Sub-study Primary Endpoint and Additional Tertiary Endpoints

Exercise performance—the co-primary endpoint, which consists of Peak VO_2 and Six-Minute Walk, is designed to demonstrate improvement in exercise performance with CRT (CONTAK TR and CONTAK CD pooled data) compared to OPT at six months post-baseline.

Additional tertiary endpoints included Quality of Life as measured by the Minnesota Living with Heart Failure Questionnaire® and NYHA Class.

FOLLOW-UP SCHEDULE

The follow-up schedule included the following:

- Enrollment—initial assessment of patient eligibility; taking of patient history
- Baseline screening—special testing (included a Symptom-Limited Treadmill Test with measurement of oxygen uptake (Peak VO_2), a Six-Minute Walk, Quality of Life [QOL] questionnaire and NYHA Classification)
- Randomization—randomization status (OPT, CRT-P, or CRT-D) was assigned
- Implant (CRT-P or CRT-D arm)—implant of investigational devices and acute device testing for those randomized to a CRT therapy arm
- Routine follow-up—routine evaluation of device function and patient condition at pre-discharge, one week, and one month post-implant
- Three- and six-month visits—evaluation of randomized therapy with special testing and device function at three and six months after the Post-Recovery Visit
- Quarterly Visits—after the six-month visit, patients were seen for routine evaluation of device function and patient condition

DEMOGRAPHIC DATA

All baseline patient characteristics are presented in Table B-5 on page B-16.

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Table B-5. Patient population characteristics for COMPANION (OPT and CRT-D)

Characteristic		OPT (N = 308)	CRT-D (N = 595)	P-value
Age (years)	Mean ± SD	66.7 ± 10.7	65.6 ± 11.2	0.14
Gender [N (%)]	Female	97 (31.4)	194 (32.6)	0.73
	Male	211 (68.5)	401 (67.3)	0.73
NYHA Classification [N (%)]	Class III	253 (82.1)	512 (86.1)	0.12
	Class IV	55 (17.8)	83 (13.9)	0.12
Ischemic Etiology (%)	Ischemic	58.7	54.6	0.13
	Non-ischemic	41.3	45.4	0.13
LVEF (%)	Mean ± SD	22.8 ± 7.2	22.5 ± 6.8	0.47
Resting Heart Rate (bpm)	Mean ± SD	72 ± 12	73 ± 13	0.37
QRS Width (ms)	Mean ± SD	156 ± 24	159 ± 24	0.09
Conduction Abnormality (%)	LBBB	69.8	72.9	0.21
	Non-specific	21.4	16.8	0.21
	RBBB	8.77	10.2	0.21
Duration of Heart Failure (years)	Mean ± SD	4.86 ± 4.41	4.44 ± 3.83	0.43
Heart Failure Medications [(%)]	Diuretic	94.4	96.6	0.12
	ACE inhibitor or ARB	88.6	89.6	0.66
	Beta Blockers	66.2	67.6	0.69
	Aldosterone Antagonist	54.8	55.1	0.94
	Digoxin	67.2	70.9	0.25

PATIENT ACCOUNTABILITY AND FOLLOW-UP DURATION

The COMPANION study enrolled 1638 patients, with 1520 patients randomized to a treatment group and one hundred eighteen patients (118) not randomized due to changes in patient condition or consent between time of enrollment and time of randomization, such that the inclusion criteria were no longer satisfied. Of the 1520 patients, 595 were randomized to CRT-D with a mean follow-up of 1.3 years and 308 were randomized to OPT with a mean follow-up of 1.1 years. Figure B-1 on page B-18 provides an overview of patient enrollment.

Table B-6 on page B-17 gives a summary (by treatment group) of patient disposition over time through 12 months after randomization. This does not

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account for patients that had a hospitalization or death event that contributed to the primary endpoint or secondary endpoint of all-cause mortality.

Table B-6. Patient follow-up disposition 12 months post-randomization

	CRT-D				OPT			
	# of Withdrawn Patients	**# of Deceased Patients**	**(N = 595) # Reached end of study (Nov. 30, 2002)**	**# of Active Patients at end of time interval**	**# of Withdrawn Patients**	**# of Deceased Patients**	**(N = 308)# Reached end of study (Nov. 30, 2002)**	**# of Active Patients at end of time interval**
1 Day - 7 Days	4	3	0	588	6	0	0	302
7 Days - 1 Month	4	3	5	576	10	3	1	288
1 Month - 3 Months	4	15	6	551	11	11	1	265
3 Months - 9 Months	12	28	49	462	26	22	29	188
9 Months - 12 Months	1	12	35	414	11	11	19	147

