and Tachy Default Programs • Pacing Impedance Measurements • Shock Impedance Measurements • P/R Wave Measurements • DFT Testing • ATP Testing • Pacing Threshold Testing • Retrograde Conduction Testing
Sensor Response Threshold	<ul style="list-style-type: none"> • Only Affected by Frequencies Between 2 and 10 Hz • Appropriate Return to Baseline when Motion Removed • Response During Patient Activity • Automatic Gain
Characteristics of Pacing Terminal (Input/Output) Pulse Response Based on:	<ul style="list-style-type: none"> • Temperature • Pacemaker • ATP • HF Burst • Shock • Trigger Time after Pulse Generation • Battery Voltage • Pacemaker • ATP • HF Burst • Shock • Pacing Load • Atrial, LV and RV Pulse Widths • Various Pulse Amplitudes
Intra-Electrograms (IEGM)	<ul style="list-style-type: none"> • IEGM Transmission – Pulse Generator to Programmer • Far-Field IEGM

Firmware Tests	Successfully Performed
Battery Management	<ul style="list-style-type: none"> • During Capacitor Charging – Direct Mode • During Capacitor Charging – Substrate Charge Pump Switching • Current Consumption During Various Cardiac Rhythms • Pacing Behavior During Capacitor Reformations • Pacing Behavior During Reset
Programming Wand	<ul style="list-style-type: none"> • Programming and Interrogation Distances • Magnet Response at Various Distances • Wand Location / Orientation • Telemetry Circuit Behavior and Current Draw • Programming Depending on Load • Impact of Programmer from other Manufacturers • Communication Protocols • Response Under Magnet Application
Emergency Functions	<ul style="list-style-type: none"> • Emergency Brady Pacing • Emergency Shock
Home Monitoring	<ul style="list-style-type: none"> • Crosstalk – Detailed Investigation • Automatic Measurement Functions

EMI Testing

BIOTRONIK has performed a comprehensive set of electromagnetic interference testing of the Tupos LV/ATx CRT-D according to three separate industry standards, including the DIN VDE 0750, EN 45502-2-2, and the AAMI standard PC-69. 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 standards EN 45502-2-2, and the AAMI standard PC-69.

Test Performed	Sample Size	Test Results (Pass/Fail)
Safety During EMI: EMI-Induced currents	1	Pass
Safety During EMI: Static Fields	1	Pass
Test of the Safety Against Malfunction Caused by Outside Electromagnetic Fields	1	Pass
Safety Against Malfunction Caused by Unmodulated Electromagnetic Influence	1	Pass
Protection Against Detecting Modulated EMI	1	Pass
EMI Resistance Measurements according to AAMI PC69 in the Range 450 MHz to 3 GHz	1	Pass
Use of a Cautery on an ICD in Saline Solution	1	Pass

Table 17 EMI Testing of CRT-Ds		
Test Performed	Sample Size	Test Results (Pass/Fail)
HF Surgery Test	9	Pass
Influence of Alternating Magnetic Fields	1	Pass
Programming Behavior at EMI	1	Pass

C. COROX OTW STEROID LEAD

The following tables summarize the validation testing (safety and performance) conducted on the components of BIOTRONIK's Corox OTW Steroid Lead, 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.

Table 18 Corox OTW Steroid Validation Testing	
Test Performed	Test Results (Pass/Fail)
Biocompatibility and Sterilization	
Biocompatibility (of Pellethane 2363-55DE) according to ISO 10993-1	Pass
Hemocompatibility (final product) according to ISO 10993:4	Pass
Cell Toxicity (final product and Polyurethane Pellethane 2363-55 DE) according to ISO 10993-5: 1999	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	Pass
Proof of Sterilization Success according to EN 550: 1994	Pass
Residual Gas Analysis: Ethylene Oxide and Ethylene Chlorohydrin according to ISO 10993-7: 1995	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
Stylet Performance according to FDA Lead Guidance*	Pass
Fatigue Test (Bending Fatigue Test on Lead Body between Connector and Tip, at Connector Transition, at Transitions in Distal Section of Lead: Head Proximally) according to FDA Lead Guidance*	Pass
Connector Testing to ISO 5841-3 (IS-1) (on Lead Body between Connector and Tip, at Connector Transition)	Pass
Anchoring Sleeve Performance according to FDA Lead Guidance*	Pass

