Boston Scientific

CLINICAL SUMMARY

DECREASE-HF

CAUTION: Federal law restricts this device to sale by or on the order of a physician trained or experienced in device implant and follow-up procedures.

Boston Scientific Corporation acquired Guidant Corporation in April 2006. During our transition period, you may see both the Boston Scientific and Guidant names on product and patient materials. As we work through the transition, we will continue to offer doctors and their patients technologically advanced and high quality medical devices and therapies.

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CLINICAL STUDY - DECREASE-HF

CLINICAL STUDY POPULATIONS

Patients enrolled in the DECREASE-HF study had an indication for an ICD and severe heart failure (NYHA Class III/IV) including left ventricular dysfunction (EF ≤ 35%) and QRS duration ≥ 150 ms and remained symptomatic despite stable, optimal heart failure drug therapy.

SUMMARY

The DECREASE-HF study was designed to determine if LV-CRT and LV Offset are safe and effective as compared to the control treatment (BiV-CRT) in patients with heart failure and an indication for an implantable cardioverter defibrillator (ICD). The primary effectiveness endpoint was a composite of peak VO_2 and left ventricular end systolic diameter (LVESD). The primary safety endpoints were heart failure related adverse event free rate and system related adverse event free rate. The LV Offset arm supports the safety and effectiveness of the LV Offset feature.

Background

The DECREASE-HF Study was a prospective, randomized, controlled, multicenter, double-blind study conducted at 57 sites in the United States and enrolled a total of 360 patients. The study was designed to assess the safety and effectiveness of the CONTAK RENEWAL® 2/4/4HE CRT-D devices in patients with heart failure and an indication for an ICD. Left ventricular CRT (LV-CRT or LV Only) and BiV-CRT with an LV Offset (referred to as LV Offset for brevity) were investigational treatments tested for equivalence to simultaneous biventricular pacing (BiV-CRT), which served as the control. All implanted patients (n = 342) who successfully completed the two-week randomization visit (n = 306) were randomized in equal allocation (1:1:1) to receive LV Offset, LV Only, or BiV-CRT.

Patients were followed at hospital discharge, randomization (approximately two weeks post-implant), three and six months post-randomization, and at quarterly intervals thereafter.

The DECREASE-HF clinical investigation used CONTAK RENEWAL 2/4/4HE devices to study the LV Offset feature as well as other features that are not available in the CONTAK RENEWAL 1/3/3HE devices. The 2/4/4HE devices are physically and mechanically identical to the 1/3/3HE devices and they both contain the LV

Offset feature. As such, the data from the DECREASE-HF clinical study regarding the LV Offset feature, studied by using the 2/4/4HE devices, applies to the CONTAK RENEWAL 1/3/3HE devices. Data on all patients enrolled is reported in this section.

ADVERSE EVENTS

In the DECREASE-HF study an adverse event was defined as any undesirable clinical occurrence related to the patient's heart failure condition, investigational device, investigational therapy, system components, and/or related procedures that affect the health or safety of the patient.

Table 1 includes adverse events occurring in the first six months after implant (including attempts).

Table 1. Adverse Events Occurring During the First Six Months After Implant

Adverse Event	Number Of Events (Number of Patients)[a]	Complications		Observations	
		% of Patients (N Patients)	N Events/ 100 Device Months (N Events)	% of Patients (N Patients)	N Events/ 100 Device Months (N Events)
Total Adverse Events	**397 (215)**	**27.1 (97)**	**7.3 (146)**	**46.9 (168)**	**12.6 (251)**
EASYTRAK 2 Lead Related Events (N=334)					
Diaphragmatic stimulation during threshold testing - LV	3 (3)	0.0 (0)	0.0 (0)	0.9 (3)	0.2 (3)
Dislodgment	31 (28)	6.9 (23)	1.3 (26)	1.5 (5)	0.3 (5)
Elevated threshold - LV	7 (7)	0.0 (0)	0.0 (0)	2.1 (7)	0.4 (7)
Extracardiac stimulation - LV	54 (44)	2.1 (7)	0.4 (7)	11.1 (37)	2.4 (47)
Unable to capture - LV	1 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.1 (1)
Subtotal EASYTRAK 2 Lead Related Events	96 (75)	9.0 (30)	1.7 (33)	14.1 (47)	3.2 (63)
EASYTRAK Lead Related Events (N=7)					
Extracardiac stimulation - LV	2 (2)	28.6 (2)	0.1 (2)	0.0 (0)	0.0 (0)
Subtotal EASYTRAK Lead Related Events	2 (2)	28.6 (2)	0.1 (2)	0.0 (0)	0.0 (0)

Table 1. Adverse Events Occurring During the First Six Months After Implant

PG Related Events (N=342)					
Elevated DFT - Defibrillation	6 (6)	1.8 (6)	0.3 (6)	0.0 (0)	0.0 (0)
Erosion	1 (1)	0.3 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Extracardiac stimulation - LV	3 (3)	0.0 (0)	0.0 (0)	0.9 (3)	0.2 (3)
Hematoma - Pocket (> 30 days post-implant)	2 (2)	0.3 (1)	0.1 (1)	0.3 (1)	0.1 (1)
Inappropriate tachy therapy - NSR	2 (2)	0.0 (0)	0.0 (0)	0.6 (2)	0.1 (2)
Inappropriate tachy therapy - Other	1 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.1 (1)
Inappropriate tachy therapy - SVT	11 (11)	0.0 (0)	0.0 (0)	3.2 (11)	0.6 (11)
Infection (> 30 days post-implant)	5 (5)	1.2 (4)	0.2 (4)	0.3 (1)	0.1 (1)
Migration	1 (1)	0.3 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Oversensing - RA	5 (4)	0.0 (0)	0.0 (0)	1.2 (4)	0.3 (5)
Oversensing - RV	1 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.1 (1)
Pacemaker-mediated tachycardia (PMT)	20 (19)	0.0 (0)	0.0 (0)	5.6 (19)	1.0 (20)
Psychological effect due to device therapy	10 (9)	0.0 (0)	0.0 (0)	2.6 (9)	0.5 (10)
Seroma - Pocket (> 30 days post-implant)	1 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.1 (1)
Set screws not tightened	1 (1)	0.3 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Upper rate limit behavior	1 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.1 (1)
Subtotal PG Related Events	71 (61)	4.1 (14)	0.7 (14)	14.3 (49)	2.9 (57)
RA Lead Related Events (N=342)					
Dislodgment	13 (11)	2.6 (9)	0.6 (11)	0.6 (2)	0.1 (2)
Elevated atrial impedance - RA	1 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.1 (1)
Oversensing - RA	1 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.1 (1)
Undersensing - RA	1 (1)	0.3 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Subtotal RA Lead Related Events	16 (13)	2.9 (10)	0.6 (12)	0.9 (3)	0.2 (4)
RV Lead Related Events (N=342)					
Dislodgment	4 (4)	1.2 (4)	0.2 (4)	0.0 (0)	0.0 (0)
Subtotal RV Lead Related Events	4 (4)	1.2 (4)	0.2 (4)	0.0 (0)	0.0 (0)