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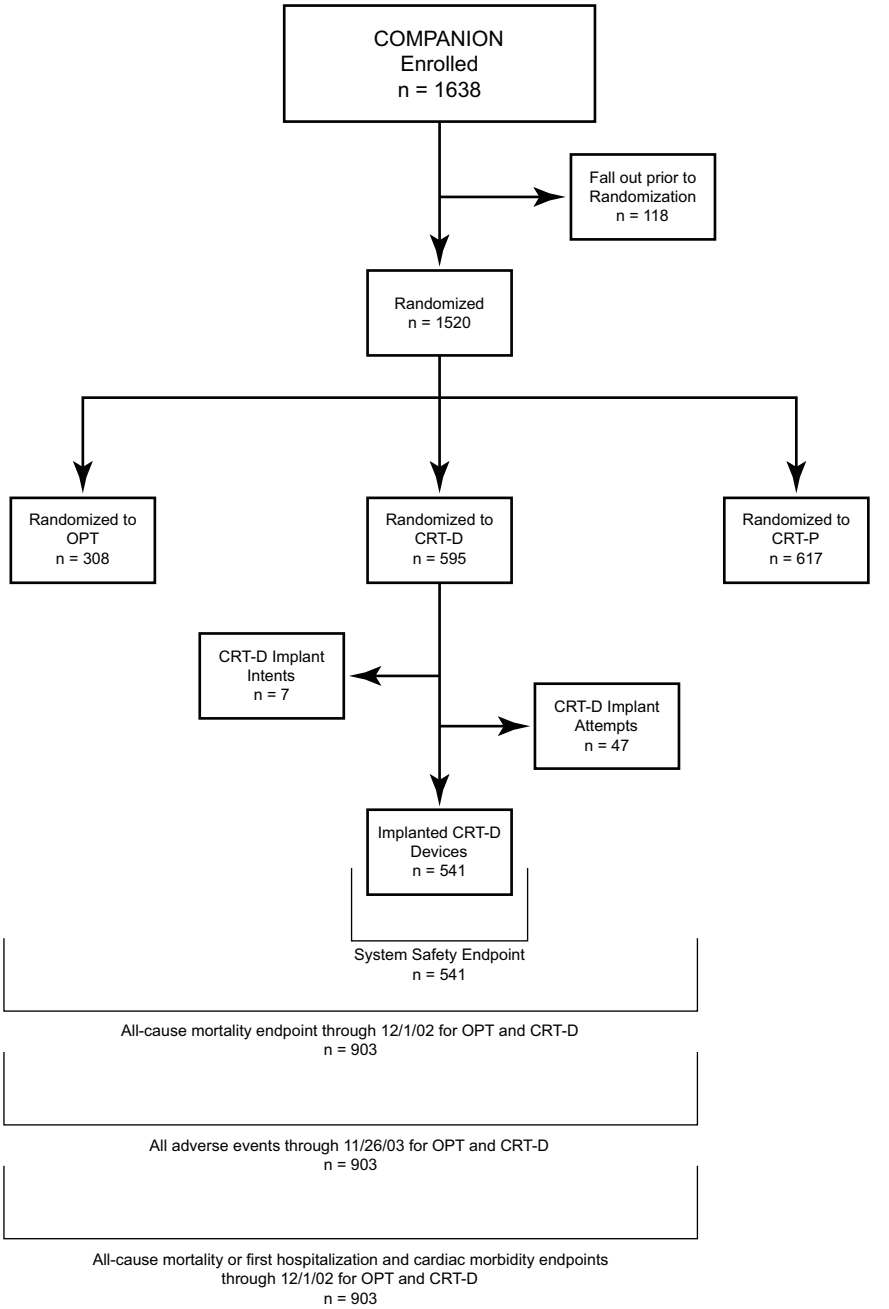

Figure B-1. Study patient enrollment and randomization for CRT-D and OPT

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Event Contributing to Primary Endpoint and Secondary Endpoint of All-cause Mortality

A total of 903 COMPANION patients in the CRT-D (595) and OPT (308) groups were eligible for the primary endpoint. Figure B-2 on page B-19 provides patient randomization and status for the primary endpoint and Figure B-3 on page B-19 provides patient randomization and status for the secondary mortality endpoint.

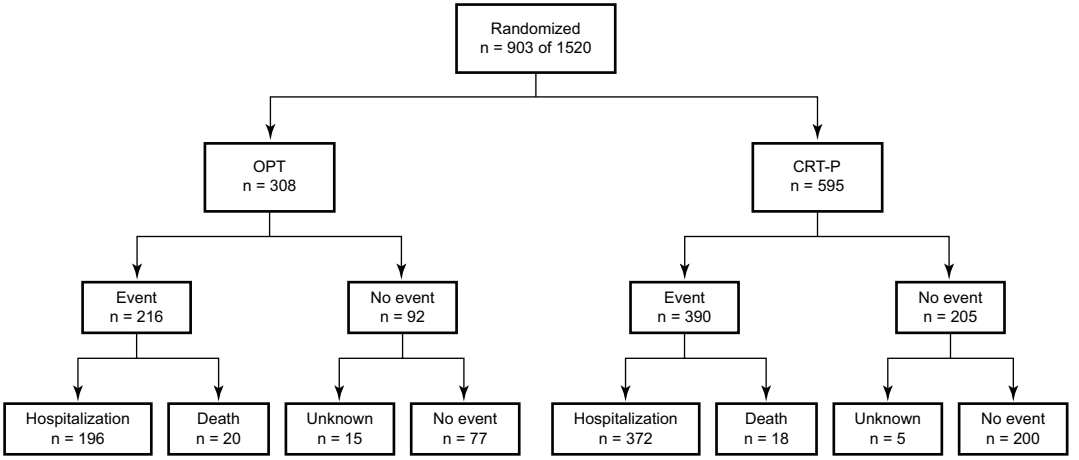

Figure B-2. CRT-D and OPT patient randomization for primary endpoint

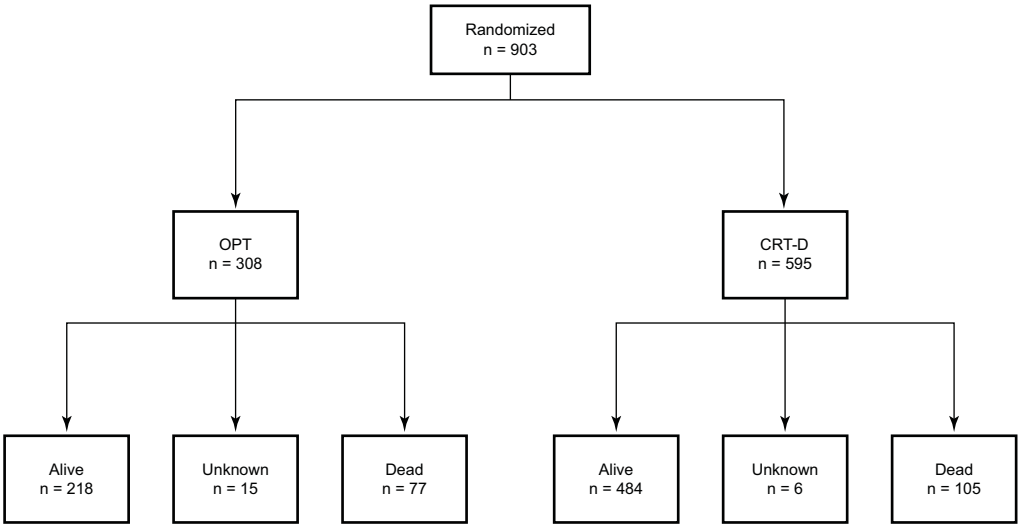

Figure B-3. CRT-D and OPT patient randomization for mortality endpoint

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DATA ANALYSIS AND RESULTS FOR PRIMARY ENDPOINT AND SECONDARY ALL-CAUSE MORTALITY ENDPOINT

Sequential Monitoring

The COMPANION DSMB met approximately every six months to review the trial's progress and to review the safety and effectiveness data collected. An "O'Brien-Fleming" type boundary as implemented by Lan and DeMets was used in monitoring the trial. The Group sequential procedure ensured that the total alpha spent across repeated analyses did not exceed the total type I error, in this case a = 0.03.

