SUMMARY OF SAFETY AND EFFECTIVENESS (SSED)

I. GENERAL INFORMATION

Device Generic Name: Implantable Cardioverter Defibrillator with Cardiac Resynchronization Therapy
Steroid-eluting endocardial left ventricular pacing lead
Programmer

Device Trade Name: Ovatio CRT-D Model 6750
Situs OTW Left Ventricular Over-the-Wire Lead Model UW28D
Situs OTW Stylet kit
Elaview 1.34 UG2 programming software

Applicant's Name and Address:
ELA Medical, Inc.
2950 Xenium Lane North, Suite 120
Plymouth, MN 55441

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P060027

Date of FDA Notice of Approval: May 15, 2008

Expedited: Not applicable

II. INDICATIONS FOR USE

Ovatio CRT-D is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening arrhythmias. The device is also indicated for the reduction of heart failure symptoms in medically optimized NYHA Functional Class III and IV patients with left ventricular ejection fraction of 35% or less, and a QRS duration of 150 ms or longer.

Situs OTW is designed to pace the left ventricle through a coronary vein. It is intended to be used in conjunction with ELA Medical cardiac resynchronization therapy pulse generators.

III. CONTRAINDICATIONS

Ovatio CRT-D is contraindicated in:

- Patients whose ventricular tachyarrhythmias may have transient or reversible causes such as: acute myocardial infarction, digitalis intoxication, drowning,

11

electrocution, electrolyte imbalance, hypoxia, sepsis, or unstable ischemic episodes.

- Patients with incessant tachyarrhythmia.
- Patients who already have an implanted pacemaker.
- Patients whose primary disorder is bradyarrhythmia or atrial tachyarrhythmias.
- Dual-chamber and single-chamber atrial pacing is contraindicated in patients with chronic refractory atrial tachyarrhythmias.

Situs OTW is contraindicated in patients for whom a single dose (1 mg) of dexamethasone sodium phosphate may be contraindicated.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Ovatio CRT-D, Situs OTW, Situs OTW stylet kit, and Elaview 1.34 UG2 programming software labeling.

V. DEVICE DESCRIPTION

Ovatio CRT-D implantable cardioverter defibrillator description

Ovatio CRT-D is a rate responsive implantable cardioverter defibrillator with biventricular pacing for cardiac resynchronization therapy (CRT). The device has five ports: two DF-1 and three IS-1 ports.

Ovatio CRT-D is based on the marketed Ovatio DR ICD (P980049/S20). Both devices have the same circuitry and hybrids. The tachyarrhythmia detection and therapy and bradycardia pacing parameters are identical to those in the marketed Ovatio DR. The only difference between Ovatio CRT-D and the Ovatio DR is its ability to pace the left ventricle, which is accomplished through software and a third IS-1 port. Ovatio CRT-D has a maximum stored energy of 34 J.

Ovatio CRT-D is programmed with the Orchestra programmer using Elaview 1.34 UG2 or higher programming software.

Situs OTW lead description

The Situs OTW left ventricular lead model UW28D is an IS-1 compliant, unipolar, silicone-insulated, steroid eluting pacing lead with a vitreous carbon electrode. The distal portion of the lead has a silicone molded helix. A polyurethane sheath is intended to provide abrasion resistance.

Situs OTW stylet kit description

The Situs OTW stylet kit contains accessories used for implanting the Situs OTW. The kit contains two straight stylets, one flat-tipped (or screwdriver) stylet, one anchoring sleeve, one vein lifter and a funnel. All of the items, except the screwdriver stylet, are identical to those included in the Situs package.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of heart failure and sudden cardiac death: pharmacological therapy, heart transplantation, other marketed biventricular ICDs or other surgical procedures. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Ovatio CRT-D, Situs OTW, and Situs OTW stylet kit are currently distributed in the European Community. None of the devices have been withdrawn from the market in any country for any reason related to safety and effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

Potential adverse events Ovatio CRT-D

- Acceleration of arrhythmia (caused by device)
- Air embolism
- Bleeding
- Chronic nerve damage
- Erosion
- Excessive fibrotic tissue growth
- Extrusion
- Fluid accumulation
- Formation of hematoma or cysts
- Inappropriate shocks
- Infection
- Keloid formation
- Lead abrasion and discontinuity
- Lead migration/dislodgment
- Myocardial damage
- Pneumothorax
- Shunting current or insulating myocardium during defibrillation with internal or external paddles
- Potential mortality due to inability to defibrillate or pace
- Thromboemboli
- Venous occlusion
- Venous or cardiac perforation

Patients susceptible to frequent shocks despite medical management may develop psychological intolerance to an ICD system that may include the following:

- Dependency
- Depression
- Fear of premature battery depletion
- Fear of shocking while conscious
- Fear that shocking capability may be lost
- Imagined shocking (phantom shock).

Potential adverse events Situs OTW left ventricular lead

- Air embolism
- Allergic reaction
- Arrhythmia at implant
- Bleeding
- Cardiac or venous perforation
- Cardiac tamponade
- Coronary sinus or venous trauma
- Death
- Extracardiac stimulation
- Infection
- Lead conductor fracture
- Lead dislodgement

IX. SUMMARY OF PRECLINICAL STUDIES

Ovatio CRT ICD

Pre-clinical testing of the Ovatio CRT ICD is summarized in the table below. Ovatio CRT-D uses all of the same components, except for the connector, as the marketed Ovatio DR ICD (P980049/S20). The Ovatio DR ICD uses some components from previously marketed devices. Testing was performed on the components, finished device, and software. A result of "Pass" indicates that the component, device, or software met required pass/fail criteria.

COMPONENT DEVICE TESTING		
Bench Test Performed	**Sample Size***	**Test Result (Pass/Fail)**
Capacitor qualification: dimensional inspection, electrical measurements, terminal strength, thermal shocks, pull testing, burn-in	2-140	Pass
Shielded inductor: life test, electrical measurements, burn-in under bias, visual inspection, dimensional inspection	5	Pass
Transformer: incoming inspection, high temperature storage, burn-in under bias, visual inspection, dimensional inspection	5	Pass

* When a range of values is given, the exact sample size is determined based on the requirements for a specific component or a specific test.

COMPONENT DEVICE TESTING		
Bench Test Performed	**Sample Size***	**Test Result (Pass/Fail)**
Shock capacitors: extended charge/discharge, surge voltage and current, short circuit, thermal shock, high temperature storage, low temperature storage, high pressure, low pressure, mechanical shock, mechanical vibration, reverse charge, visual inspection, hermeticity, dimensional inspection, electrical measurements	10	Pass
Flex circuits: dimensional inspection, bending stress, thermal stress, soldering, detachment	1-5	Pass
Low-power module with integrated circuits and electronic components: probe card test, visual inspection, heating, thermal cycling, electrical testing, humid heat under bias, burn-in	5-6	Pass
PROT6 module: probe card test, visual inspection, heating, thermal cycling, burn-in under bias, heating, electrical measurements	5	Pass
High-voltage module: probe card test, visual inspection, heating, thermal cycling, electrical measurements, humid heat under bias, burn-in under bias	5	Pass
Connector: visual inspection, dimensional inspection, insertion/extraction of gages, low voltage electrical isolation, electrical resistance of the circuits, variation of resistance, maximum insertion force of competitor leads, mechanical stresses, connector-case attachment strength, bending of the connector-case assembly, angular stress on the IS-1/DF-1 cavity, low voltage electrical isolation after immersion, setscrew cover punching, high voltage electrical isolation	1-4	Pass
Feedthrough: visual inspection, hermeticity, electrical characterization, thermal shocks, mechanical stresses, burn-in, dielectric breakdown, shocks	3-6	Pass
Batteries: high pressure, low pressure, mechanical shock, vibration, high temperature exposure, low temperature exposure, temperature shock, storage temperature, short circuit, short circuit in series, forced overdischarge, temperature shock, varying orientation pulse test, accelerated pulse test, slow dent puncture, crushing, charge, end-of-life discharge	4-23	Pass
Antenna: visual inspection, high temperature storage, electrical measurements, stress testing, cleaning	10	Pass
Crystal: visual inspection, dimensional inspection, electrical measurements, burn-in, thermal shocks, humid heat, vibration, mechanical shocks, soldering, pull testing, hermeticity	12-296	Pass