Table 18 Corox OTW Steroid Validation Testing	
Test Performed	Test Results (Pass/Fail)
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	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	Pass
Area Calculation of Tip Electrode according to Internal BIOTRONIK Specification; Leads were checked for conformance with the dimensions detailed in BIOTRONIK's drawing 346049. The surface areas of the tip electrodes were calculated from the design specifications to verify the electrodes had the specified surface area ($A = 5.0 \pm 0.2 \text{ mm}^2$)	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: <ul style="list-style-type: none"> • 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	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 $0.5 \text{ mg} \pm 30\%$.	Pass
Liberation of DXA from the Collar and Lead Tip 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

Table 18 Corox OTW Steroid Validation Testing	
Test Performed	Test Results (Pass/Fail)
Accessories	
Use of Corox OTW 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
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 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 with Torque 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 0.36mm 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 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 test 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 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

D. 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).

E. BIOCOMPATIBILITY TESTING

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

All tissue-contacting materials of BIOTRONIK's Corox OTW Steroid Left Ventricular Lead are currently utilized in BIOTRONIK products market-released in the US, except for Pellethane 2363-55DE. Biocompatibility testing of Pellethane 2363-55DE as well as all tissue-contacting materials utilized in BIOTRONIK's Corox OTW Steroid has been successfully completed in accordance with ISO 10993-1, "Biological Evaluation of Medical Devices."

F. SHELF LIFE

A 9-month expiration date, "Use Before Date" (UBD), has been established for the Tupos LV/ATx and Kronos LV-T CRT-Ds based on device longevity and internal battery characteristics. The use before date is assigned as the last date of the ninth month after battery connection is made during the manufacturing process. It is guaranteed that the projected longevity of the device remains valid until implantation.

A 24-month expiration date, "Use Before Date" (UBD), has been established for the Corox OTW Steroid 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.

G. ANIMAL STUDIES

BIOTRONIK conducted an animal study in foxhound dogs to evaluate the safety, electrical performance, and biocompatibility of the Corox OTW unipolar leads. A total of 12 dogs were randomized into two study groups: steroid or non-steroid Corox OTW leads. In the steroid eluting model of the Corox OTW leads, the steroid effectively reduced any pacing threshold increases compared to the non-steroid lead model. The complication rates for all dogs were clinically acceptable for the animal model. Therefore, the Corox OTW LV pacing lead animal study supported the safety and effectiveness of the Corox OTW-UP (both steroid and non-steroid models).

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

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

Study Overview

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.

Methods

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 effectiveness of atrial therapy to automatically convert atrial tachyarrhythmias, 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.