On November 18, 2002 the DSMB reviewed the study progress for the final time. The CRT-D arm of the Study had reached the target number of events for both the combined mortality and hospitalization endpoint as well as the all-cause mortality endpoint prompting the DSMB to recommend to the Steering Committee that enrollment be stopped. All effectiveness follow-ups ended on December 1, 2002.

Results

Primary Endpoint: All-cause Mortality or First Hospitalization

The Kaplan-Meier curves illustrate the time to all-cause mortality or first hospitalization (Figure B-4 on page B-21). There were 216 primary endpoint events observed in the OPT arm and 390 in the CRT-D arm (p = 0.010; p = 0.011 after adjustment for interim analyses). The median time to first event was 209 days in the OPT group and 269 days in the CRT-D group. The annual event rates for OPT and CRT-D, respectively, were 68.0% and 55.9%, with a hazard ratio of 0.80; 95% CI (0.68, 0.95). This result demonstrated that CRT-D significantly reduced the relative risk of all-cause mortality or first hospitalization by 20% when compared to OPT alone.

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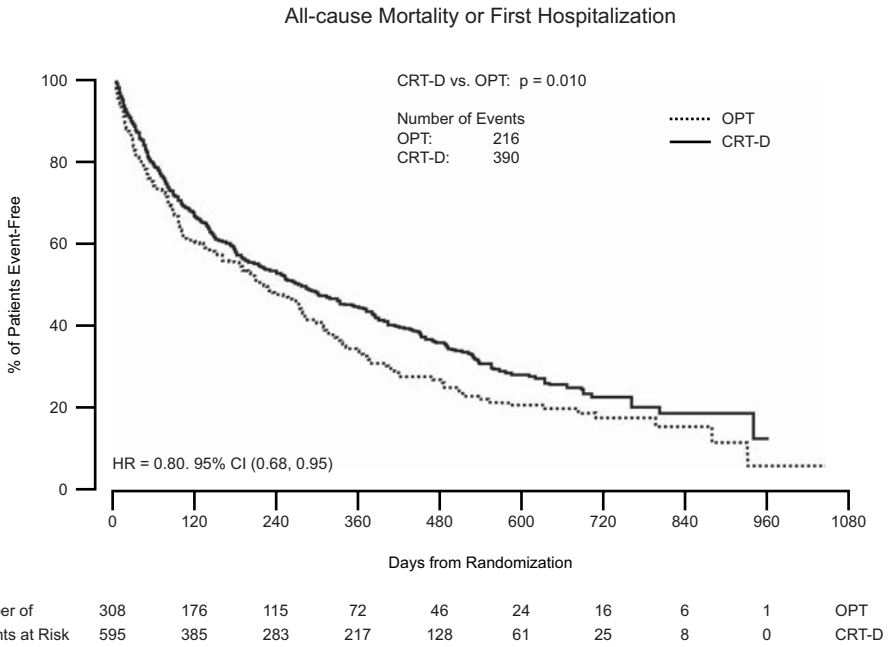

Figure B-4. Primary Endpoint: All-cause mortality or first hospitalization

In addition to the hazard ratio, point estimates of risk reduction were also calculated (Table B-7 on page B-21). These estimates will vary with time from the true treatment effect, and thus should be interpreted with caution.

Table B-7. Risk reduction point estimates

	% Failure		Absolute Risk Reduction	Relative Risk Reduction
	OPT	CRT-D		
6 months	44.9% (38.9%, 50.3%)	42.9% (38.7%, 46.7%)	2.0%	4.5%
12 months	68.0% (61.7%, 73.2%)	55.9% (51.6%, 59.8%)	12.1%	17.8%
18 months	77.8% (71.6%, 82.7%)	69.0% (64.5%, 73.1%)	8.8%	11.3%

Secondary Endpoints

All-cause Mortality—deaths from any cause were reported in 77 patients randomized to OPT and 105 patients randomized to CRT-D (p = 0.003, p = 0.004 after adjusting for interim analyses). The Kaplan-Meier curves are

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depicted in Figure B-5 on page B-22. These numbers correspond to an annual mortality rate of 19% in the OPT arm and 12% in the CRT-D arm, with a hazard ratio of 0.64, 95% CI (0.48, 0.86). These results demonstrated that CRT-D was associated with a 36% reduction in the risk of all-cause mortality when compared to OPT alone.

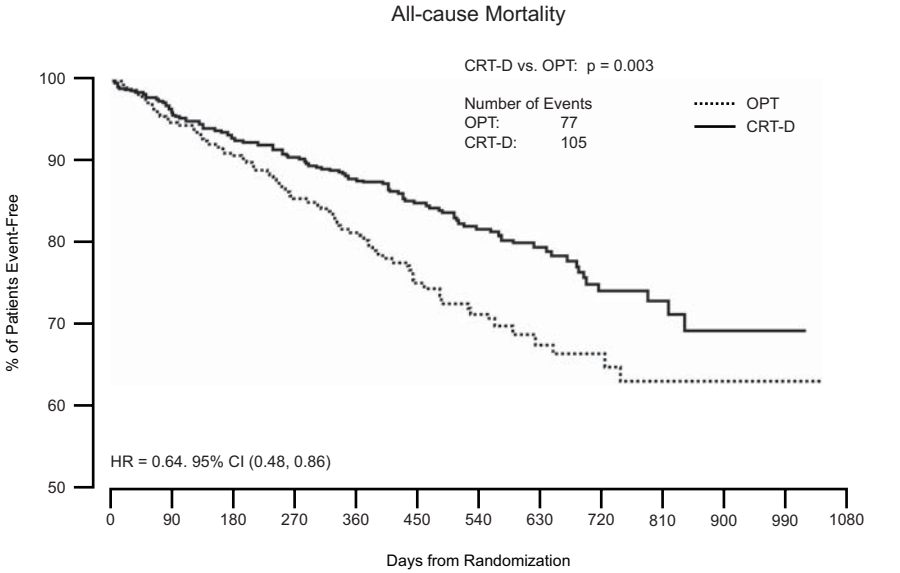

Figure B-5. Secondary Endpoint: All-cause mortality

In addition to the hazard ratio, point estimates of risk reduction were also calculated (Table B-8 on page B-22). These estimates will vary with time from the true treatment effect, and thus should be interpreted with caution.