Table 1. Adverse Events Occurring During the First Six Months After Implant

Procedure Related Events (N=358)					
Adverse reaction - General	9 (9)	1.1 (4)	0.2 (4)	1.4 (5)	0.3 (5)
Coronary venous dissection	6 (6)	0.0 (0)	0.0 (0)	1.7 (6)	0.3 (6)
Coronary venous perforation without tamponade	4 (4)	0.0 (0)	0.0 (0)	1.1 (4)	0.2 (4)
Hematoma - Pocket (<=30 days post-implant)	16 (16)	0.8 (3)	0.2 (3)	3.6 (13)	0.7 (13)
Physical trauma	4 (4)	0.0 (0)	0.0 (0)	1.1 (4)	0.2 (4)
Post-surgical infection (<= 30 days post-implant)	8 (8)	0.6 (2)	0.1 (2)	1.7 (6)	0.3 (6)
Post-surgical wound discomfort	12 (12)	0.0 (0)	0.0 (0)	3.4 (12)	0.6 (12)
Other[b]	25 (24)	2.5 (9)	0.5 (9)	4.2 (15)	0.8 (16)
Subtotal Procedure Related Events	**84 (76)**	**4.7 (17)**	**0.9 (18)**	**16.8 (60)**	**3.3 (66)**
Protocol Testing Related Events (N=358)					
Atrial fibrillation (AF)	2 (2)	0.0 (0)	0.0 (0)	0.6 (2)	0.1 (2)
Atrial flutter	1 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.1 (1)
Chronotropic incompetence	1 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.1 (1)
Hypotension - Heart failure	1 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.1 (1)
Subtotal Protocol Testing Related Events	**5 (5)**	**0.0 (0)**	**0.0 (0)**	**1.4 (5)**	**0.3 (5)**
Cardiovascular - HF Related Events (N=342)					
Chest pain - Heart failure	1 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.1 (1)
Dehydration - Heart failure	2 (2)	0.3 (1)	0.1 (1)	0.3 (1)	0.1 (1)
Dizziness - Heart failure	3 (3)	0.3 (1)	0.1 (1)	0.6 (2)	0.1 (2)
Dyspnea - Heart failure	16 (15)	2.3 (8)	0.4 (8)	2.3 (8)	0.4 (8)
Elevated BNP - Heart failure	1 (1)	0.3 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Fatigue - Heart failure	4 (4)	0.3 (1)	0.1 (1)	0.9 (3)	0.2 (3)
Gastrointestinal - Heart failure	3 (3)	0.3 (1)	0.1 (1)	0.6 (2)	0.1 (2)
Heart failure symptoms - Unspecified	17 (16)	3.2 (11)	0.6 (11)	1.8 (6)	0.3 (6)
Hypotension - Heart failure	10 (9)	1.2 (4)	0.3 (5)	1.5 (5)	0.3 (5)
Multi-system failure - Heart failure	3 (3)	0.9 (3)	0.2 (3)	0.0 (0)	0.0 (0)
Multiple heart failure symptoms	44 (36)	5.8 (20)	1.2 (24)	5.6 (19)	1.0 (20)

Table 1. Adverse Events Occurring During the First Six Months After Implant

Peripheral edema - Heart failure	1 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.1 (1)
Pulmonary edema - Heart failure	5 (5)	0.9 (3)	0.2 (3)	0.6 (2)	0.1 (2)
Renal insufficiency - Heart failure	3 (3)	0.6 (2)	0.1 (2)	0.3 (1)	0.1 (1)
Weight gain - Heart failure	6 (5)	0.6 (2)	0.1 (2)	0.9 (3)	0.2 (4)
Subtotal Cardiovascular - HF Related Events	**119 (76)**	**12.3 (42)**	**3.2 (63)**	**14.3 (49)**	**2.8 (56)**

[a] The total number of patients for a given event represents the unique number of patients who experienced that event. The total may not be equal to the sum of the patients with complications or observations because some patients experienced more than one event that fell into both categories.

[b] Other procedure-related events occurred in three patients or fewer: Transient AV block (2), Bradycardia (1), Hypotension (1), Adverse respiratory reaction (3), Chest pain (1), Hemothorax (1), Myocardial perforation without tamponade (1), Pericardial effusion (1), Pleural effusion (1), Pneumothorax (3), Post-surgical pocket hemorrhage (3), Renal failure due to contrast media (3), Seroma (1), Thrombus (1), Venous occlusion (2).

Deaths

There were a total of 42 deaths that occurred during the DECREASE-HF study as of August 4, 2005 as presented in Table 2.

Table 2. DECREASE-HF Study Cause of Death

Cause of Death	Implants (N=342)	Attempts (N=16)	Total (N=358)
Cardiac: Arrhythmic	1	0	1
Cardiac: Ischemic	1	0	1
Cardiac: Other	1	1	2
Cardiac: Pump failure	16	0	16
Cardiac: Unknown	1	0	1
Non-Cardiac	4	0	4
Unknown	7	0	7
Not yet Classified[a]	8	0	8
Total Deaths	41	1	42

a. Deaths not yet classified by the Events Committee were classified by the investigator as: cardiac: pump failure (2), cardiac: unknown (1), non-cardiac (3), and unknown (1). Information has not yet been received for one recent death.