SOFTWARE DEVICE TESTING	
Bench Test Performed	**Test Result (Pass/Fail)**
Device software testing	Pass
Programmer software testing	Pass

FINISHED DEVICE TESTING			
Bench Test Performed	**Source**	**Minimum Sample Size**	**Test Result (Pass/Fail)**
Measurement of Pulse Generator electrical characteristics	EN 45502-2-2.6.1†	1	Pass
Shocks and ATP shipped OFF	EN 45502-2-2.7.3	1	Pass
Shock, compression, vibration, temperature	EN 45502-1.10.1‡	6	Pass
Humidity during storage	EN 45502-1.10.2	1	Pass
Markings indelible on sales package	EN 45502-1.10.3	1	Pass
Microbiological impermeability	EN 45502-1.12.x	6	Pass
Markings indelible on sterile package	EN 45502-1.12.3	1	Pass
Markings indelible on implant	EN 45502-1.13.1	1	Pass
Radio-opaque identification	EN 45502-1.13.3	6	Pass
Sterilization Validation	EN 45502-1.14.1 / EN 550§ / EN 556**	According to Standard	Pass
Sterility Test	EN 45502-1.14.1 USP <71>†† / ISO 11737-2‡‡	6	Pass
Bioburden	ISO 11797-1 NF EN 1174§§	6	Pass
Endotoxins	LAL test	6	Pass
Particulates	EN 45502-2-2.14.2	6	Pass
Biocompatibility	EN 45502-1.14.3 / ISO 10993-x***	According to Standard	Pass
EtO residuals	ISO 10993-7	According to Standard	Pass
DC leakage	EN 45502-2-2.16.2	1	Pass
AC leakage	EN 45502-2-2 16.4	1	Pass
DC leakage, charged	EN 45502-2-2 16.5	1	Pass
Protect patient from heat	EN 45502-2-2.17.1	6	Pass

† EN 45502-2-2: Active Implantable Medical Devices Part 2-2: Particular Requirements for Active Implantable Medical Devices Intended to Treat Tachyarrhythmia (Includes Implantable Defibrillators)

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

§ Sterilization of Medical Devices - Validation and Routine Control of Ethylene Oxide Sterilization

** Sterilization of Medical Devices - Requirements for Medical Devices to Be Designated "Sterile" - Part 1: Requirements for Terminally Sterilized Medical Devices

†† Bacteriostasis and Fungistasis test

‡‡ Sterilization of medical devices -- Microbiological methods -- Part 2: Tests of sterility performed in the validation of a sterilization process

§§ Sterilization of medical devices - Estimation of the population of micro-organisms on product.

*** ISO 10993 - Biological Evaluation of Medical Devices Package

FINISHED DEVICE TESTING			
Bench Test Performed	**Source**	**Minimum Sample Size**	**Test Result (Pass/Fail)**
Battery ERI and EOL	EN 45502-2-2.19.2	11	Pass
Protect implant from its own defibrillation	EN 45502-2-2.19.5†	1	Pass
Protect implant from external defibrillation	EN 45502-2-2.20.2	1	Pass
Protect implant from diathermy	EN 45502-1.21.1 ‡	6	Pass
Protect implant from HF surgical exposure	EN 45502-2-2.21.2	6	Pass
Protect implant from ultrasound	EN 45502-1.22.1	6	Pass
Protect implant from vibration	EN 45502-2-2.23.2	6	Pass
Protect implant from mechanical shock	EN 45502-2-2 23.7	6	Pass
Protect implant from pressure changes	EN 45502-1.25	6	Pass
Protect implant from temperature changes	EN 45502-1.26.2	6	Pass
Protect implant from EMI permanent damage	EN 45502-2-2 27.1	3	Pass
Protect patient from EMI induced current	EN 45502-2-2 27.2	According to Standard	Pass
Temporary response to EMI modulated fields	EN 45502-2-2 27.3	According to Standard	Pass
Temporary response to EMI continuous fields	EN 45502-2-2 27.4	According to Standard	Pass
Temporary response to EMI burst-modulated	EN 45502-2-2 27.5	According to Standard	Pass
Protect patient from EMI radiated interference	ANSI/AAMI PC69†††	According to Standard	Pass
Temporary response to 1 mT magnetic field	EN 45502-2-2 27.6	According to Standard	Pass
Permanent response to 10 mT magnetic field	EN 45502-2-2 27.7	According to Standard	Pass
Permanent response to AC magnetic field	EN 45502-2-2 27.8	According to Standard	Pass
Insertion: connector cavity GO gauge	FDA lead guidance 8‡‡‡ / ISO 5841-3.4.3.2.1§§§	6	Pass
Maximum insertion force: gauge pin	FDA lead guidance 8 / ISO 5841-3.4.3.2.2	6	Pass

††† ANSI/AAMI Active implantable medical devices—Electromagnetic compatibility— EMC test protocols for implantable cardiac pacemakers and implantable cardioverter defibrillators

‡‡‡ 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

§§§ ISO 5841-3 - Implants for surgery -- Cardiac pacemakers -- Part 3: Low-profile connectors (IS-1) for implantable pacemakers

17

FINISHED DEVICE TESTING			
Bench Test Performed	**Source**	**Minimum Sample Size**	**Test Result (Pass/Fail)**
Insertion and withdrawal forces	FDA lead guidance 8‡‡‡ / ISO 11318.4.3.2.1§§§	6	Pass
Current-carrying requirement	FDA lead guidance 8 / ISO 11318.4.3.2.2	6	Pass

Ovatio CRT-D biocompatibility

All materials used in Ovatio CRT-D are currently used in marketed ELA Medical pulse generators for which biocompatibility has been previously demonstrated. Specifically, the tissue contacting materials that are used in the pulse generator are identical to those used in Ovatio DR Model 6550 ICD which was approved via P980049/S20 on April 28, 2006.

Sterilization, packaging, and shelf life of Ovatio CRT-D

The sterilization process for Ovatio CRT-D is identical to that for the marketed Ovatio DR. Routine validation is performed according to the company's approved sterilization validation protocol.

The packaging process and packaging materials for Ovatio CRT-D are identical to that for the marketed Ovatio DR ICD (P980049/S20).

Based on battery capacity testing and longevity projections, the shelf life for Ovatio CRT-D has been established at 12 months. This is the same as that for the Ovatio DR ICD (P980049/S20).

Situs OTW left ventricular lead

The table below summarizes pre-clinical testing of the Situs OTW left ventricular lead. A result of "Pass" indicates that the component, device, or software met required pass/fail criteria.