Table B-8. Mortality endpoint risk reduction point estimates

	% Failure		Absolute Risk Reduction	Relative Risk Reduction
	OPT	CRT-D		
6 months	9.0% (5.7%, 12.2%)	7.3% (5.1%, 9.3%)	1.7%	18.9%

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Table B-8. Mortality endpoint risk reduction point estimates (continued)

	% Failure		Absolute Risk Reduction	Relative Risk Reduction
	OPT	CRT-D		
12 months	18.9% (14.1%, 23.5%)	12.1% (9.3%, 14.8%)	6.8%	36.0%
18 months	28.4% (22.3%, 34.1%)	18.0% (14.4%, 21.5%)	10.4%	36.6%

Results for Secondary Cardiac Morbidity Endpoint

During a hospitalization more than one of the pre-specified cardiac morbid events could occur. The Anderson-Gill extension to the Cox proportional hazard model was used to analyze time to multiple cardiac morbid events. Caution must be used in interpreting p-values in this analysis because this analysis does not account for the competing risk of death.

In Figure B-6 on page B-24, the frequency and duration of cardiac morbid events are illustrated. CRT-D was associated with a 36% reduction ($p < 0.0001$) in the proportion of patients with at least one event, a 52% reduction ($p < 0.0001$) in events on an annual basis, and a 41% reduction ($p < 0.0001$) in the hospital duration on an annual basis. These reductions are primarily due to the reduction of hospitalizations for acute decompensation of heart failure, worsening heart failure resulting in IV inotrope or vasoactive therapy > 4 hours (during an inpatient hospitalization) and cardiac surgery (including percutaneous intervention) (Figure B-7 on page B-24).

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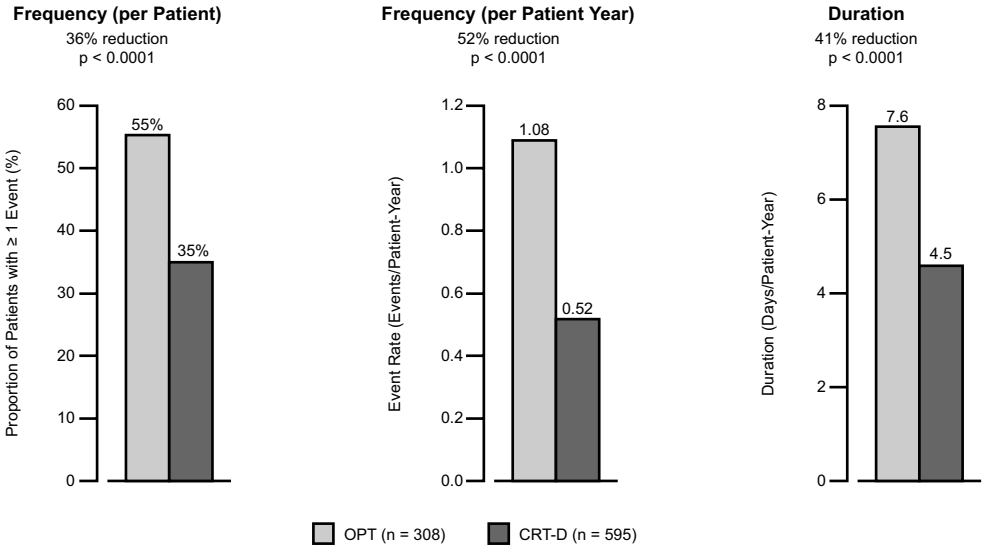

Figure B-6. Secondary Endpoint: cardiac morbidity

Caution must be used in interpreting p-values; analysis does not account for competing risk of death.

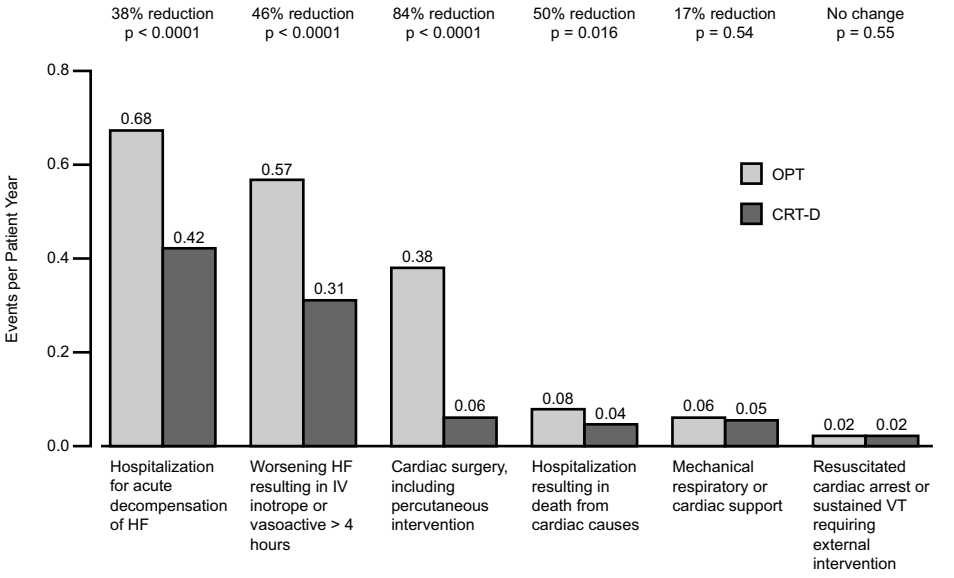

Figure B-7. Cardiac morbidity by major component

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For a given cardiac hospitalization, patients may have events in more than one category, and if there are multiple occurrences in a single category, then only the first occurrence was counted.