STUDY DESIGN

The DECREASE-HF Study design has been previously described in the medical literature.[1]

Patients were randomized (1:1:1) to receive one of these three therapies. Patients who could not be randomized due to their inability to complete baseline testing or because Expert Ease recommended BiV-CRT were followed for safety data only in a separate “safety arm.” Available data for all patients were analyzed by randomization group assignment, regardless of actual therapy received (i.e., intent to treat).

The DECREASE-HF clinical investigation used CONTAK RENEWAL 2/4/4HE devices to study the LV Offset feature as well as other features that are not available in the CONTAK RENEWAL 1/3/3HE devices. The 2/4/4HE devices are physically and mechanically identical to the 1/3/3HE devices and they both contain the LV Offset feature. As such, the data from the DECREASE-HF clinical study regarding the LV Offset feature, studied by using the 2/4/4HE devices, applies to the CONTAK RENEWAL 1/3/3HE devices. The LV Offset arm supports the safety and effectiveness of the LV Offset feature.

Follow-up Schedule

Pre-Implant	Initial assessment of patient eligibility; taking of patient history. Administration of baseline Quality of Life (QOL) questionnaire.
Implant	Implant of investigational devices and acute device testing.
Two-week visit	Physical assessment, including NYHA assessment, and device evaluation. Special Testing[a] to establish the patient’s baseline condition, after which the randomization assignment was assigned.
Three- and six-month visit	Evaluation of randomized therapy with Special Testing and device function[b].
Quarterly visits	After the six-month visit, patients were seen for routine evaluation of device function and patient condition.

1. De Lurgio D, Foster E, Higginbotham M, Larntz K, Saxon L. A Comparison of cardiac resynchronization by sequential biventricular pacing and left ventricular pacing to simultaneous biventricular pacing: Rationale and design of the DECREASE-HF clinical trial. J Card Fail. 2005;11(3):233-239

a. Special Testing included a Symptom-Limited Treadmill Test with measurement of oxygen uptake (Peak VO_2), Echocardiography, QOL questionnaire.
b. Holter monitor recordings were taken at the three-month visit for patients in the Holter Substudy.

Inclusion/Exclusion Criteria

Patients enrolled in the investigation were required to meet the following inclusion criteria:

- Patients who meet the general indications for a CRT-D implant
- Moderate or severe heart failure, defined as NYHA Class III-IV despite optimal pharmacological heart failure therapy
- A 12-lead electrocardiogram (ECG) obtained no more than 90 days prior to enrollment documenting a sinus rate > 50 bpm, QRS duration ≥ 150 ms, PR interval ≤320 ms measured from any two leads and a P-wave duration < 150 ms measured from lead V_1
- Creatinine ≤ 2.5 mg/dL obtained no more than 14 days prior to enrollment
- Left ventricular ejection fraction ≤ 35% [measured by echo, multiple gated acquisition (MUGA) scan, cardiac catheterization, etc.] no more than 14 days prior to enrollment
- Willing and capable of undergoing a device implant and participating in all testing associated with this clinical investigation
- Have a life expectancy of more than 180 days, per physician discretion
- Age 18 or above, or of legal age to give informed consent specific to state and national law

Patients were excluded from the investigation if they met any one of the following exclusion criteria:

- Right bundle branch block morphology (per World Health Organization Guidelines), on a 12-lead ECG obtained no more than 90 days prior to enrollment
- Had previous cardiac resynchronization therapy, a previous coronary venous lead, or met the general indications for antibradycardia pacing

- Had a neuromuscular, orthopedic, or other non-cardiac condition that prevented normal, unsupported walking
- Had an atrial tachyarrhythmia that was permanent (i.e., did not terminate spontaneously and could not be terminated with medical intervention) or persistent (i.e., could be terminated with medical intervention, but did not terminate spontaneously) within 180 days prior to enrollment
- Had a hypersensitivity to a 0.7 mg dose of dexamethasone acetate
- Had surgically uncorrected primary valvular heart disease
- Required dialysis at the time of enrollment
- Had chronic obstructive pulmonary disease (COPD), defined as $FEV_1/FVC < 60\%$
- Had a myocardial infarct, unstable angina, percutaneous coronary intervention, or coronary artery bypass graft during the 30 days prior to enrollment
- Had hypertrophic obstructive cardiomyopathy or infiltrative cardiomyopathy (e.g., amyloidosis, sarcoidosis)
- Had a mechanical tricuspid prosthesis
- Were enrolled in any concurrent study, without Guidant written approval, that may confound the results of this study

Endpoints

Therapy Effectiveness

- **Primary:** Composite Score combining six-month change in peak VO_2 and ventricular end systolic diameter (LVESD)
- **Secondary:** Six-month change in peak VO_2, LVESD, NYHA Class, and Quality of Life (QOL)

Device Effectiveness

- **Primary:** Ventricular fibrillation detection time

Therapy Safety

- **Primary:** Freedom from heart failure-related adverse events through six months

Device Safety

- **Primary:** Freedom from system-related complications through six months
- **Secondary:** Ability to deliver continuous appropriate CRT pacing during activities of daily living and during exercise
- **Ancillary Endpoints:** Consistency between device counters and Holter monitor

STUDY RESULTS

Demographic data and safety endpoints will include data from all patients enrolled in the study. Effectiveness endpoints will focus on the comparison of LV Offset to BiV-CRT.

Demographic Data

Figure 1 provides an overview of patient enrollment and baseline characteristics are presented in Table 3.