Bench Test Performed	**Source**	**Minimum Sample Size**	**Test Result (Pass/Fail)**
Measurement of lead electrical characteristics	EN 45502-2-1.6.2 †	1	Pass
Shock, compression, vibration, temperature	EN 45502-1.10.1 ‡	6	Pass
Humidity during storage	EN 45502-1.10.2	1	Pass
Markings indelible on sales package	EN 45502-1.10.3	1	Pass
Microbiological impermeability	EN 45502-1.12.x	1	Pass
Markings indelible on sterile package	EN 45502-1.12.3	1	Pass
Sterilization Validation (sample size from standard)	EN 45502-1.14.1 / EN 550§ / EN 556 **	According to Standard	Pass
Sterility Test	EN 45502-1.14.1 / USP <71>†† ISO 11737-2 ‡‡/	6	Pass
Particulates	EN 45502-2-1.14.2	6	Pass
Biocompatibility (sample size from standard)	EN 45502-1.14.3 / ISO 10993-x***	According to Standard	Pass
Ethylene Oxyde Degassing Curve	EN 45502-1.14.3 / ISO 10993-7 (Ethylene Oxyde Residuals)	According to Standard	Pass

Bench Test Performed	Source	Minimum Sample Size	Test Result (Pass/Fail)
Ethylene Chlorhydrine Degassing Curve	EN 45502-1.14.3‡ / ISO 10993-7 (Ethylene Chlorhydrine Residuals) ***	According to Standard	Pass
Aging of implant	EN 45502-1.19.1	11	Pass
Protect implant from tensile forces	EN 45502-2-1.23.3†	6	Pass
Protect implant from flexion, leads, body	EN 45502-2-1.23.5 test 1	11	Pass
Protect implant from flexion, leads, connector	EN 45502-2-1.23.5 test 2	11	Pass
Protect implant from stiffness gradients, leads, body	EN 45502-2-1.23.5 test 2 (Previous Edition)	11	Pass
Protect implant from temperature changes	EN 45502-1.26.2 / FDA lead guidance III.C-0‡‡‡	6	Pass
Bioburden	ISO 11737 NF EN 1174§§	6	Pass
Endotoxins	LAL test	6	Pass
Lead electrical continuity and DC resistance	FDA lead guidance III.C-1	1	Pass
Lead leakage current (after soaking, before drying)	FDA lead guidance III.C-2	11	Pass
Lead leakage current (after soaking, before drying)	Derived from FDA lead guidance III.C-2	6	Pass
Lead bond strength, pull test on entire lead	FDA lead guidance III.C-3	6	Pass
Lead leak proof	FDA lead guidance III.C-4	6	Pass
Lead corrosion resistance	FDA lead guidance III.C-5	11	Pass
Lead stylet insertion and removal	FDA lead guidance III.C-6	6	Pass
Lead distal fatigue testing (400 M cycles)	FDA lead guidance III.C-7	11	Pass
Dimensions	FDA lead guidance III.C-8 / ISO 5841-3.4.2.1.2	6	Pass
Electrical continuity and function	FDA lead guidance III.C-8 / ISO 5841-3.4.2.1.3	6	Pass
Maximum insertion and withdrawal force	FDA lead guidance III.C-8 / ISO 5841-3.4.2.2.1	6	Pass
Electrical impedance	FDA lead guidance III.C-8 / ISO 5841-3.4.2.2.2	6	Pass
Deformation due to set-screw forces	FDA lead guidance III.C-8 / ISO 5841-3.4.2.2.3§§§	6	Pass
Effect of ring set screw	FDA lead guidance III.C-8 / ISO 5841-3.4.2.2.4	6	Pass
Lead anchoring sleeve performance	FDA lead guidance III.C-9	6	Pass
Lead tip pressure	FDA lead guidance III.C-10	NA	NA: the lead lodges in the vein with a large-surface-area silicone helix, rather than with tip pressure
Lead helix extension, retraction, and seal	FDA lead guidance III.C-11	NA	NA: no helix mecanism
Lead in vitro steroid elution rate	FDA lead guidance III.C-12	6	Pass
Lead shelf life of steroid	FDA lead guidance III.C-13	6	Pass
Lead steroid drug/matrix swelling	FDA lead guidance III.C-14	6	Pass
Lead traction-torsion	ELA Internal Reqt1	6	Pass
Torque measurement with screwdriver stylet	ELA Internal Reqt2	1	Pass

Bench Test Performed	Source	Minimum Sample Size	Test Result (Pass/Fail)
Traction of the tip assembly	ELA Internal Reqt3	1	Pass
Traction to rupture after 15-day at 100degC immersion	ELA Internal Reqt4	6	Pass
Traction to rupture after 30-day at 100degC immersion	ELA Internal Reqt5	6	Pass
Lead insertion into an introducer	ELA Internal Reqt6	6	Pass

Abrasion resistance of the Situs OTW left ventricular lead

The Situs lead was evaluated for abrasion resistance under simulated use conditions. Based on these results, the lead is expected to withstand 50.25 years of use. A three-month animal implant study confirmed the simulated results.

Biocompatibility of the Situs OTW left ventricular lead

The steroid collar, silicone insulation, stainless steel pin, and vitreous carbon electrode are all materials that are identical to those in the approved Stelid II, Stelix, and Stelix II endocardial pacing leads (P020030). The only new material in the Situs lead is the polyurethane sleeve. Biocompatibility testing was performed according to ISO 10993 and all tests were passed.

Sterilization, packaging, and shelf-life of Situs OTW left ventricular lead

The sterilization and packaging process of the Situs lead are identical to those used for the company's marketed Stelid II, Stelix, and Stelix II leads. Verification testing including sterility, bioburden, sterilization residues, LAL, and particulate contamination, was performed.

The packaging and packaging process used for the Situs lead is identical to the marketed Stelid II, Stelix, and Stelix II leads. Tests on the packaging for the marketed leads are applicable to the Situs OTW left ventricular lead.

Based on the above, the Situs OTW shelf-life has been established at 3 years, which is identical to that of the Stelid II, Stelix, and Stelix II leads.

Situs OTW stylet kit

Testing of the items included in the stylet kit was performed with the Situs OTW lead. Additional bioburden and LAL tests were performed on the stylet kit. All tests passed. The shelf-life for this kit has been established at 2 years, which is the same as that for other marketed lead accessories having the same types of materials and packaging.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of its cardiac resynchronization system, with ELA Medical CRT-D, commercially available right atrial and ventricular leads, and a Situs UW28D left ventricular lead. Patients were ICD-indicated, New York Heart Association (NYHA)

class III or IV congestive heart failure patients who do not have pacing indications, included in the US under IDE # G030019, as well as in France, Germany, Italy, Poland and UK .

A. Study Design

Subjects were treated between December 17, 2003, and May 01, 2006. The database for this PMA reflects data collected through September 08, 2006. 210 patients consented to participate in the study, 196 patients were enrolled, and 182 patients were implanted. 177 patients were randomized, 114 to the treatment group and 63 to the control group. There were 27 investigational sites.

The study was an international, multi-center, prospective, randomized, double-blinded, parallel two-arm clinical trial with a six-month randomized treatment period. The treatment arm was programmed for CRT therapy. The control arm was not programmed with CRT therapy. Both arms were implanted with the study device.