ADDITIONAL STUDY DATA

Implant Disposition

Table B-9 on page B-25 identifies the number of initial and subsequent implant procedures attempted in patients randomized to CRT-D and the rate of success for each additional implant procedure. There were 81 CRT-D patients that had an unsuccessful initial implant for the CRT-D system. Fifty (50) of these patients had a second implant procedure, of which 33 were successful and 17 were unsuccessful. Three patients had a third implant procedure, of which one was successful. Therefore, there were 541 patients implanted with the CRT-D system.

Table B-9. CRT-D system implant disposition

		Attempt successful	Failed implant	Reattempt not done after this procedure
Initial implants	588 (98.8%)	507 (85.0%)	81 (14.0%)	31 (5.2%)
First reattempt	50 (8.4%)	33 (5.5%)	17 (2.9%)	14 (2.3%)
Second reattempt	3 (0.5%)	1 (0.2%)	2 (0.3%)	2 (0.34%)

ADDITIONAL OUTCOME MEASURES

First Heart Failure Hospitalizations

An additional outcome that was not pre-specified in the protocol provides further insight into the results observed in the composite primary endpoint. This post-hoc analysis was conducted using cause-specific hospitalizations as adjudicated by the morbidity and mortality committee and therefore should be interpreted with caution.

The outcome of all-cause mortality or first heart failure hospitalization was analyzed on an intention-to-treat basis and time to first event.

Hospitalizations were defined per any of the following:

- Care provided at a hospital for any reason in which the duration is associated with a date change

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- Use of intravenous inotropes and/or vasoactive drugs for a duration > 4 hours (inpatient or outpatient)

NOTE: *Hospitalizations associated with a device implant attempt or re-attempt are excluded.*

Those contributing to the heart failure hospitalization outcome were required by the Morbidity and Mortality committee to meet at least one of the following additional criteria:

- IV diuretics
- IV inotrope/vasoactive therapy
- Other parenteral therapy for the treatment of heart failure
- Significant alterations in oral therapy for the treatment of heart failure

All-cause Mortality or First Heart Failure Hospitalization

The Kaplan-Meier curves for all-cause mortality or first heart failure hospitalization is shown in Figure B-8 on page B-27. OPT and CRT-D had annual event rates of 45% and 29%, respectively with a hazard ratio of 0.60, 95% CI (0.49-0.75), $p < 0.001$. Therefore, CRT-D was associated with a 40% relative reduction in the risk of all-cause mortality or first heart-failure hospitalization when compared to OPT alone.

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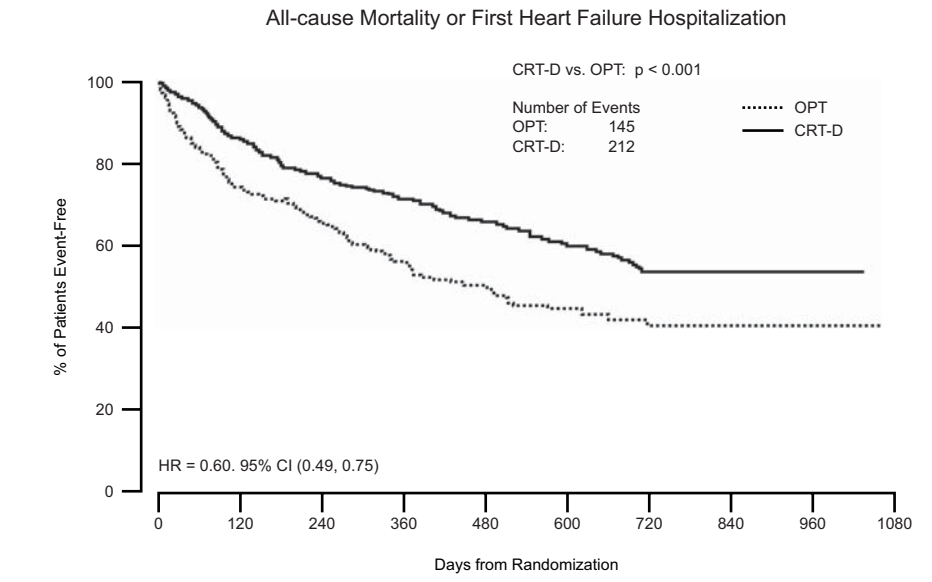

Figure B-8. All-cause mortality or first heart failure hospitalization

Disposition of Hospitalization

Implantation of the CRT-D system generally requires hospitalization. To differentiate between the hospitalization required to implant the system and those hospitalizations that occurred after the system was implanted, the following terms are used:

- Implant hospitalization—the elective hospitalization associated with either the implant procedure or a repeat implant procedure if the initial procedure was unsuccessful.

- All other hospitalizations—patients who required a revision for an implanted system (e.g., lead dislodgment or infection) were included in this category as were hospitalizations for non-elective device related implants.

The hospitalizations analysis (Figure B-9 on page B-28) and hospitalization days analysis (Figure B-10 on page B-28) depicts hospitalization data stratified by implant and non-elective hospitalizations. This analysis was on an intention-to-treat basis and includes patients who underwent an attempted implant procedure. Patients randomized to CRT-D had a follow-up duration approximately 30% longer than OPT patients. Thus, hospitalization data

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are normalized per patient-year of follow-up. An additional comparison of hospitalization days for heart failure hospitalizations is shown in Figure B-11 on page B-29.