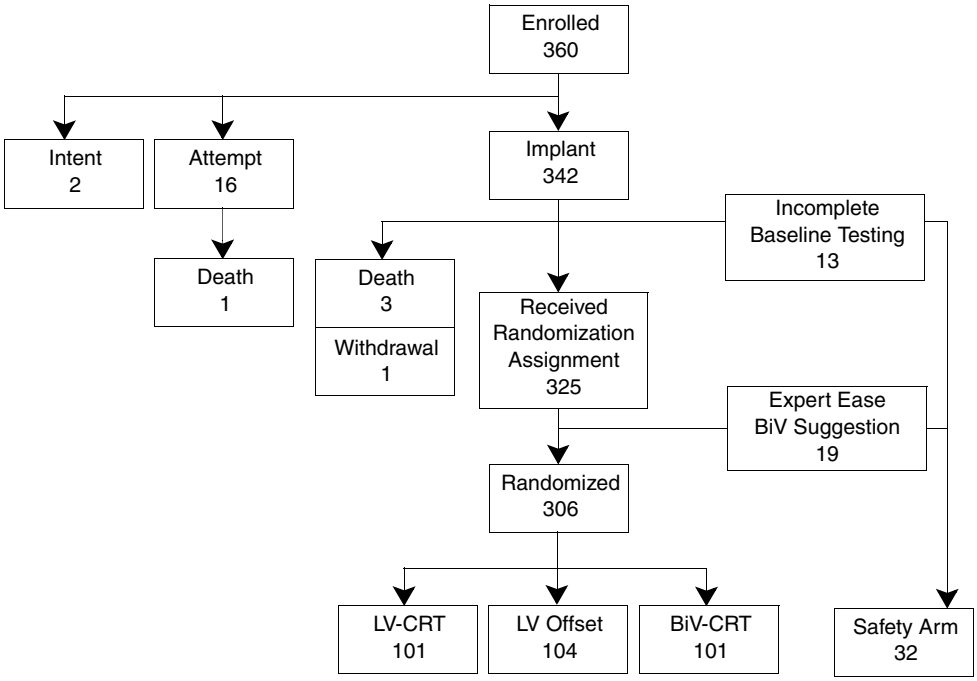

Figure 1. DECREASE-HF Study Patient Enrollment and Randomization.

Table 3. DECREASE-HF Study Patient Characteristics

Characteristic	Measurement	LV-CRT (N=101)	LV Offset (N=104)	BiV-CRT (N=101)	P-value[a]
Age at Implant (years)	N	101	104	101	
	Mean ± SD	67.4 ± 9.6	66.6 ± 10.5	66.2 ± 10.6	0.69
	Range	45.4 - 87.3	32.4 - 85.6	40.6 - 86.2	
Gender [N (%)]	Male	66 (65)	70 (67)	69 (68)	0.90
	Female	35 (35)	34 (33)	32 (32)	
NYHA Class [N (%)]	III	98 (97)	100 (96)	101 (100)	0.16
	IV	3 (3)	4 (4)	0 (0)	
LVEF (%)	N	101	104	100	
	Mean ± SD	22.6 ± 6.6	22.4 ± 6.7	23.2 ± 7.1	0.67
	Range	8.0 - 35.0	9.0 - 35.0	5.0 - 35.0	
QRS Duration (ms)	N	101	104	101	
	Mean ± SD	165 ± 15	167 ± 16	168 ± 15	0.29
	Range	150 - 220	150 - 220	150 - 218	
PR Interval (ms)	N	101	104	101	
	Mean ± SD	195 ± 42	195 ± 42	194 ± 39	0.98
	Range	120 - 318	100 - 320	88 - 320	
P-Wave Duration (ms)	N	101	104	101	
	Mean ± SD	91 ± 22	96 ± 22	95 ± 24	0.21
	Range	39 - 140	40 - 140	40 - 145	
Concomitant Medications[b] [N (%)]	ACE Inhibitor/ARB	88 (87)	88 (85)	91 (90)	0.50
	Beta Blocker	84 (83)	84 (81)	82 (81)	0.89
	Digoxin	47 (47)	55 (53)	46 (46)	0.52
	Diuretic	89 (88)	93 (89)	82 (81)	0.19
	Loop Diuretic	87 (86)	91 (88)	80 (79)	0.22
	Nonloop Diuretic	8 (8)	8 (8)	8 (8)	1.00
	Aldosterone Antagonist	40 (40)	37 (36)	40 (40)	0.79
	Antiarrhythmic	21 (21)	14 (13)	13 (13)	0.22
Etiology [N (%)]	Ischemic	67 (66)	70 (67)	58 (57)	0.27
	Nonischemic	34 (34)	34 (33)	43 (43)	

Table 3. DECREASE-HF Study Patient Characteristics

Conduction Disorder [N (%)]	Left Bundle Branch Block	94 (93)	95 (91)	97 (96)	0.68
	Nonspecific Intraventricular Conduction	6 (6)	8 (8)	4 (4)	
	Right Bundle Branch Block	1 (1)	1 (1)	0 (0)	

a. P-values for continuous variables were calculated from a Student's t-test; p-values for discrete variables were calculated from a Chi-squared test.
b. Patients may appear in more than one category.

Therapy Effectiveness

Primary Endpoint: Composite Score

Effectiveness of LV Offset was measured using a Composite Score that combines six-month changes in peak VO_2 and LVESD as depicted in Figure 2 and the accompanying table. Based on these estimates of clinically meaningful improvement (1 ml/kg/min and -5 mm, for Peak VO_2 and LVESD, respectively), a scaling factor of 5 was chosen to give each component approximately equal weight, as follows: Composite Score = (5 x change in peak VO_2) - (change in LVESD).

To evaluate the effectiveness of LV Offset, the Composite Score was compared to the control arm using a longitudinal analysis. The null hypothesis was to be rejected if the upper one-sided confidence bound of the difference were less than 10 points.

The observed mean differences from the BiV-CRT control arm was 3.6 ± 2.4 in the LV Offset arm, with upper one-sided confidence bound of 8.2 showing statistical equivalence to BiV-CRT.