Frequentist statistical analysis was employed. Sample sizes were calculated prospectively based on prior studies of similar therapies, with an alpha of 5 % and a beta of 20 %. Disjoint one-sided null and alternate hypotheses were defined quantitatively and prospectively for primary safety and effectiveness endpoints. Statistical analyses assumed a T-distribution for calculating p-values. Kaplan-Meyer actuarial survival tables were also presented. The table below summarizes primary objectives and prospectively-determined minimum sample sizes:

Objective	Required sample size
CRT effectiveness composite (Peak V02, LHFQ)	132
System complication free rate	61
LV lead implant success rate	93
Chronic LV lead pacing threshold	7
Chronic biventricular impedance	2
LV lead-related complication free rate	110

A central core laboratory analyzed all ventilatory gas exchange data collected during the study. This core laboratory was blinded. A second central core laboratory analyzed all echocardiographic data. Because of electrocardiograms collected along with these data, this second core laboratory could not be blinded.

The control group was placebo. After implant, patients were randomized following a 2:1 ratio, with two patients receiving cardiac resynchronization therapy (CRT) for every one patient that did not receive pacing (control group). In control patients, the device was programmed to VVI mode with a basic rate of 30 beats per minute (bpm) to eliminate pacing virtually. Any pacing that did occur was limited to the right ventricle. CRT patients' devices were programmed

to DDD mode with a basic rate of 30 bpm, a short AV delay to promote atrial-synchronous biventricular pacing, and with BiV pacing enabled with an optimal delay between RV and LV pacing (VV delay). After the six-month randomized treatment period, all patients' devices might be programmed to provide biventricular pacing at the investigators' discretion. Throughout the study, ICD therapy was enabled for all patients.

1. Clinical Inclusion and Exclusion Criteria

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

   a. Accepted indication for ICD implant.
   b. Severe heart failure (NYHA Class III or IV) at the time of enrollment.
   c. If the patient has a pre-existing ICD, the patient must be on a stable, optimal (as determined by the enrolling physician) medical regimen
   d. Sinus rhythm with spontaneous QRS duration ≥ 150 ms or, a QRS duration ≥ 130 ms with an interventricular mechanical delay (IVMD) ≥ 40 ms.
   e. Left-ventricular ejection fraction (LVEF) of 35 % or less

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

   a. Any generally accepted indication for standard cardiac pacing, or any contraindication for standard cardiac pacing or ICD therapy.
   b. Hypertrophic or obstructive cardiomyopathy, Acute myocarditis,,unstable coronary symptoms, recent cardiac revascularization or coronary angioplasty.
   c. Correctable valvular disease that is the primary cause of heart failure or mechanical tricuspid valve.
   d. Receiving continuous IV infusion of positive inotropic therapy or intermittent therapy (IV infusion) more than twice per week

2. Follow-up Schedule

All subjects were scheduled to return for follow-up examinations within the following time windows:

Visit	Earliest	Latest
Enrollment	--	--
Pre-implant baseline	0 days post enrollment	14 days post enrollment
Implant	0 days post pre-implant baseline	7 days post pre-implant baseline
Pre-discharge	0 days post implant	Prior to CPX familiarization
CPX familiarization test	0 days post enrollment	24 hours prior to CPX baseline
CPX baseline	2 days post implant	14 days post implant
Randomization	2 days post implant (and post CPX baseline)	14 days post implant
1-month follow-up	23 days post randomization	37 days post randomization
3-month follow-up	77 days post randomization	105 days post randomization
6-month follow-up	160 days post randomization	197 days post randomization
9-month follow-up	240 days post randomization	300 days post-randomization
Recurring follow-ups	Every 6 months (± 30 days) after the 6-month follow-up	

No subgroup population received additional types of evaluations.

Preoperatively, patients provided informed consent, were assessed for compliance with enrolment criteria and for current medications and medical history. Enrolled patients completed the Minnesota Living with Heart Failure Questionnaire (LHFQ) and performed symptom-limited cardiopulmonary exercise testing (CPX), for baseline data.

Postoperatively, the objective parameters measured during the study included:

Visit name	Purpose	Tests or assessments performed
Implant	Implant CRT-D system and verify lead and ICD function.	Lead measurements LVAS and Situs OTW handling assessments
Pre-discharge	Verify device function	Lead measurements ATP therapy history
CPX familiarization	Familiarize patients with procedure and equipment for cardiopulmonary exercise testing.	
Baseline CPX	Collect baseline CPX data	CPX test
Randomization	Calculate optimal AV and VV delays, assign patient to randomized treatment group.	NYHA Vitals Lead measurements ATP therapy history
One-month	Device and medical follow-up visit.	NYHA Vitals Lead measurements ATP therapy history
Three-month	Device and medical follow-up visit.	NYHA Vitals Lead measurements ATP therapy history QOL
Six-month	Device and medical follow-up visit. Collect six-month values.	NYHA Vitals Lead measurements ATP therapy history QOL Echocardiography CPX test
Nine-month	Device and medical follow-up visit for control patients to assess function of biventricular pacing	NYHA Vitals Lead measurements ATP therapy history
Twelve-month and later	Device and medical follow-up visit.	NYHA Vitals Lead measurements ATP therapy history

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

3. Clinical Endpoints

With regards to safety, the following endpoints were evaluated:

Objective	Category
System complication-free rate ≥ 67 % at 6 months	System safety
Situs UW28D complication-free rate ≥ 75 % at 6 months	LV lead safety

With regards to effectiveness:

Objective	Category
Composite endpoint combining %Peak VO_2 improvement (increase) and %Minnesota Living with Heart Failure® Questionnaire score improvement (decrease) 6 months after randomization greater for CRT patients than for control patients	CRT effectiveness
Situs UW28D LV lead implant success rate ≥ 75 %	LV lead effectiveness
Mean chronic Situs UW28D LV lead pacing threshold ≤ 3.25 V	LV lead effectiveness
Mean chronic biventricular pacing impedance with Situs UW28D ≥ 100 Ohms	LV lead effectiveness

With regard to success/failure criteria, the study was to be deemed successful if all primary safety and effectiveness endpoints listed above were demonstrated at the requisite alpha level (5 %).

B. Accountability of PMA Cohort

At the time of database lock, of 197 subjects enrolled in PMA study, 77 % (152) subjects are available for analysis at the completion of the study, the six month post-operative visit. Please refer to the accountability summary table below. Intent-to-treat patients were defined by the protocol as "patients who leave the study prior to implant or in whom the system cannot be placed." Only patients who were enrolled in the study and not successfully implanted with an ELA Medical CRT-D system are intent-to-treat patients. There were 15 intent-to-treat patients in the study.

Consented to participate	**210**	
Did not meet enrollment criteria	-10	
Lost to follow-up	-2	
Died before enrollment	-1	
Enrolled	**197**	
Adverse event causing withdrawal from study	-3	
Re-evaluation of enrollment criteria	-1	
Patient withdrew informed consent	-1	
Physician unwilling to randomize	-1	
Lost to follow-up	-1	
Unable to implant	-8	
Implanted	**182**	
Unable to randomize (no LV lead implanted)	-1	
Died before randomization	-4	
Presented for randomization	**177**	
Randomization group (Test = CRT on, Control = off)	Test	Control
Randomized	**114**	**63**
Patients still in randomized treatment period	-8	-6
Withdrawn before six-month visit	-5	-1
Died before six-month visit	-1	-4
Presented for six-month visit	**100**	**52**

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a CRT-D study performed in the US.

Data were collected on age (first table below) and gender (22% women, 78% men) but not on race.