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

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

Summary of Clinical Results

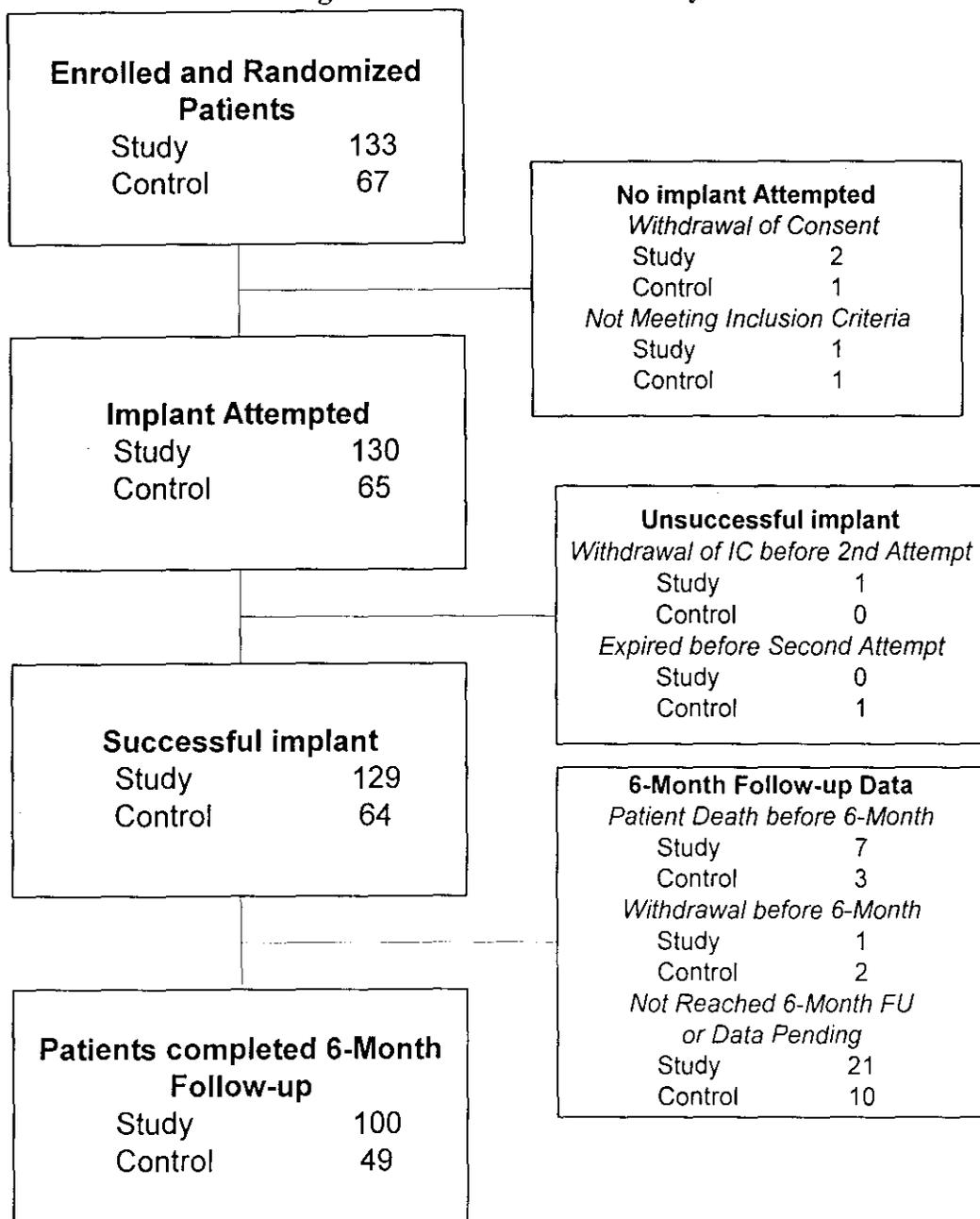
A total of 200 patients were enrolled in the OPTION CRT/ATx clinical study at 25 sites:

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.

Patient Accountability

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



Overall Results

- 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.
- For the study group, there have been 278 adverse events (210 observations in 104 patients and 68 complications in 50 patients). There has been one unanticipated adverse device effect reported.

- For the control group, there have been 105 adverse events (81 observations in 44 patients and 24 complications in 19 patients). There have been no unanticipated adverse device effects reported.
- 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.

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 19 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 19: 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	13.08 ± 13.05	0.322
	17.27% ± 5.59%	8.71% ± 5.26%	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	11.58 ± 3.45	0.376
	19.08% ± 12.21%	-13.42% ± 34.54%	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.

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).

Primary Endpoint 2: Complication-Free Rate (Safety)

The purpose of Primary Endpoint 2 was to evaluate complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Tupos LV/ATx, the right atrial lead, the right ventricular ICD lead, the left ventricular lead, and the implant procedure. The target complication-free rate at Six-Months is 85%.

Table 20 provides the categorized complication rates at 6-months for the study and the control group as well as a comparison between the study and the control group.

Table 20: Complications at 6-Month – Study and Control

Category	Study N = 133	Control N = 67	Study versus Control Comparison		
			Difference	95% CI	P-value
Procedure Related	6 (4.51%)	1 (1.49%)	3.02%	[-3.64%, 8.45%]	0.428
Atrial Lead Related	3 (2.26%)	1 (1.49%)	0.76%	[-5.74%, 5.37%]	1.000
ICD Lead Related	3 (2.26%)	0 (0%)	2.26%	[-3.03%, 6.53%]	0.552
LV Lead Related	26 (19.55%)	9 (13.43%)	6.12%	[-5.50%, 16.45%]	0.329
Device Related	7 (5.26%)	5 (7.46%)	-2.20%	[-11.42%, 4.77%]	0.541
Other Medical Related	9 (6.77%)	2 (2.99%)	3.78%	[-3.82%, 10.13%]	0.341
Total Procedure, Lead and Device Related	39 (29.32%)	15 (22.39%)	6.94%	[-6.46%, 19.17%]	0.317
Total	46 (34.59%)	17 (25.37%)	9.21%	[-4.96%, 21.99%]	0.201