NOTE: *CRT-D was associated with a reduction in all-cause mortality and therefore there is a competing risk for hospitalizations. This data should be interpreted with caution.*

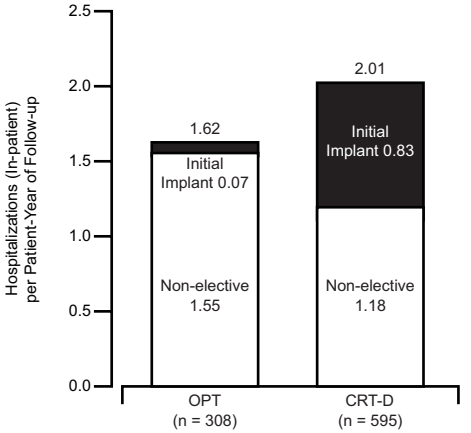

Figure B-9. Hospitalizations per patient year

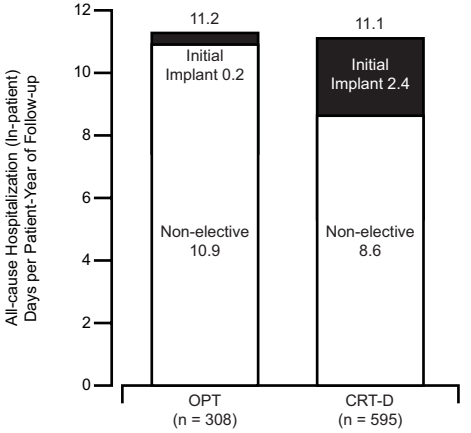

Figure B-10. Hospitalization days per patient year

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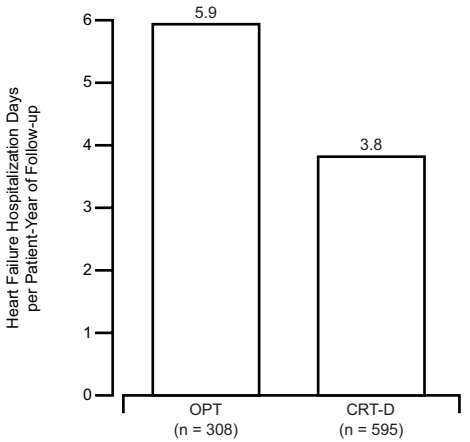

Figure B-11. Heart failure hospitalization days per patient year

DATA ANALYSIS AND RESULTS - CRT-D SYSTEM SAFETY

The system-related complication-free rate analysis was not a predefined endpoint in the protocol. The intent of this analysis is to provide reasonable assurance of safety of the CONTAK CD system in this patient population.

The system-related complication-free rate was defined over a six-month follow-up period as the proportion of patients who are free of complications attributed to:

- Any implanted component (e.g, pulse generator, coronary venous lead, right atrial pace/sense lead, cardioversion/defibrillation lead)
- The surgical procedure required to implant the CRT-D system

In the COMPANION study, this analysis was performed on an intention-to-treat basis and also extends to those patients who underwent an implant procedure but did not ultimately receive a device. Of the 595 patients analyzed, 522 (87.7%) were free of system-related complications.

Of the 73 (12.3%) patients who experienced a system-related complication, the most common were loss of left ventricular capture (25 patients, 4.2%), loss of right atrial capture (9 patients, 1.5%), and phrenic nerve/diaphragmatic stimulation (8 patients, 1.3%).

When analyzed on a time-to-event basis, the system-related complication-free rate was 87.7%. The safety performance of the CONTAK CD system compares favorably with the safety performance observed in the prior CONTAK CD study (P010012, May 2, 2002).

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DATA ANALYSIS AND RESULTS - COMPANION SUB-STUDY

The Exercise Performance Sub-study consisted of the following components.

CRT Effectiveness

Primary Co-primary endpoint consisting of Peak VO_2 derived from a symptom-limited exercise test and Six-Minute Walk, with CRT results pooled from the CONTAK TR and CONTAK CD arms.

Effectiveness was determined by assessing both Peak VO_2 and Six-Minute Walk distance improvements with CRT compared to OPT.

Prospectively, success was defined as occurring if either of the following occurred:

- Peak VO_2 improved ≥ 0.7 ml/kg/min ($p < 0.05$) and 6 MWD improvement resulted in $p < 0.10$
- Peak VO_2 improved ≥ 0.5 ml/kg/min ($p < 0.10$) and 6 MWD improvement resulted in $p < 0.05$

Additional: Quality of Life as measured by the Minnesota Living with Heart Failure Questionnaire®, and NYHA Class

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Patient Accountability (Figure B-12 on page B-31)

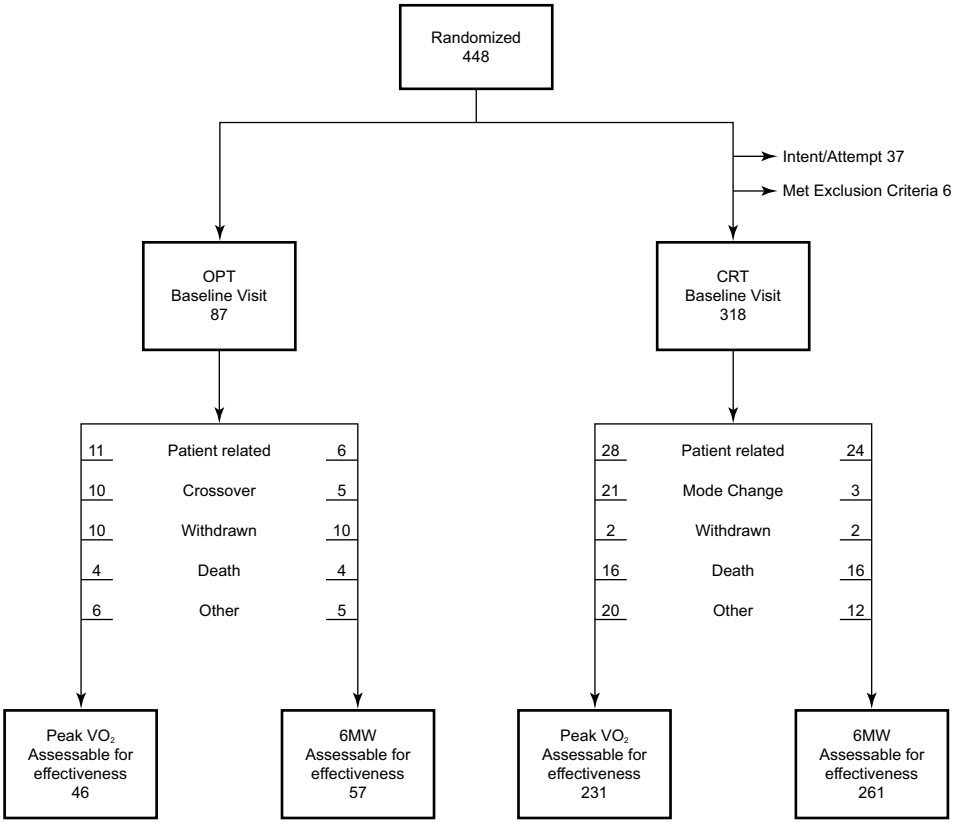

Figure B-12. Enrollment and follow-up of randomized patients

Baseline Characteristics— (Table B-10 on page B-31)