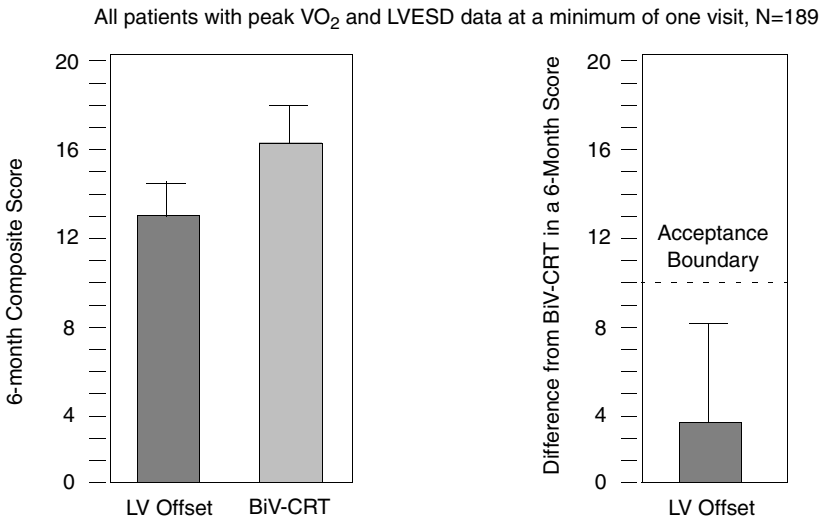

Figure 2. Composite Score Equivalence to BiV-CRT at Six Months.

Statistic	LV Offset		BiV-CRT	
	N[a]	Estimate ± SE	N[a]	Estimate ± SE
3-Month Composite Score	71	12.4 ± 1.5	70	16.0 ± 1.5
6-Month Composite Score	70	12.8 ± 1.7	76	16.4 ± 1.7
Difference at 6 Months (BiV-CRT - LV Offset)	3.6 ± 2.4			
Confidence Interval Upper Bound	8.2			

a. N refers to the number of patients with paired data.

Secondary Endpoints

- **Peak VO_2**

  A patient's capacity for performing physical activity was assessed using six-month change in peak VO_2 achieved during CPX testing. The endpoint analysis includes only CPX tests that are representative of maximal patient effort, defined as achievement of a Borg RPE ≥ 16 or RER ≥ 1.1. As defined in the Protocol, patients with a baseline peak VO_2 greater than 20 ml/kg/min were excluded from the analysis. A longitudinal analysis that included all patients with data at a minimum of one visit was performed to estimate six-month change from baseline in each group.

  As shown in Figure 3, both treatment arms showed a statistically significant and clinically meaningful (≥ 1.0 ml/kg/min) improvement in peak VO_2, an endpoint considered clinically meaningful in previous randomized controlled trials of CRT. The null hypothesis was to be rejected if the lower one-sided 95% confidence bound were greater than zero. The observed lower one-sided confidence bound for LV Offset is 1.1 ml/kg/min.

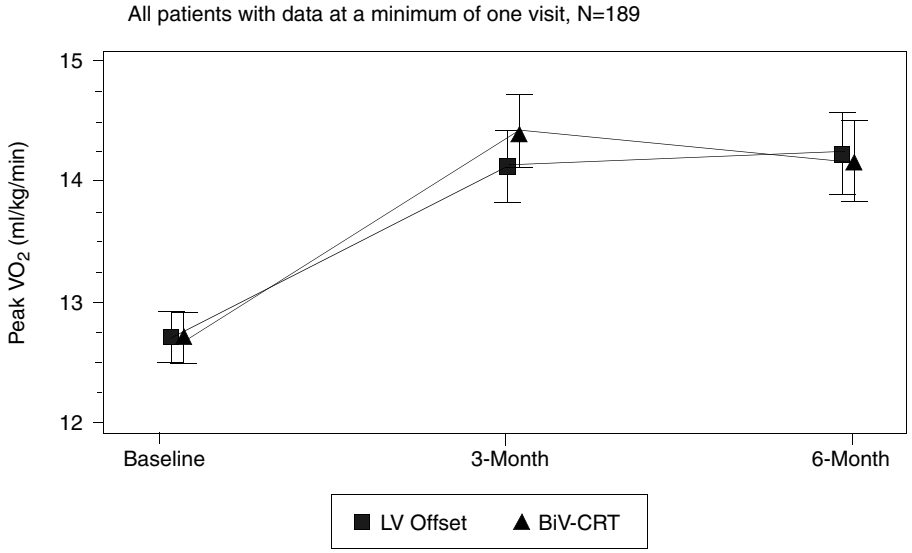

Figure 3. Improvement in Peak VO2 at Six Months.

Statistic	LV Offset		BiV-CRT	
	N[a]	Estimate ± SE	N[a]	Estimate ± SE
Baseline	89	12.7 ± 0.2	88	12.7 ± 0.2
3 Months	72	14.2 ± 0.3	71	14.5 ± 0.3
6 Months	71	14.3 ± 0.3	76	14.2 ± 0.3
Improvement at 6 Months		1.6 ± 0.3		1.5 ± 0.3
Confidence Interval Lower Bound		1.1		1.0

a. N refers to the number of patients with paired data.

- **Left Ventricular End Systolic Diameter (LVESD)**

  The effect of LV Offset was also assessed using six-month change in LVESD. A recorded echocardiographic examination was performed at the randomization visit (prior to CRT initiation) and subsequently at the three-month and six-month visits. A longitudinal analysis that included all patients with data at a minimum of one visit was performed to estimate six-month change from baseline in each group.

  As shown in Figure 4, both arms showed a statistically significant and clinically meaningful improvement (≤ -5 mm) in LVESD. The null hypothesis was to be rejected if the upper one-sided 95% confidence bound were less than zero. The observed upper one-sided bound for LV Offset is -4.2 mm.