Primary Safety Endpoint Analysis and Conclusions

The observed procedure, lead and device related complication-free rate at 6 months was 70.68%. The 95% confidence interval for the complication-free rate was [62.16%, 78.25%]. The lower, one-sided 95% confidence bound for the complication-free rate was 63.50%. Therefore, the procedure, lead and device related complication-free rate at 6 months did not meet the pre-specified acceptance criterion for this endpoint.

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Post-Hoc Safety Analyses

Biotronik did not meet their pre-specified objective performance criteria of 85 percent within 10 percent for the safety endpoint, therefore, a post-hoc safety analysis was conducted. It was noted that 79.80% (39 out of 49 events) of the complications were right atrial lead, right ventricular ICD lead, left ventricular lead and procedure related. The atrial, ICD and LV leads used during this study are legally marketed devices.

This post-hoc analysis evaluated the LV lead complications that were “related” or “possibly related” to the Tupos LV/ATx CRT-D, but excludes the complications that were “not related” to the Tupos LV/ATx device (see Table 21- Summary of Complications-Tupos LV/AT). There were 11 patients who had an attempt to implant the LV lead, but the physician was unsuccessful in either obtaining coronary sinus (CS) access or unable to find a stable position for the LV lead. Additionally, there were 4 patients with a documented LV lead dislodgement that has no direct relationship to the implanted Tupos LV/ATx.

Table 21: Complications at 6-Months (Excluding LV Lead Related) - Study versus Control

Category	Study N=133	Control N=67	Difference - Study versus Control
Procedure Related	6 (4.51%)	2 (2.99%)	1.53%
Atrial Lead Related	3 (2.26%)	1 (1.49%)	0.76%
ICD Lead Related	3 (2.26%)	0 (0%)	2.26%
LV Lead Related	11 (8.27%)	1 (1.49%)	6.78%
Device Related	7 (5.26%)	5 (7.46%)	-2.20%
Other Medical Related	9 (6.77%)	2 (2.99%)	3.78%
Total Procedure, Lead and Device Related	27 (20.30%)	8 (11.94%)	8.36%
Total	35 (26.32%)	10 (14.93%)	11.39%

The pulse generator related complication rate is higher in the control group as compared to the study group. The complication rates for procedure related, atrial lead related, ICD lead related, LV lead related and other medical related are higher in the study group as compared to the control group.

Conclusion

There are no clinically substantial differences in the total complication rate or in the rates for the different complication rate categories between the study and the control group.

Table 22 compares this post-hoc Safety Endpoint analysis to previous CRT-D clinical studies:

Table 22 Safety Endpoint Comparisons

CRT-D Study	Estimated freedom from Complications @ 6mos.	Lower 95% CI	95% lower bound criteria
BIOTRONIK OPTION (Original Analysis)	70.68%	63.5%	75%
BIOTRONIK OPTION (Post-hoc Analysis)	78.95%	72.29%	75%
Company A	81.1%	77.6%	67%
Company B	N/A	N/A	70%
Company C	93.4%	90.6%	70%

This analysis confirmed that the safety profile of the Tupos LV/ATx is within a similar range determined during trials of other legally marketed CRT-D devices.

Secondary Endpoint Results

1. The purpose of Secondary Endpoint 1 is to evaluate the overall ability of the Tupos LV/ATx to appropriately convert spontaneous AT (atrial tachycardia) and AF (atrial fibrillation). The results from the OPTION study were compared to the results from BIOTRONIK’s TACT study (P000009/S4, dated 09-09-2002) that demonstrated the effectiveness of these atrial therapy features in the Tachos DR - Atrial Tx ICD.

Table 23 summarizes success rates for each individual atrial tachyarrhythmia therapy type and overall success rate from the OPTION study compared to the TACT study. The number of episodes and patients receiving any therapy is less than the total episodes of each therapy type, as episodes may have included more than one type of therapy.