All patients	CRT Off	CRT On	Not randomized	European Patients	U.S. Patients	Small sites****	Large sites
65.07	66.22	64.46	64.9	64.49	66.27	64.9	65.16
(10.66)	(11.13)	(9.85)	(13.56)	(10.04)	(11.83)	(10.94)	(10.55)
N = 197	N = 63	N = 114	N = 20	N = 133	N = 64	N = 68	N = 129

The table below shows the distribution of baseline parameters for clinically relevant variables important for understanding the treatment effect, and other population characteristics that have important implications for the extent to which the PMA study results can be generalized. The table below lists the average (± standard deviation) value and number of enrolled patients contributing for each variable.

Variable	All patients	CRT Off	CRT On	Not randomized	European Patients	U.S. Patients	Small sites	Large sites
Age	65.07 (10.66) N = 197	66.22 (11.13) N = 63	64.46 (9.85) N = 114	64.9 (13.56) N = 20	64.49 (10.04) N = 133	66.27 (11.83) N = 64	64.9 (10.94) N = 68	65.16 (10.55) N = 129
QRS duration	164.49 (20.21) N = 197	165.03 (21.91) N = 63	162.63 (17.47) N = 114	173.4 (27) N = 20	166.24 (21.86) N = 133	160.86 (15.82) N = 64	169.09 (21.84) N = 68	162.07 (18.94) N = 129
LVEF	24.22 (6.71) N = 197	24.67 (6.82) N = 63	24.36 (6.33) N = 114	22 (8.27) N = 20	25.12 (6.7) N = 133	22.34 (6.37) N = 64	23.68 (6.8) N = 68	24.5 (6.67) N = 129
LVEDD	68.57 (9.34) N = 155	69.09 (9.14) N = 52	67.76 (8.43) N = 86	71.09 (13.59) N = 17	69.69 (9.27) N = 100	66.54 (9.22) N = 55	69.28 (9.82) N = 57	68.16 (9.07) N = 98
Baseline MN LHFQ score	51.82 (22.04) N = 195	47.37 (19.73) N = 63	52.32 (22.62) N = 112	63.02 (22.37) N = 20	53.77 (20.25) N = 131	47.82 (25.01) N = 64	47.4 (22.03) N = 68	54.18 (21.77) N = 127
Baseline peak VO_2	12.03 (4.03) N = 170	12.57 (4.35) N = 59	11.74 (3.83) N = 111		12.06 (4.38) N = 117	11.97 (3.15) N = 53	12.28 (4.32) N = 64	11.88 (3.85) N = 106

**** The average number of patients per site is 7.8. Therefore, small sites are those with 7 or less patients and large sites are those with 8 or more patients.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the control and test cohorts of patients available for the six month evaluation as specified below. For both primary objectives, the null hypothesis was rejected at the requisite level of significance:

Parameter	Definition	Result
Π	Six-month system complication-free Kaplan-Meier estimate	
Ho	$\pi < 67\ \%$	
Ha	$\pi \geq 67\ \%$	
	Number of patients contributing to complication free rate	190
	Six-month complication-free Kaplan-Meier estimate	89.5%
$S_{0.95}$	One-sided, 95% lower confidence level of Kaplan-Meier estimate	84.1%

Parameter	Definition	Result
Π	Six-month LV-lead complication-free Kaplan-Meier estimate	
Ho	$\pi < 75\%$	
Ha	$\pi \geq 75\%$	
	Number of patients contributing to complication free rate	152
	Six-month complication-free Kaplan-Meier estimate	94.8%
S0.95	One-sided, 95% lower confidence level of Kaplan-Meier estimate	90.0 %

Adverse effects that occurred in the PMA clinical study:

The clinical study presented in this PMA was a prospective, multi-center, randomized, clinical trial to evaluate the safety and effectiveness of ELA's cardiac resynchronization therapy (CRT) system in NYHA Class III or IV heart failure patients that were indicated for an ICD. The tables below summarize the adverse events observed in the study. The first table is for the CRT-D System and the second one is for the Situs lead. No deaths were related to the CRT-D system.

Event	Number of patients	Percent of patients (%)	Number of events	Events per 100 device months
Deaths not system related	16	8.4	16	0.8
Complications related to the system	28	14.7	35	2.1
Complications related to the implant procedure	18	9.5	21	1.3
Observations related to the system	23	12.1	27	1.7
Observations related to the implant procedure	24	12.6	28	1.7
Serious adverse events not related to the system	85	44.7	176	10.8
Not serious adverse events not related to the system	58	30.5	121	7.4

Event	Number of patients	Percent of patients (%)	Number of events	Events per 100 device months
Deaths not related to the lead	10	6.6	10	0.6
Complications related to the lead	14	9.2	17	1.0
Most common complications				
Dislodgment	6	3.95	7	-
Extracardiac stimulation	7	4.6	7	-
Complications related to the implant procedure	14	9.2	17	1.0
Observations related to the lead	12	7.9	14	0.9
Most common observation:				
Extracardiac stimulation	10	6.58	12	-
Observations related to the implant procedure	20	13.2	24	1.5
Serious adverse events not related to the lead	69	45.4	142	8.7
Not serious adverse events not related to the lead	47	30.9	99	6.1

The following definitions were used to classify adverse events:

- Complication: Adverse device effect which cannot be treated or resolved by simple adjustments and requires intervention (surgery or external shock), or which results in loss of significant device function (e.g. lead dislodgement).
- Observation: A symptomatic or asymptomatic clinical event with potential adverse device effects that does not require intervention or can be corrected by simple adjustments (e.g. reprogramming).

Death Summary

A total of 16 deaths occurred in the Alto MSP Study. These are presented in the table below.

Deaths, not device related	All Patients	Therapy On	Therapy Off	Not Randomized
Cardiac arrest	5	0	3	2
Cardiomyopathy	1	0	1	0
Low output syndrome related to untreatable sepsis	1	0	0	1
Multi-organ dysfunction	2	1	1	0
Myocardial infarction	1	0	1	0
Pancreatic cancer	1	1	0	0
Unknown	1	0	0	1
Worsening CHF / CHF decompensation	3	1	1	1
Worsening CHF and atrial fibrillation	1	0	0	1

Adverse Event Detail:

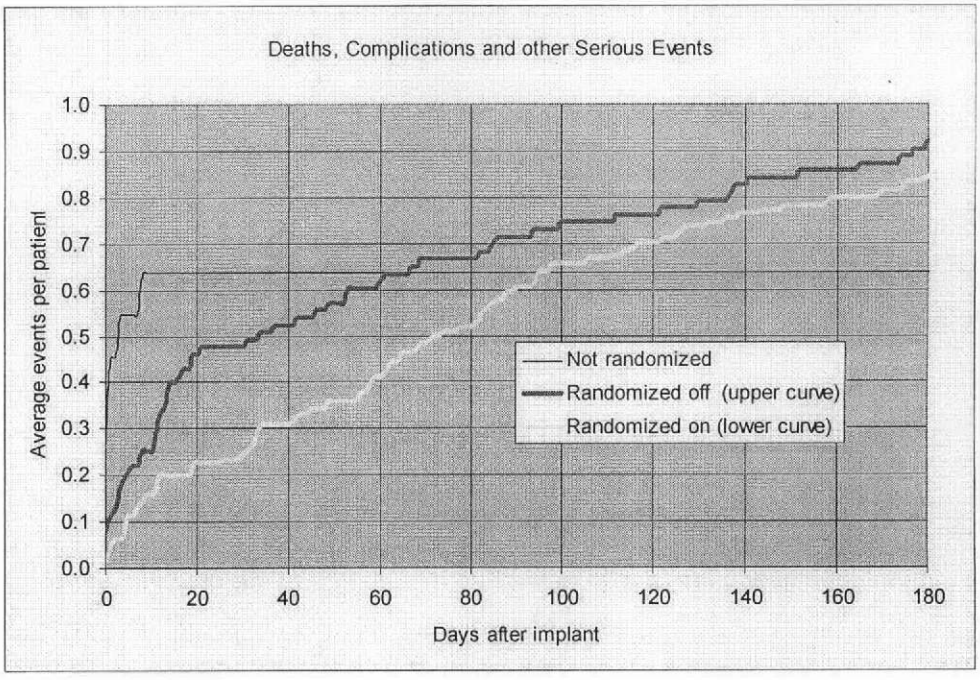
The following table lists all adverse events observed during the Alto MSP Clinical Study. Adverse events occurring at a rate >1% or reported.