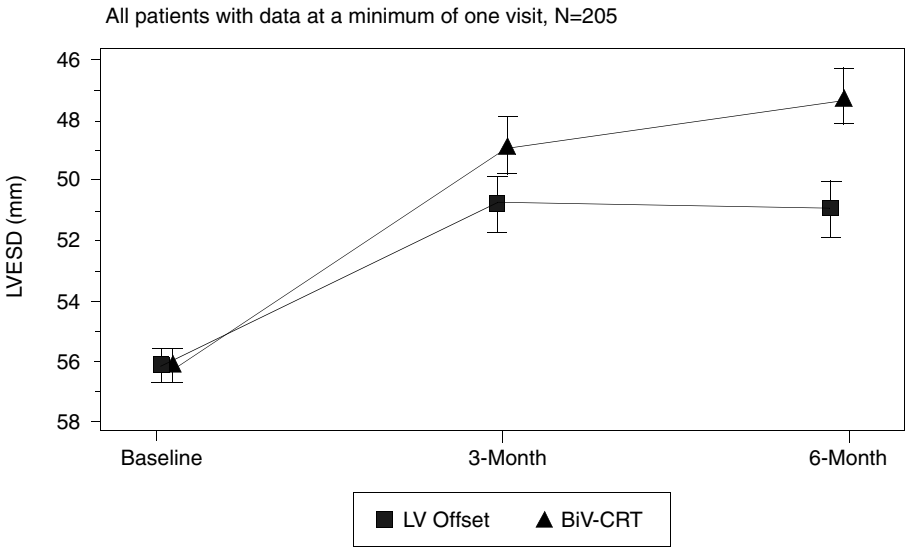

Figure 4. Improvement in LVESD at Six Months.

Statistic	LV Offset		BiV-CRT	
	N[a]	Estimate ± SE	N[a]	Estimate ± SE
Baseline	104	55.7 ± 0.5	100	55.7 ± 0.5
3 Months	97	50.5 ± 0.9	97	48.9 ± 0.9
6 Months	92	50.3 ± 0.9	91	47.1 ± 0.9
Improvement at 6 Months		-5.4 ± 0.7		-8.7 ± 0.7
Confidence Interval Upper Bound		-4.2		-7.5

a. N refers to the number of patients with paired data.

- **Quality of Life (QOL)**

  The effect of CRT on the patient's perceived quality of life was assessed using six-month change in QOL score. The Minnesota Living with Heart Failure Questionnaire® was administered prior to implant and subsequently at the three-month and six-month visits. A longitudinal analysis that included all patients with data at a minimum of one visit was performed to estimate six-month change from baseline in each group.

  As shown in Figure 5, both arms showed a statistically significant and clinically meaningful improvement (≤10 points) in QOL, an endpoint considered clinically meaningful in previous randomized controlled trials of CRT. The null hypothesis

was to be rejected if the upper one-sided 95% confidence bound were less than zero. The observed upper one-sided confidence bound for LV Offset was -19.4 points.

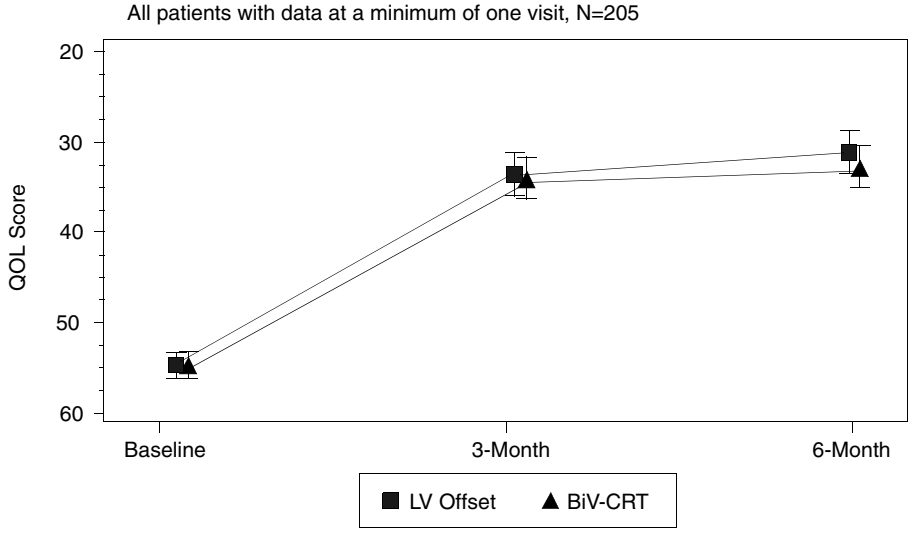

Figure 5. Improvement in Quality of Life at Six Months.

Statistic	LV Offset		BiV-CRT	
	N	Estimate ± SE	N	Estimate ± SE
Baseline	100	54.6 ± 1.4	98	54.6 ± 1.4
3 Months	94	33.5 ± 2.4	95	34.0 ± 2.3
6 Months	88	31.3 ± 2.4	91	32.5 ± 2.4
Improvement at 6 Months		-23.4 ± 2.4		-22.1 ± 2.4
Confidence Interval Upper Bound		-19.4		-18.1

- **NYHA Class**

  The effect of CRT on the patient's heart failure related symptoms (as measured by NYHA Class) was assessed prior to implant and subsequently at the three-month and six-month visits. The analysis of NYHA Class included all patients with data at enrollment and six months.

  As shown in Figure 6, both arms showed a statistically significant percentage of patients who improved at least one NYHA Class, an endpoint considered clinically meaningful in previous randomized controlled trials of CRT. The null

hypothesis was to be rejected if the lower one-sided 95% confidence bound of the percentage of patients improving one or more NYHA Class were greater than zero. The observed lower one-sided confidence bound for LV Offset was 47.9%.

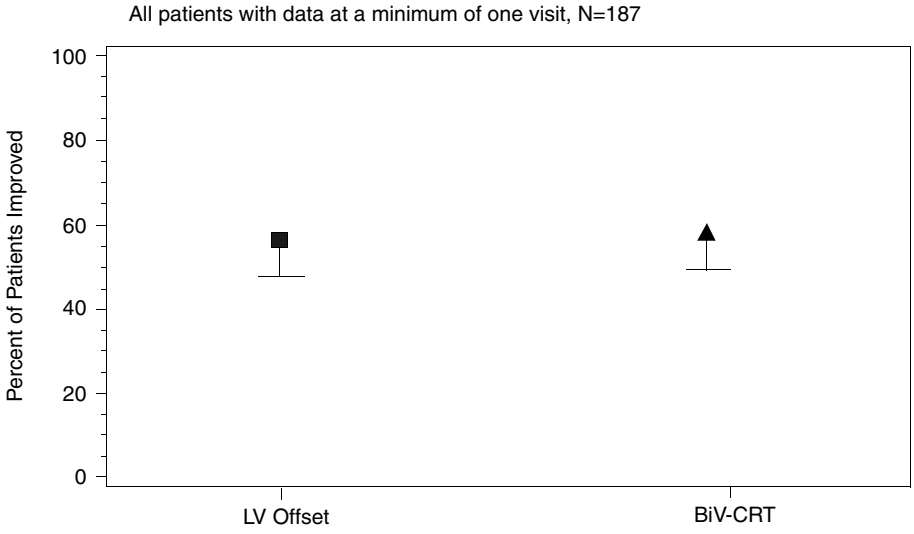

Figure 6. Improvement in NYHA Class at Six Months.