Table 23 Overall Atrial Conversion Rate

Patients	TACT Study				OPTION Study			
	Patients	Success	Episodes	Conversion rate	Patients	Success	Episodes	Conversion rate
ATP	29	62	142	43.6 %	3	3	5	60.0%
HF Burst	49	156	408	38.2 %	17	45	111	40.5%
Shock	42	84	108	77.8 %	12	30	34	88.2%
All Therapies	66	302	542	55.7 %	25	78	129	60.5%

The overall conversion rate and the conversion rates for each therapy are comparable to the conversion rates observed in the TACT study, demonstrating that the Tupos LV/ATx device has similar atrial conversion capabilities as the legally marketed Tachos DR - Atrial Tx ICD.

2. The purpose of Secondary Endpoint 2 is to evaluate VT (ventricular tachycardia) and VF (ventricular fibrillation) detection times of the Tupos LV/ATx. This is a measure of the ability of the ventricular detection algorithm to detect VT and VF in an appropriate timeframe. This endpoint was evaluated based on the review of electrograms following induced VT/VF episodes. A comparison of data from the TACT study that utilized the legally marketed Tachos DR - Atrial Tx ICD (P000009/S4, dated 09-09-2002) to data collected during the OPTION study for the Tupos LV/ATx was performed.

Table 24 summarizes and compares the results from these two clinical studies.

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Table 24: Summary of Detection Times

Detection Time	Tachos DR - Atrial Tx ICD Mean (SE) / N	Tupos LV/ATx Mean (SE) / N	Difference
Individual Readings	2.27 (0.06) / 52	2.26 (0.06) / 71	0.01
By Patient	2.27 (0.07) / 26	2.24 (0.06) / 35	0.03

The analysis demonstrates that the average detection times of the Tupos LV/ATx are comparable to the detection times observed with the legally marketed Tachos DR - Atrial Tx ICD. Both devices utilize identical ventricular detection algorithms and only sense with the right ventricular lead. This clinical data demonstrates that the ventricular detection times are similar in both devices.

- The purpose of Secondary Endpoint 3 is to evaluate the percentage of ventricular pacing (thus, CRT) as demonstrated by the device diagnostics at required follow-ups. This data was based on diagnostic data stored by the Tupos LV/ATx.

Table 25 summarizes the percentage of ventricular pacing between follow-ups as shown by device diagnostics for patients in the study group.

Table 25: Percentage of Ventricular Pacing – 3-Month and 6-Month Follow-up

Percentage of Ventricular Pacing	Three-Month		Six-Month	
	Number of Patients	Percentage of Patients	Number of Patients	Percentage of Patients
<80%	9	7.4%	4	4.0%
81 – 85 %	4	3.3%	2	2.0%
86 – 90 %	13	10.7%	9	9.1%
91 – 95 %	19	15.7%	20	20.2%
96 – 100 %	76	62.8%	64	64.7%
Totals	121	100%	99	100%

The majority of the follow-ups (84.9%) show a percentage of ventricular pacing of 91% or more at Six-Months.

- The purpose of secondary endpoint 4 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 26 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.

Table 26: Six Minute Walk Distance

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 Secondary Endpoint 5 is to evaluate the improvement in the patient's NYHA classification. **Table 27** summarizes the average improvement in NYHA from Baseline to Six-Months for 140 patients that were able to complete both NYHA classification evaluations.

Table 27: Improvement in NYHA Classification at Six-Months from Baseline

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.

- The purpose of Secondary Endpoint 6 is to evaluate the rate of hospitalization, for CHF and for all other causes. The occurrence rate and reasons for hospitalization of the study group were compared to the control group. To be consistent with other large-scale clinical trials, clinical sites were instructed to report hospitalizations for CHF using the following definitions: 1) hospitalization for heart failure management, 2) outpatient visit in which IV inotropes or vasoactive infusion are administered continuously for at least 4 hours, or 3) emergency room (ER) visit of at least 12 hours duration in which intravenous heart failure medications including diuretics are administered.

Table 28 summarizes hospitalization, ER visits and outpatient visits for enrolled patients.