Adverse Events		Total (n=190)			Therapy on (n=114)			Therapy off (n=63)			Not randomized (n=2)		
Device Related	Final Diagnosis	Events	Patients	% of patients	Events	Patients	% of patients	Events	Patients	% of patients	Events	Patients	% of patients
Complications related to the system													
LV Lead	Dislodgment or migration	9	8	4.2%	7	6	5.3%	2	2	3.2%	0	0	0.0%
	Extracardiac stimulation	9	9	4.7%	5	5	4.4%	4	4	6.3%	0	0	0.0%
RA Lead	Undersensing/loss of sensing	2	2	1.1%	0	0	0.0%	2	2	3.2%	0	0	0.0%
RV Lead	Oversensing	2	2	1.1%	1	1	0.9%	1	1	1.6%	0	0	0.0%
ICD	Other	2	2	1.1%	2	2	1.7%	0	0	0.0%	0	0	0.0%
Complications related to the implant procedure													
ICD	Pocket infection	3	2	1.1%	3	2	1.7%	0	0	0%	0	0	0.0%
LV Lead	Dislodgment or migration	2	2	1.1%	1	1	0.9%	1	1	1.6%	0	0	0.0%
RV Lead	Undersensing/loss of sensing	2	2	1.1%	1	1	0.9%	1	1	1.6%	0	0	0.0%
RA Lead	Dislodgment or migration	2	2	1.1%	1	1	0.9%	1	1	1.6%	0	0	0.0%
Observations Related to the system													
LV Lead	Extracardiac stimulation	13	11	6%	9	8	7%	4	3	4.8%	0	0	0.0%
System	Inappropriate shock	2	2	1.1%	0	0	0.0%	1	1	1.6%	1	1	50.0%
Observations related to the implant procedure													
Implant Procedure	Heart block	6	6	3.2%	3	3	2.6%	2	2	3.2%	1	1	50.0%
	Cardiac perforation	3	3	1.6%	1	1	0.9%	1	1	1.6%	1	1	50.0%
LV Lead	Extracardiac stimulation	5	3	1.6%	5	3	2.6%	0	0	0.0%	0	0	0.0%
Serious adverse events not related to the system													
	Worsening CHF/CHF decompensation	42	24	12.6%	21	13	11.4%	21	11	17.4%	0	0	0.0%
	Other: Medical Non-Cardiac	39	28	14.7%	26	18	15.8%	13	10	15.9%	0	0	0.0%
	Atrial fibrillation/flutter	14	14	7.4%	8	8	7.0%	6	6	9.5%	0	0	0.0%
	Angina	7	5	2.6%	6	4	3.5%	1	1	1.6%	0	0	0.0%
	Pulmonary edema	7	6	3.2%	2	2	1.1%	5	4	6.3%	0	0	0.0%

Adverse Events		Total (n=190)			Therapy on (n=114)			Therapy off (n=63)			Not randomized (n=2)		
Device Related	Final Diagnosis	Events	Patients	% of patients	Events	Patients	% of patients	Events	Patients	% of patients	Events	Patients	% of patients
	Ventricular tachycardia	7	7	3.7%	5	5	4.4%	2	2	3.2%	0	0	0.0%
	Heart block	5	5	2.6%	1	1	0.9%	4	4	6.3%	0	0	0.0%
	Renal dysfunction	4	3	1.6%	4	3	2.6%	0	0	0.0%	0	0	0.0%
	CVA/stroke	3	3	1.6%	2	2	1.7%	0	0	0.0%	1	1	50.0%
	Diabetes	3	3	1.6%	2	2	1.7%	0	0	0.0%	1	1	50.0%
	Infection	3	2	1.1%	1	1	0.9%	2	1	1.6%	0	0	0.0%
	Pneumonia	3	3	1.6%	3	3	2.6%	0	0	0.0%	0	0	0.0%
	Pocket infection	3	3	1.6%	2	2	1.7%	1	1	1.6%	0	0	0.0%
	Sepsis	3	3	1.6%	3	3	2.6%	0	0	0.0%	0	0	0.0%
	Anemia	2	2	1.1%	2	2	1.7%	0	0	0.0%	0	0	0.0%
	Ischemia	2	2	1.1%	1	1	0.9%	1	1	1.6%	0	0	0.0%
	Peripheral vascular disease	2	2	1.1%	1	1	0.9%	1	1	1.6%	0	0	0.0%
	Syncope	2	2	1.1%	2	2	1.7%	0	0	0.0%	0	0	0.0%
Not serious adverse events not related to the system													
	Other: Medical Non-Cardiac	30	20	10.5%	18	12	10.5%	12	8	12.7%	0	0	0.0%
	Worsening CHF/CHF decompensation	16	13	6.8%	8	7	6.1%	8	6	9.5%	0	0	0.0%
	Atrial fibrillation/flutter	8	7	3.7%	3	3	2.6%	4	3	4.8%	1	1	50.0%
	Ventricular tachycardia	7	7	3.7%	5	5	4.4%	2	2	3.2%	0	0	0.0%
	Peripheral edema	6	6	3.2%	3	3	2.6%	3	3	4.8%	0	0	0.0%
	Hypotension	5	3	1.6%	5	3	2.6%	0	0	0.0%	0	0	0.0%
	Angina	4	3	1.6%	3	2	1.7%	1	1	1.6%	0	0	0.0%
	Hypertension	4	4	2.1%	4	4	3.5%	0	0	0.0%	0	0	0.0%
	Peripheral vascular disease	4	4	2.1%	1	1	0.9%	2	2	3.2%	1	1	50.0%
	Atrial tachycardia	3	2	1.1%	2	1	0.9%	1	1	1.6%	0	0	0.0%
	Infection	3	2	1.1%	2	1	0.9%	1	1	1.6%	0	0	0.0%
	Other arrhythmia	3	3	1.6%	3	3	2.6%	0	0	0.0%	0	0	0.0%
	COPD	2	2	1.1%	1	1	0.9%	0	0	0.0%	1	1	50.0%
	Pleural effusion	2	2	1.1%	0	0	0.0%	2	2	3.2%	0	0	0.0%
	Shortness of breath	2	2	1.1%	2	2	1.7%	0	0	0.0%	0	0	0.0%

The incidence of adverse events was as expected. There were no unanticipated adverse device effects or device-related deaths. It might be noted that in some instances the rate of specific adverse events was higher in the Therapy on group. This can be explained by the fact that the study was a 2:1 randomization; twice as many patients existed in the Therapy on group.