Statistic	LV Offset	BiV-CRT
Total Patients	95	92
Number (Percent) of Patients Improved	54 (56.8%)	54 (58.7%)
Lower Bound of One-Sided Exact 95% Confidence Interval	47.9%	49.6%

Table 4 provides additional detail, showing the percent of patients who improved two or three classes, as well as the percent of those who had no change or worsened.

Table 4. Six-Month Change in NYHA, by Treatment Group[a]

6-Month Change in NYHA	LV Offset (N=95)	BiV-CRT (N=92)	Total (N=187)
Improved 3 Classes	1 (1.1)	0 (0.0)	1 (0.5)
Improved 2 Classes	16 (16.8)	8 (8.7)	24 (12.8)
Improved 1 Class	37 (38.9)	46 (50.0)	83 (44.4)
No Change	35 (36.8)	36 (39.1)	71 (38.0)
Worsened 1 Class	6 (6.3)	2 (2.2)	8 (4.3)

a. All patients with paired data; N=187.

Device Effectiveness

Primary Endpoint: Ventricular Tachycardia/Fibrillation Detection Time The objective of this endpoint was to demonstrate that CRT does not affect the ability to detect VT/VF. The results for VT/VF detection time are shown in Table 5.

Table 5. VT/VF Detection Time[a]

Number of Patients	Mean	SD	Upper Bound of One-Sided 95% Confidence Interval
338	2.46	0.58	2.50

a. All patients implanted with non-missing data; N=338.

The null hypothesis was to be rejected if the upper one-sided 95% confidence bound for mean VF detection time were less than 6 seconds. The observed upper one-sided 95% confidence bound for VF detection time was 2.50 seconds. These data demonstrate device effectiveness in the detection of VT/VF.

Therapy Safety

Primary Endpoint: Heart Failure Related Adverse Event Free Rate Therapy safety was assessed by the heart failure related adverse event free rate observed through six months of therapy delivery (randomization visit through six months post-randomization). The heart failure related adverse event free rate is defined as the number of patients who do not experience a heart failure related adverse event divided by the total number of patients implanted and active at the randomization visit. All patients who were successfully implanted and remained active at the randomization visit were included in the analysis.

Table 6 summarizes the heart failure related adverse event rates through the six-month visit. A Kaplan-Meier analysis is also presented in Figure 7 to show time to events.

Table 6. Heart Failure Related Adverse Event Free Rate at Six Months[a]

Adverse Event	Number of Events	Number of Patients	Heart Failure Adverse Event Free Rate	Lower One-Sided 95% Confidence Bound
Multiple heart failure symptoms	38	29	91.4	88.5
Dyspnea - Heart failure	13	13	96.2	94.0
Heart failure symptoms - Unspecified	13	12	96.4	94.3
Hypotension - Heart failure	10	9	97.3	95.4
Weight gain - Heart failure	5	4	98.8	97.3
Fatigue - Heart failure	4	4	98.8	97.3
Pulmonary edema - Heart failure	4	4	98.8	97.3
Renal insufficiency - Heart failure	4	3	99.1	97.7
Gastrointestinal - Heart failure	3	3	99.1	97.7
Multi-system failure - Heart failure	2	2	99.4	98.1
Peripheral edema - Heart failure	2	2	99.4	98.1
Chest pain - Heart failure	1	1	99.7	98.6
Dehydration - Heart failure	1	1	99.7	98.6
Dizziness - Heart failure	1	1	99.7	98.6
Elevated BNP - Heart Failure	1	1	99.7	98.6
Total	102	67	80.2	76.3

a. All patients implanted and active at the randomization visit; N=338.

The null hypothesis was to be rejected if the lower one-sided 95% confidence bound for heart failure adverse event free rate through six months post-implant were greater than 50%. The heart failure related adverse event free rate at six months was 80.2% with a lower one-sided 95% confidence bound of 76.3%.

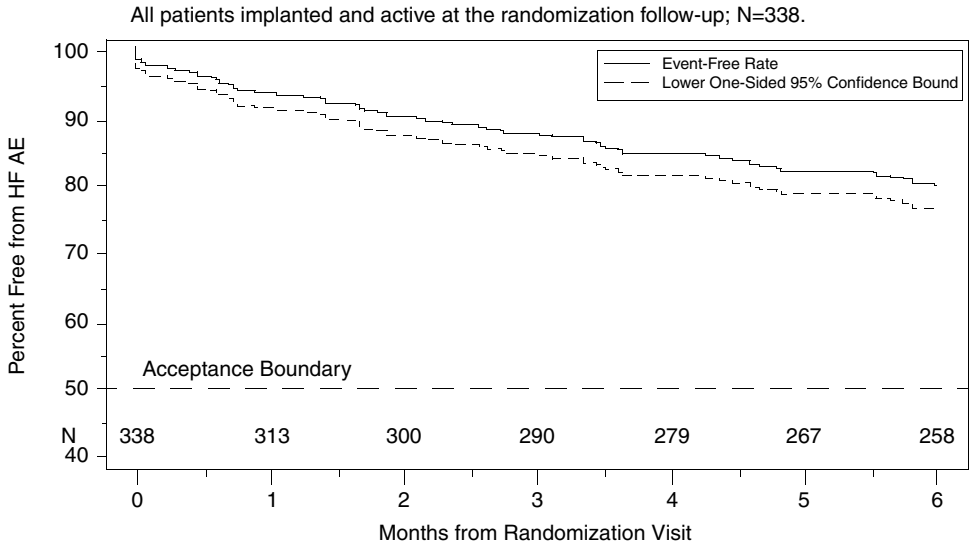

Figure 7. Time to Heart Failure Related Adverse Event.