Table 28: Hospitalization, ER Visits and Outpatient Visits

Medical Visits	Study (N=128)	Control (N=65)
Hospital Admissions	CHF Related:	CHF Related:
Patients	20 (15.6%)	5 (7.7%)
Hospitalizations	28	9
	All causes:	All causes:
Patients	68 (53.1%)	29 (44.6%)
Hospitalizations	76	46
Emergency Room Visits	CHF Related:	CHF Related:
Patients	1 (0.8%)	0 (0.0%)
Visits	1	0
	All causes:	All causes:
Patients	13 (10.1%)	2 (3.1%)
Visits	16	2
Outpatient Visits	CHF Related:	CHF Related:
Patients	1 (0.8%)	0 (0.0%)
Visits	1	0
	All causes:	All causes:
Patients	5 (3.9%)	2 (3.1%)
Visits	5	2

A large percentage of All Cause hospitalizations can be attributed to pacing lead revisions, device infections, or other device-related interventions (e.g., pocket revision or device replacements for ERI or device recall). The CHF hospitalization rate for both the study and control groups is clinically acceptable considering the enrollment CHF status of the patients.

7. The purpose of Secondary Endpoint 7 is to evaluate the observation rate. Observations are defined as clinical events that do not require additional invasive intervention to resolve. For the study group, there were 210 observations in 104 patients with cumulative implant duration of 1240.4 months (101.9 patient years). 78.2% of the enrolled study patients have a reported observation. The rate of observations per patient-year is 2.06. For the control group, there were 81 observations in 44 patients with cumulative implant duration of 596.5 months (49.0 patient years). 65.7% of the enrolled control patients had a reported observation. The rate of observations per patient-year was 1.65.
8. The purpose of Secondary Endpoint 8 is to evaluate peak VO₂ as a measure of effectiveness of the Tupos LV/ATx system in providing CRT. The core lab was blinded to study randomization assignments during evaluation of the results of the cardiopulmonary exercise (CPX) testing in order to minimize the potential for bias. According to the protocol, to be included in the analysis, patients were required to attain a respiratory exchange ratio (RER) of ≥ 1 .

Table 29 provides a summary of peak VO₂ results for 42 patients with CPX testing completed at Baseline and the Six-Month follow-up and with an RER of ≥ 1 .

Table 29: Peak VO₂ Testing Results – Patients with RER ≥ 1

Results	Study	Control
Peak VO₂ (ml/kg/min)	N=32	N=10
	Baseline:	Baseline:
	Mean 13.46 ± 0.57	Mean 12.58 ± 0.75
	Range 6.9 to 21.1	Range 8.0 to 14.8
	Six-Month:	Six-Month:
	Mean 13.39 ± 0.53	Mean 12.89 ± 0.94
	Range 7.6 to 20.70	Range 7.0 to 17.2
	Difference:	Difference:
	Mean -0.06 ± 0.42	Mean 0.31 ± 0.67
Range -7.9 to 4.9	Range -2.7 to 4.6	

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.

Kronos LV-T OUS Clinical Study – HOME-CARE Observational study

The purpose of the HOME-CARE Observational Study is to demonstrate the safety of the CE-marked Kronos LV-T cardiac resynchronization defibrillator (CRT-D) in patients with congestive heart failure (CHF).

Methods

The multi-center, non-randomized observational study was designed to evaluate the safety of the Kronos LV-T through an analysis of the complication-free rate through three months.

The Home-CARE Observational Study Primary Endpoint was to evaluate complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT

system which includes the Kronos LV-T, the right atrial lead, the right ventricular ICD lead, and the left ventricular lead.

Inclusion Criteria

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

- Indication for Cardiac Resynchronization Therapy
- Sufficient GSM-network coverage in the patient's area
- Age greater than or equal to 18 years

Exclusion Criteria

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

- Permanent atrial fibrillation
- Myocardial infarction or unstable angina pectoris within the last 3 prior to enrollment
- Planned cardio-surgical intervention within 3 months after enrollment (e.g. PTCA, CABG, HTX)
- Acute myocarditis
- Life expectancy less than 6 months
- Pregnant or breast-feeding woman
- Drug or Alcohol abuse
- The patient is mentally or physically unable to take part in the observational study
- No signed declaration of consent for the patient

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 are implanted with the Kronos LV-T CRT-D. Evaluations at the One- and Three-Month follow-up include resting ECG, NYHA classification, medications, activation of Home Monitoring.