Table B-10. Patient population characteristics

Characteristic		CRT (N = 318)	OPT (N = 87)	P-value[a]
Age (years)	Mean ± SD	62.1 ± 11.8	63.1 ± 10.6	0.48
	Range	32.0–86.0	27.0–85.0	
Gender [N (%)]	Female	109 (34.3)	24 (27.6)	0.24
	Male	209 (65.7)	63 (72.4)	
NYHA Classification [N (%)]	III	294 (92.5)	79 (90.8)	0.61
	IV	24 (7.5)	8 (9.2)	

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Table B-10. Patient population characteristics (continued)

Characteristic		CRT (N = 318)	OPT (N = 87)	P-value[a]
Ischemic Etiology	Ischemic	141 (44.3)	42 (48.3)	0.51
	Non-ischemic	177 (55.7)	45 (51.7)	
LVEF (%)	Mean ± SD	22.5 ± 6.9	22.2 ± 8.0	0.79
	Range	5.0–35.0	5.0–35.0	
Resting Heart Rate (bpm)	Mean ± SD	73.1 ± 12.8	73.5 ± 11.5	0.78
	Range	46.0–122.0	54.0–103.0	
QRS Width (ms)	Mean ± SD	159.2 ± 25.0	155.7 ± 25.8	0.26
	Range	120.0–276.0	120.0–224.0	
LBBB/NSIVCD (%)	LBBB	230 (72.3)	62 (71.3)	0.60
	Nonspecific	54 (17.0)	18 (20.7)	
	RBBB	34 (10.7)	7 (8.0)	
Peak VO_2 (ml/kg/min)	Mean ± SD	12.7 ± 3.3	12.4 ± 3.3	0.42
	Range	3.0–21.2	4.8–21.5	
Six-MInute Walk Distance (m)	Mean ± SD	292.4 ± 65.5	291.6 ± 70.5	0.92
	Range	152.0–411.5	162.4–414.0	
Quality of Life Score (points)	Mean ± SD	59.8 ± 23.1	55.4 ± 23.3	0.12
	Range	0.0–105.0	0.0–97.0	
Heart Failure Medications [N (%)]	Diuretic	300 (94.3)	82 (94.3)	0.98
	ACE Inhibitor or ARB	286 (89.9)	82 (94.3)	0.22
	Beta Blockers	240 (75.5)	60 (69.0)	0.22
	Aldosterone Antagonist	178 (56.0)	51 (58.6)	0.66
	Digoxin	239 (75.2)	65 (74.7)	0.93

a. Continuous data were analyzed using a two-tailed t-test procedure, and categorical data were analyzed using a two-tailed chi-square procedure. A p-value < 0.05 is considered significant.

CRT Effectiveness

Peak VO_2— Peak VO_2 was determined from a standardized protocol for exercise testing as a means of measuring a patient's capacity for performing physical activity (Figure B-13 on page B-33, Table B-11 on page B-33).

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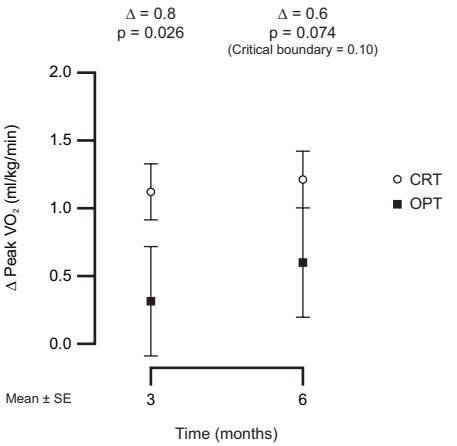

Figure B-13. Maximal Oxygen Consumption Results

Table B-11. Maximal Oxygen Consumption Results

Peak VO_2 (ml/kg/min)	CRT		OPT		P-value[a]
	N	Mean ± S.E.	N	Mean ± S.E.	
Change at 3 months	247	1.1 ± 0.2	52	0.3 ± 0.4	0.026
Change at 6 months	230	1.2 ± 0.2	46	0.6 ± 0.4	0.074

a. P-values obtained using one-tailed longitudinal analysis methods.

The longitudinal analysis was performed on all available data. The percentages of missing data at the six-month endpoints for Peak VO_2 and Six-Minute Walk were 36 percent and 28 percent for the CRT arm and 47 percent and 34 percent for the OPT arm. The longitudinal analysis performed is most appropriate when missing data occurs at the percentages found in this trial.

Six-Minute Walk—the Six-Minute Walk test is a measure of a patient's ability to sustain exercise during an activity similar to that which a patient may typically perform on a daily basis. For this test, patients are instructed to walk as far as possible in 6 minutes in a level corridor (Figure B-14 on page B-34, Table B-12 on page B-34).

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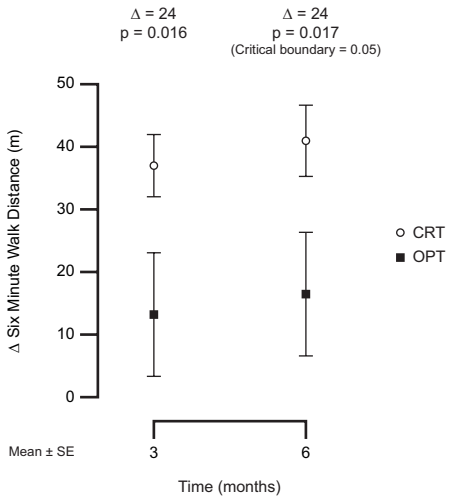

Figure B-14. Change in six-minute walk

Table B-12. Change in six-minute walk

Six-Minute Walk (m)	CRT		OPT		P-value[a]
	N	Mean ± S.E.	N	Mean ± S.E.	
Change at 3 months	274	37 ± 5	63	13 ± 10	0.016
Change at 6 months	260	41 ± 5	57	17 ± 10	0.017

a. P-values obtained using one-tailed longitudinal analysis methods.