A time course of the occurrence of serious adverse events as compared to the control treatment, in relation to the initial treatment. is provided in the graph below:



No adverse events led to any device design modifications during the PMA clinical study.

2. Effectiveness Results

The analysis of effectiveness was based on the control and test cohorts evaluable at the six-month time point as specified in the tables below. Key effectiveness outcomes are presented below. In each case the null hypothesis was rejected in favor of the alternate at the requisite level of significance:

Objective: To demonstrate a greater improvement for patients receiving CRT in a composite endpoint combining percent peak VO2 improvement and percent Minnesota Living with Heart Failure Questionnaire® (LHFQ) score improvement measured six months after randomization. Results: The CRT group had a mean improvement in the composite endpoint of 24.9 %. This is greater than that achieved by the control group, which was 15.5%. The table below shows the statistical analysis performed to evaluate the objective.

Parameter	Definition	Result
μ%	(%Δ peak VO2 + %ΔLHFQ)/2	
%Δ peak VO2	100*(peak VO2 6-month – peak VO2 baseline)/ peak VO2 baseline	
%ΔLHFQ	100*(LHFQ baseline – LHFQ 6-month)/ LHFQ baseline	
Ns	Number of patients in control group	41
Ne	Number of patients in CRT group	91
μs%	Mean composite percent improvement in control group	15.5
μe%	Mean composite percent improvement in CRT group	24.9
σs%	Standard deviation composite percent improvement in control group	28.8
σe%	Standard deviation composite percent improvement in CRT group	29.8
Ho	μs% ≥ μe%	
Ha	μs% < μe%	
D	e% - s%	9.4
SE(D)	Sqrt(Se%2/ Ne + Ss%2/ Ns)	5.5
T-statistic	D/SE(D)	1.72
p-value		0.046

The table below presents the percentage of patients in each group who improved, worsened, or remained unchanged in each element of the composite score and the composite score itself.

	QOL Score		VO2 Score		Composite Score	
	Control Group	Test Group	Control Group	Test Group	Control Group	Test Group
% Improved	75.6	74.7	48.8	67.0	62.2	70.9
% Worsened	24.4	25.3	51.2	31.9	37.8	28.6
% Unchanged	0.0	0.0	1.1	0.0	0.0	0.0

To properly characterize the effect of the device, the following tables show the absolute changes in the endpoints.

Absolute difference between test and control groups' change in peak V02 over 6 months

		Baseline Mean ± SD (range)	6-month Mean ± SD (range)	Difference within group	Difference between groups
Change in Peak VO_2	Control group (n=41)	13.39 ± 4.58 (5.02, 24.10)	13.12 ± 3.99 (3.30, 20.70)	-0.28	1.85
	Test group (n=91)	11.84 ± 3.90 3.50, 26.31	13.41 ± 4.28 (6.18, 27.67)	1.57	

Absolute difference between test and control groups' change in QOL score over 6 months

		Baseline Mean ± SD (range)	6-month Mean ± SD (range)	Difference within group	Difference between groups
Change in QOL	Control group (n=41)	47.5 ± 19.29 (9, 90.3)	31.21 ± 23.96 (0, 95)	16.29	1.28
	Test group (n=91)	52.81 ± 21.84 (9, 92)	35.24 ± 23.73 (0, 93)	17.57	

Objective: To demonstrate a Situs UW28D lead implant success rate that is greater than or equal to 75 %. Results: 149 patients were successfully implanted out of 177 attempts. The implant success rate for the Situs UW28D lead was 84%.

Parameter	Definition	Result
π	Population Situs UW28D implant success rate	
Ho	$\pi < 75$ %	
Ha	$\pi \geq 75$ %	
	Number of patients contributing to implant success rate	177
	Number of patients successfully implanted	149
	Population Situs UW28D implant success rate	84 %
CI95%	Exact, one-sided, 95% lower confidence level of implant success rate	77.9%

Objective: To demonstrate a mean chronic Situs UW28D lead pacing threshold less than or equal to 3.25 V. Results: The mean chronic (six months) pacing threshold observed in patients with Situs UW28D leads was 1.83 V.

Parameter	Definition	Result
μ	Population mean chronic Situs UW28D pacing threshold	
Ho	$\mu > 3.25$ V	
Ha	$\mu \leq 3.25$ V	
	Number of patients contributing	98
	Mean chronic (six-month) pacing threshold	1.83 V
	Standard deviation of chronic (six-month) pacing threshold	1.04 V
$CI_{95\%}$	Upper one-sided 95% confidence interval	2.00 V

Objective: To demonstrate a mean chronic Situs UW28D biventricular pacing impedance greater than or equal to 100 Ohms. Results: The mean chronic biventricular pacing impedance for Situs UW28D observed during the study was 390 Ω.

Parameter	Definition	Result
μ	Population mean chronic Situs UW28D biventricular pacing impedance	
Ho	μ < 100 Ohms	
Ha	μ ≥ 100 Ohms	
	One-sided, 95% lower confidence level of mean chronic biventricular pacing impedance	
	Number of patients contributing	118
	Mean chronic (six-month) biventricular pacing impedance	390.0
	Standard deviation of chronic (six-month) biventricular pacing impedance	92.1
CI95%	Lower one-sided 95% confidence interval	376.05

4. Subgroup Analyses

Per programming sub-analysis

A sub-analysis was performed of the effectiveness between the control and test cohorts up to the six month follow-up for patients programmed for the majority of the randomized treatment period.

Five patients crossed over before their one-month visit. Four patients were originally randomized to the control group and later had biventricular pacing enabled, and the other patient was originally randomized to the CRT group and had biventricular pacing disabled due to diaphragmatic stimulation. In the results of the per-programming analysis presented below, the four patients with biventricular pacing enabled have been analyzed with the CRT group, and the patient who had biventricular pacing turned off is analyzed with the control group.

Parameter	Per programming
Ns	38
Ne	95
Average percent change in VO2, control group	0.4
Average percent change in VO2, CRT group	18.0
Average percent change in LHFQ, control group	26.9
Average percent change in LHFQ, CRT group	32.1
Standard deviation of percent change in VO2, control group	22.9
Standard deviation of percent change in VO2, CRT group	36.2
Standard deviation of percent change in LHFQ, control group	53.8
Standard deviation of percent change in LHFQ, CRT group	44.4
Is%	13.6
Ie%	25.0
D	11.4
SE(D)	5.7
T-statistic	2.0
p-value	0.026

Conclusion: The effectiveness of ELA Medical's CRT system is confirmed by the statistically-significant difference between patients when they are analyzed according to their programming during the majority of the randomized treatment period.

VV delay optimization sub-analysis

Fifteen patients randomized to the CRT group did not undergo echo-guided optimization at randomization. The sub-analyses below compare how patients in the CRT group with and without optimized VV delays improved in the composite endpoint compared to the control group.

The first sub-analysis below (in the column entitled "With VV optimization") compares the 41 control patients with the 77 test patients who underwent echo-guided optimization at randomization.

The second sub-analysis below (in the column entitled "Without VV optimization") compares the same 41 control patients with the 15 test patients who did not undergo echo-guided optimization.

Consequently, the two sub-analyses below present data on 77 + 41 + 15 = 133 patients, the same 133 patients who contributed to the per-randomization sub-analysis above.