Summary of Clinical Results

The study involved 45 patients (37 males, 82.2%, and 8 females, 17.8%), with a mean age of 64 years (range: 36-79), a left ventricular ejection fraction of 26 % (range: 15-43), NYHA Class III (NHYA Class I (2.3%), Class II (11.4%), Class III (79.5%), Class IV (6.8%)) and QRS duration of 154 ms (range: 84-208). The mean implant duration was 4.5 months with a cumulative implant duration of 202 months. The patient follow-up compliance rate was 95.9% out of 221 required follow-ups.

Primary Endpoint

The safety of the Kronos LV-T was evaluated based on complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Kronos LV-T, the right atrial lead, the right ventricular ICD lead, and the left ventricular lead. 5 complications were seen in 3 patients with cumulative implant duration of 202 months (16.8 patient-years). 6.7% of the patients had a reported complication. The rate of complications per patient-year is 0.30.

The freedom from Kronos LV-T system-related complications is 93.3% with a two sided lower 95% confidence bound of 83.8%. The null hypothesis is rejected, and it is concluded that the complication-free rate is equivalent to 85% within 10%.

Corox OUS Clinical Study – OVID study

BIOTRONIK conducted a 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 and efficacy of the Corox OTW Steroid LV lead.

Methods

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 Corox OTW Steroid LV lead related 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.

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

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

Overall Results

The Corox OTW Steroid LV clinical evaluation included a total of 132 patients meeting indications for biventricular pacing. The coronary sinus was accessed in all patients, and of these, 121 were successfully implanted with the Corox OTW Steroid LV lead. The study population ranged in age from 34 to 84 and included 99 males (75%) and 33 females (25%).

- The cumulative implant duration is 1145 months with a mean duration of 9.6 months. Ninety-six (79%) of the patients have implant durations greater than 6 months.
- The implant success rate for the Corox OTW/Steroid LV lead was 91.7% overall.
- The Corox OTW/Steroid LV lead was implanted in combination with 8 different CRT-P and CRT-D devices marketed by 4 different manufacturers.
- The mean LV pacing threshold at implant was 0.97 volts and at 6-months was 0.92 volts.

- The mean R-wave at implant was 15 mV.
- The mean LV lead impedance at implant was 796 ohms and at 6-months was 593 ohms.
- There have been 44 adverse events (28 observations in 26 patients and 16 complications in 13 patients). There have been no unanticipated adverse device effects reported.
- There have been 12 patient deaths reported in the OVID study. The clinical investigators have determined that no deaths were related to the Corox OTW/Steroid LV lead.
- The overall follow-up compliance rate for the OVID study is 92.9%.

Primary Endpoint

132 patients were enrolled in the study, and the coronary sinus was accessed in all patients. Corox OTW Steroid LV leads were successfully placed in 121 patients, which corresponds to an implantation success rate of 91.7% (95%-confidence interval: 0.86 – 0.96). **Table 30** provides the Corox OTW Steroid implantation success rates within the clinical study.

Table 30: Corox OTW Steroid Implantation Success

Results	N	95% Confidence Interval
Coronary Sinus(CS) accessed	132 of 132 (100%)	0.97 to 1.0
Successful implantations	121 of 132 (91.7%)	0.86 to 0.96
Success rate when CS was accessed	121 of 132 (91.7%)	0.86 to 0.96

Corox OTW Steroid LV lead implantation was not successful in 11 of 132 (8.3%) patients enrolled into the study. Details for these unsuccessful implant procedures are described in **Table 31**.

Table 31: Reasons for Implant Failure of Corox OTW Steroid LV lead

Reason for Implant Failure of Corox OTW/Steroid LV lead	N
Inability to find a stable position	3 of 132 (2.3%)
Target position not reached	3 of 132 (2.3%)
Coronary vessels too small	2 of 132 (1.5%)
Lead dislodged while removing guide catheter	2 of 132 (1.5%)
Perforation of SVC with pneumothorax	1 of 132 (0.8%)
Total Implant Failures of LV lead	11 (8.3%)

Objective: The lower bound of the one-sided 95% confidence interval of the successful implantation rate of the BIOTRONIK Corox OTW Steroid LV lead will not be less than 67%. The success rate was defined as a proportion of patients who received the Corox OTW Steroid LV lead during implantation when adequate left ventricular stimulation by the Corox OTW Steroid LV lead was confirmed after having finished the implantation procedure.