Device Safety

Primary Endpoint: System Related Complication Free Rate The safety of the investigational system was assessed by the system related complication free rate observed in the period between implant and six months post-implant in all patients attempted or implanted. System related complication free rate is defined as the proportion of patients without a system related complication within six months post-implant. All patients who underwent an implant procedure were included in the analysis. Table 7 shows the system related complication free rates by event type. A Kaplan-Meier analysis is also presented in Figure 8 to show time to events.

Table 7. System Related Complication Free Rate at Six Months[a]

Complication	Number of Events	Number of Patients	Complication Free Rate	Lower One-Sided 95% Confidence Bound
LV Lead	35	31	91.3	88.5
RA Lead	11	9	97.5	95.7
RV Lead	3	3	99.2	97.8
PG	14	14	96.1	94.0
Procedure	17	16	95.5	93.3
Total[b]	80	60	83.2	79.7

a. All patients implanted or attempted; N=358
b. Includes patients in the Safety Arm.

The null hypothesis was to be rejected if the lower one-sided 95% confidence bound for system related complication rate through six months post-implant were greater than 70%. The system related complication free rate at six months was 83.2% with a lower 95% confidence bound of 79.7%.

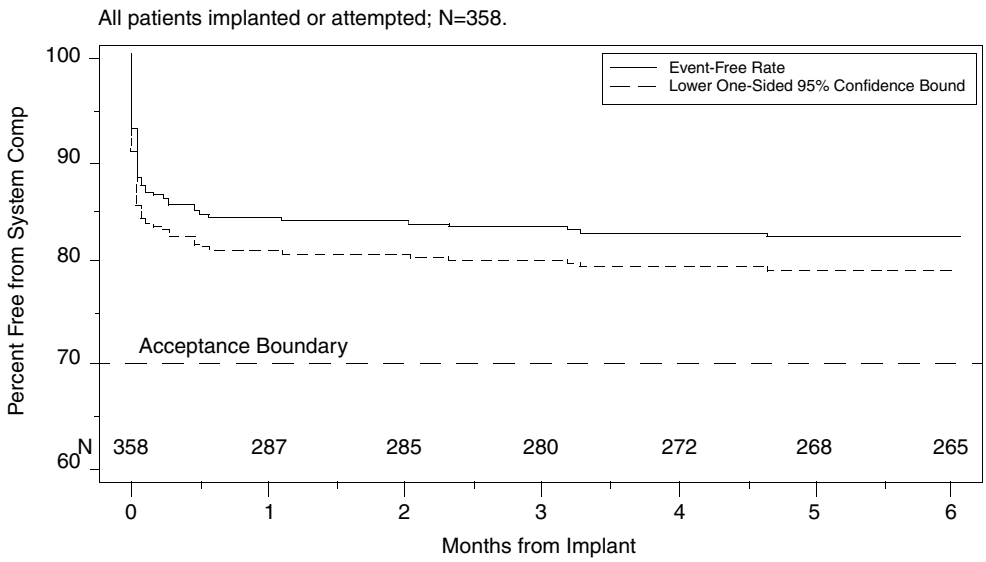

Figure 8. Time to System Related Complication.

Ancillary Endpoints: The Holter Substudy

Sixty-nine patients at nine centers were included in the Holter Substudy. Data were collected at the three-month visit at centers participating in the Holter Substudy. Holter recordings were analyzed by a Holter core laboratory.

Continuous Appropriate Pacing During Activities of Daily Living The safety of CRT therapy provided by the investigational system was assessed by the percent of time a patient is appropriately paced over a 24-hour period, as recorded with a Holter monitor at the three-month visit. The appropriateness of CRT delivery is defined by whether the device delivers CRT in accordance with the physician's programming. The objective of this endpoint was to demonstrate that patients receive continuous appropriate pacing from the device during activities of daily living.

It is expected that patients will receive pacing approximately 95% of the time on average. The null hypothesis was to be rejected if the lower one-sided 95% confidence bound of the mean time paced were greater than 90%. Due to the non-normality of the data, a non-parametric test of the median was performed, which compared the median to 90% instead of comparing the lower 95% confidence bound of the mean to 90%.

As shown in Table 8, the mean percentage of appropriately paced beats during activities of daily living was 99.5 ±1.3 with a median of 100.0% (p <0.01).

Table 8. Continuous Appropriate Pacing During Activities of Daily Living[a]

Statistic	Result
N	69
Mean ± SD	99.5 ± 1.3
Median	100.0
Range	93.1 - 100.0
P-value[b]	<0.01

a. All patients in the Holter Substudy; N=69.
b. P-value calculated from a signed-rank test.

Continuous Appropriate Pacing During Exercise The safety of CRT therapy provided by the investigational system was assessed by the percent of time a patient receives appropriate pacing during the patient's three-month CPX test, as recorded with a Holter monitor. The appropriateness of CRT delivery is defined by whether or not the device delivers CRT in accordance with the physician's programming. The objective of this endpoint was to demonstrate that patients receive continuous appropriate pacing from the device during exercise.

It is expected that patients will receive pacing approximately 95% of the time on average. The null hypothesis was to be rejected if the lower one-sided 95% confidence bound of the mean time paced were greater than 90%. Due to the non-normality of the data, a non-parametric test of the median was performed comparing the median to 90% instead of comparing the lower 95% confidence bound to 90%.

Table 9 shows that the mean percentage of appropriately paced beats during exercise was 99.4 ±1.9 with a median of 100.0% (p < 0.01).

Table 9. Continuous Appropriate Pacing During Exercise[a]

Statistic	Result
N	67
Mean ± SD	99.4 ± 1.9
Median	100.0
Range	90.3 - 100.0
P-value[b]	< 0.01

a. All patients in the Holter Substudy; N=67.
b. P-value calculated from a signed-rank test.

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