Parameter	With VV optimization	Without VV optimization
Ns	41	41
Ne	77	15
Average percent change in VO2, control group	0.9	0.9
Average percent change in VO2, CRT group	15.3	35.8
Average percent change in LHFQ, control group	30.2	30.2
Average percent change in LHFQ, CRT group	35.1	11.1
Standard deviation of percent change in VO2, control group	22.4	22.4
Standard deviation of percent change in VO2, CRT group	31.7	53.9
Standard deviation of percent change in LHFQ, control group	53.0	53.0
Standard deviation of percent change in LHFQ, CRT group	40.8	58.5
ls%	15.5	15.5
le%	24.8	23.4
D	9.3	7.9
SE(D)	5.5	11.2
T-statistic	1.7	0.7
p-value	0.05	0.24

Conclusion: The subset of CRT patients with optimized VV delays performed almost identically to all patients randomized to the CRT group.

Peak VO2 sub-analyses

The table below presents the average baseline and six-month peak VO2 values for patients who completed CPX testing at both visits.

Parameter	All patients	Control group	CRT group	Females	Males
Baseline average	12.1	12.8	11.7	10.5	12.5
Baseline standard deviation	4.3	5.3	3.7	3.2	4.5
Baseline number contributing	135	43	92	29	106
6-month visit average	13.1	13.0	13.2	12.4	13.3
6-month visit standard deviation	4.0	3.9	4.0	3.0	4.2
6-month number contributing	135	43	92	29	106

Peak LHFQ sub-analyses

The table below presents the average baseline and six-month LHFQ scores for patients who completed questionnaires at both visits.

Parameter	All patients	Control group	CRT group	Females	Males
Baseline average	51.1	48.2	52.6	56.8	49.6
Baseline standard deviation	21.1	19.9	21.7	21.1	21.0
Baseline number contributing	149	52	97	31	118
6-month visit average	34.8	33.2	35.7	34.5	34.9
6-month visit standard deviation	23.9	24.2	23.9	24.3	23.9
6-month number contributing	149	52	97	31	118

ELA performed an additional analysis on the LHFQ scores to determine if there was a difference between patients missing six-month scores and those who completed the questionnaire at their six-month visit. In this analysis the mean difference between baseline and three-month scores were compared using a Wilcoxon-Mann-Whitney test. No statistically significant difference was found between the two groups.

	Value	
Parameter	missing 6-month	not missing 6-month
Average change in LHFQ score at three months	13.1	19.0
Standard deviation of average change	26.7	21.4
Wilcoxon-Mann-Whitney p-value of difference	0.12	

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

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

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above.

The primary safety objective required 6-month complication-free rate 67% or greater for the CRT-D system and 75% for the lead only (at alpha 5% level). The actual observed rate was 89.5% by K-M method for the system (one-sided lower confidence limit = 84.1%) and 94.8% for the lead (90%). The sum of clinical outcomes data, including reported deaths and adverse events did not suggest safety issues with the device itself in this high-risk patient population.

B. Effectiveness Conclusions

The primary effectiveness objective for the CRT functionality required that a composite which was based on:

1. Change in % Peak V02
2. Change in % Minnesota Living with Heart Failure Questionnaire score showed greater improvements in the CRT (treatment) group than the control group (at alpha 5% level).

In summary, the composite averaged % change in each measure and found more improvement in the CRT treatment group by 9.4% when compared to the control group (24.9% vs. 15.5%). This was statistically significant, with a p-value of 0.046.

The primary effectiveness objective for the lead showed a mean pacing threshold of 1.83V in 98 patients and a mean chronic impedance of 390 Ω in 118 patients. Both of these values exceeded the hypothesis for these objectives.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

The Alto MSP clinical trial examined CRT clinical outcomes using appropriately sized treatment and control groups, using endpoints that were clinically relevant, and which characterized CRT safety and effectiveness.

- Design: the trial was prospective, randomized and double-blinded, with randomization to a 6-month treatment arm of 114 receiving CRT using DDD mode, base rate 30 and a short AD delay versus a 6-month treatment arm of 63 who received VVI 30 pacing without LV stimulation
- Safety: The primary safety objective required 6-month complication-free rate 67% or greater for the CRT-D system and 75% for the lead only (at alpha 5% level). The actual observed rate was 89.5% by K-M method for the system (one-

sided lower confidence limit = 84.1%) and 94.8% for the lead (90%). The sum of clinical outcomes data, including reported deaths and adverse events did not suggest safety issues with the device itself in this high-risk patient population. The rates of adverse events for the LV lead were comparable to market-approved leads and within acceptable limits for this type of device (9 dislodgements in 190 implants, 9 extracardiac stimulation). There were no unanticipated adverse events.

- Effectiveness: The primary effectiveness objective for the CRT functionality required that a composite which was based on the change in % Peak V02 and the change in % Minnesota Living with Heart Failure Questionnaire score showed greater improvements in the CRT (treatment) group than the control group (at alpha 5% level). In summary, the composite averaged % change in each measure and found more improvement in the CRT treatment group by 9.4% when compared to the control group (24.9% vs. 15.5%). This was statistically significant, with a p-value of 0.046. This improvement was primarily attributable to changes in Peak V02:

Control improvement in	VO2: 12.8→13.0	QOL questionnaire: 48.2→33.2
CRT improvement in	VO2: 11.7→13.2	QOL questionnaire: 52.6→35.7

- Compliance with the protocol: Of 197 enrollees, 152 (77%) had analyzable data through 6 months. This was because 15 patients could not be implanted or withdrew and one patient could not be implanted with an LV lead and 4 died before randomization, after implant. The 177 implanted patients were randomized 2:1 to test and control therapy but only 152 achieved 6-month follow-up due to either incomplete follow-up, withdrawal (5 test/1 control) or death (1 test/4 control).

- The study was successful overall since all primary safety and effectiveness endpoints were demonstrated successful at the requisite alpha level (5 %).

XIII. CDRH DECISION

CDRH issued an approval order on May 15, 2008. The final conditions of approval cited in the approval order are described below.

1. The sponsor has agreed to provide a test report including the results of 400 million cycle distal tip fatigue testing on 5 additional Situs UW28D lead samples no later than May 31, 2008. The report should include a copy of the results of the original 400 million cycle distal tip fatigue testing on 6 samples which was included in the original PMA submission.

2. The sponsor has also agreed to the following study outline for a post-approval study for the Situs LV Lead:

i. a prospective study design to characterize chronic lead performance following device implant, as well as a robust process to retrospectively collect implant data for each study subject;
ii. a post-approval study duration of at least 5 years;
iii. a sample size that results in a 2-sided 95% upper confidence bound of no more than 1.0% for individual adverse event rates, assuming an expected rate of 0.4%, using the exact binomial method;
iv. a total enrollment which accounts for estimated attrition, and an enrollment plan which attempts to enroll 33% of all marketed devices in the US ;
v. a primary safety endpoint as complication-free rate greater than 95% at 5 years, with any clinical adverse events omitted from the primary endpoint collected and reported as secondary data;
vi. a rigorous process to monitor the status of all study subjects, to actively follow-up missed visits, and to document the reason for all subject dropouts;
vii. inclusion of a trend analysis process in the protocol to provide a robust early warning mechanism to identify, characterize, and report adverse events, failure modes, and failure rates;
viii. post-approval study status reporting at least every 6 months and a mechanism for providing non-scheduled trend analysis reports for new information;
ix. inclusion of a full list of complications, failure modes, and definition of terms within the study protocol; and
x. collection of secondary data including implant data, demographic information, all cause adverse events, electrical performance, returned product analyses, extraction experience, and other parameters of interest.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.