Results: One hundred and thirty two patients were enrolled into the clinical study and a Corox OTW Steroid LV lead implant was attempted for each. One hundred and twenty one patients were successfully implanted. The rate of successful implant of the Corox OTW Steroid LV lead is 91.7% with a lower 95% confidence bound of 86%. The lower 95% confidence bound of the implant success rate exceeds the limit of 67% and therefore, the null hypothesis is rejected. These results demonstrate that the Corox OTW Steroid LV lead has an appropriate implant success rate.

Secondary Endpoints

Reported lead data reflect only the patients with successfully implanted LV leads. LV sensing measurements were performed at implant only because LV sensing cannot be measured through the pulse generators used in the study. These values were all clinically acceptable for LV leads, with an average R-wave amplitude of 15 ± 7 mV. Lead impedance values were collected and also were all clinically acceptable, with an average pacing impedance of 590 ± 136 Ohms at 3 months. **Table 32** provides a summary of the pacing thresholds at implant, one month and three months.

Table 32: Ventricular Pacing Thresholds – Corox OTW Steroid LV Lead

Pacing Threshold	Results (Volts @ 0.50 ms)
Implant	
Number of Tests	114
Mean \pm SD	0.98 ± 0.8
Range	0.2 - 4.0
One-month Follow-up	
Number of Tests	72
Mean \pm SD	0.94 ± 0.7
Range	0.3 - 3.9
Three-month Follow-up	
Number of Tests	71
Mean \pm SD	0.89 ± 0.7
Range	0.2 - 3.8

There were 8 LV lead related complications (including the pocket infection which could not be ruled out as related) in 121 patients successfully implanted with the Corox OTW/Steroid LV lead through six months follow-up. The freedom from Corox OTW/Steroid LV lead-related complications is 92.9% with a two-sided lower 95% confidence bound of 86.4%.

The complication and observation adverse event rates for the Corox OTW Steroid LV lead were 5.3% and 11.4%, respectively during the clinical study. Both these rates are acceptable for prospective biventricular LV pacing lead trials. Furthermore, the overall complication and observation adverse event rates for the patients were 9.8% and 19.7% respectively. This data further characterizes the overall safety performance of the Corox OTW Steroid LV lead.

XI. CONCLUSIONS DRAWN FROM STUDIES

The clinical study results support the approval of the Tupos LV/ATx and Kronos LV-T CRT-D devices as well as the Corox OTW Steroid lead.

- The IDE Clinical study (OPTION LV/ATx) demonstrated that the safety and effectiveness of the Tupos LV/ATx CRT-ICD device is comparable to that of similar legally marketed CRT-D devices. Although the study missed its primary safety endpoint, additional post hoc analyses were conducted to reassure that the safety profile of the device is comparable to other legally marketed CRT-D devices.

- The Kronos LV Clinical study (HOME-CARE) characterized the safety of the Kronos LV-T CRT-D device. Additionally, the study showed appropriate Home Monitoring transmission and utility of the Home Monitoring data. Because the Tupos LV/ATx and the Kronos LV-T have identical CRT therapy and identical ventricular ICD therapy, the effectiveness profiles of the two devices are expected to be similar.
- The Corox Clinical study (OVID) demonstrated the safety and effectiveness of the Corox OTW Steroid LV lead.

XII. PANEL RECOMMENDATION

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.

XIII. CDRH DECISION

FDA issued an approval order for P050023 on **AUG 10 2006**

Conditions of Approval included a postapproval study for the Tupos LV/AT/x CRT-D. The purpose of the study is to collect long term survival data on approximately 100 patients previously enrolled in the clinical investigation of the Tupos CRT-D. The patients will be followed every 6 months for a period of 3 years. The postapproval study will report LV capture threshold and specific LV related complications such as diaphragmatic stimulation and loss of left ventricular capture.

In addition, a postapproval study for the Corox lead will be conducted. The purpose of the study is to confirm the long term safety and effectiveness of the Corox Lead used in conjunction with a Biotronik CRT-D in at least 250 patients followed for 3 years. The postapproval study will provide data to permit a characterization of any LV lead failures contributing to patients losing CRT therapy.

The applicant's manufacturing facility was inspected and determined to be in compliance with the Quality System Regulation (21 CFR Part 820).

XIV. APPROVAL SPECIFICATIONS

Directions for Use:	See labeling
Hazards to Health from Use of the Device:	See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.
Post-approval Requirements, Restrictions:	See approval order