NYHA Class—the determination for New York Heart Association (NYHA) Class is based on mutual assessment, by the patient and physician, of the patient's heart failure symptoms both at rest and while performing ordinary physical activity (Figure B-15 on page B-35, Table B-13 on page B-35).

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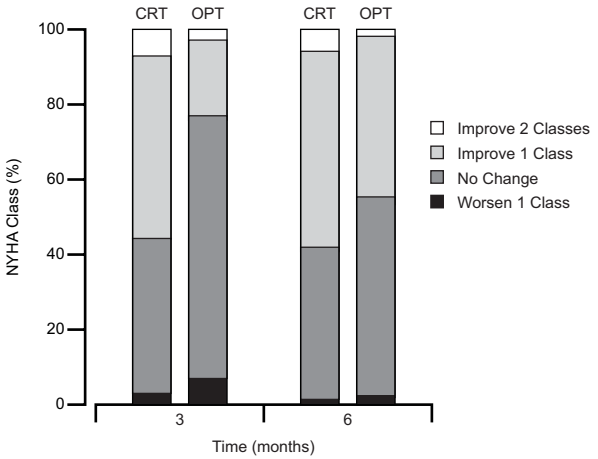

Figure B-15. Change in NYHA

Table B-13. Change in NYHA

NYHA Classification	Change	CRT		OPT		P-value[a]
		N	Patients	N	Patients	
3 months	Improve 2 Classes	294	22 (7.5%)	69	3 (4.4%)	< 0.01
	Improve 1 Class		142 (48.3%)		13 (18.8%)	
	No Change		122 (41.5%)		48 (69.6%)	
	Worsen 1 Class		8 (2.7%)		5 (7.3%)	
6 months	Improve 2 Classes	291	20 (6.9%)	65	2 (3.1%)	0.032
	Improve 1 Class		149 (51.2%)		28 (43.1%)	
	No Change		118 (40.6%)		34 (52.3%)	
	Worsen 1 Class		4 (1.4%)		1 (1.5%)	

a. P-values are not adjusted for multiplicity and were obtained using a one-tailed Mantel-Haenszel chi-square method.

Quality of Life (QOL)—Quality of Life was assessed using the 21-question Minnesota Living with Heart Failure questionnaire. Each question, answered by the patient, is ranked on a scale ranging from 0 to 5. A lower total score indicates an improved quality of life (Figure B-16 on page B-36, Table B-14 on page B-36).

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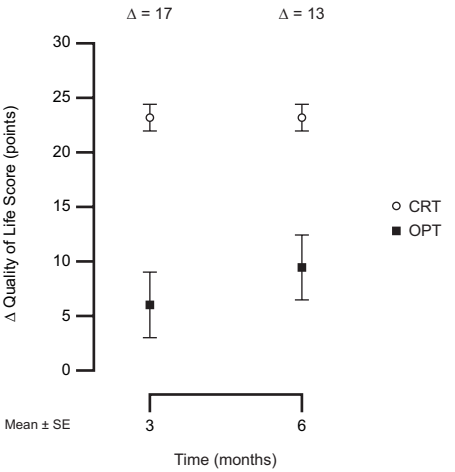

Figure B-16. Quality of Life score

Table B-14. Quality of Life score

Quality of Life (points)	CRT		OPT		P-value[a]
	N	Mean ± S.E. (95% CI)	N	Mean ± S.E. (95% CI)	
Change at 3 months	289	23 ± 1 (20.1, 25.7)	72	6 ± 3 (0.6, 11.3)	< 0.001
Change at 6 months	279	23 ± 1 (19.7, 25.4)	66	10 ± 3 (4.2, 15.2)	< 0.001

a. P-values are not adjusted for multiplicity and were obtained using one-tailed longitudinal analysis methods.

Additional Functional Capacity Data

In addition to the Exercise Performance sub-study, functional capacity was evaluated by means of NYHA Class, six-minute walk distance, and Minnesota Living with Heart Failure Questionnaire QOL for the all patients randomized to OPT and CRT-D through 6-months of follow up.

NYHA Class, six-minute walk distance, and QOL scores were significantly improved in the CRT-D group compared to the OPT group at 3 and 6 months (Table B-15 on page B-36). These findings are similar to those presented in the exercise performance sub-study and previous cardiac resynchronization therapy trials.

Table B-15. Changes in six-minute walk, QOL, and NYHA

	CRT-D		OPT		P-value[a]
Six Minute Walk Distance	N	Mean ± SD	N	Mean ± SD	
Change at 3 months	420	42 ± 98	172	8 ± 82	< 0.0001

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Table B-15. Changes in six-minute walk, QOL, and NYHA (continued)

	CRT-D		OPT		P-value[a]
Change at 6 months	377	45 ± 98	141	2 ± 92	< 0.0001
QOL	N	Mean ± SD	N	Mean ± SD	
Change at 3 months	514	-24 ± 28	243	-8 ± 21	< 0.0001
Change at 6 months	479	-23 ± 28	207	-12 ± 23	< 0.0001
NYHA	N	% Improved	N	% Improved	
Change at 3 months	543	55	242	24	< 0.0001
Change at 6 months	498	57	199	38	< 0.0001

a. P-values are not adjusted for multiplicity and were obtained using t-tests for continuous data and chi-square for categorical data.

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CLINICAL STUDY - DECREASE HF

APPENDIX C

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.

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

STUDY DESIGN

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.

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

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FOLLOW-UP SCHEDULE

The follow-up schedule for the DECREASE HF study is detailed below (Table C-1 on page C-2).

Table C-1. DECREASE HF follow-up schedule

Follow-up period	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.

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:

- Must 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

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- 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

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- Were enrolled in any concurrent study, without Guidant written approval, that may confound the results of this study

DEMOGRAPHIC DATA

Patient enrollment (Figure C-1 on page C-4) and baseline characteristics (Table C-2 on page C-4) are detailed below.

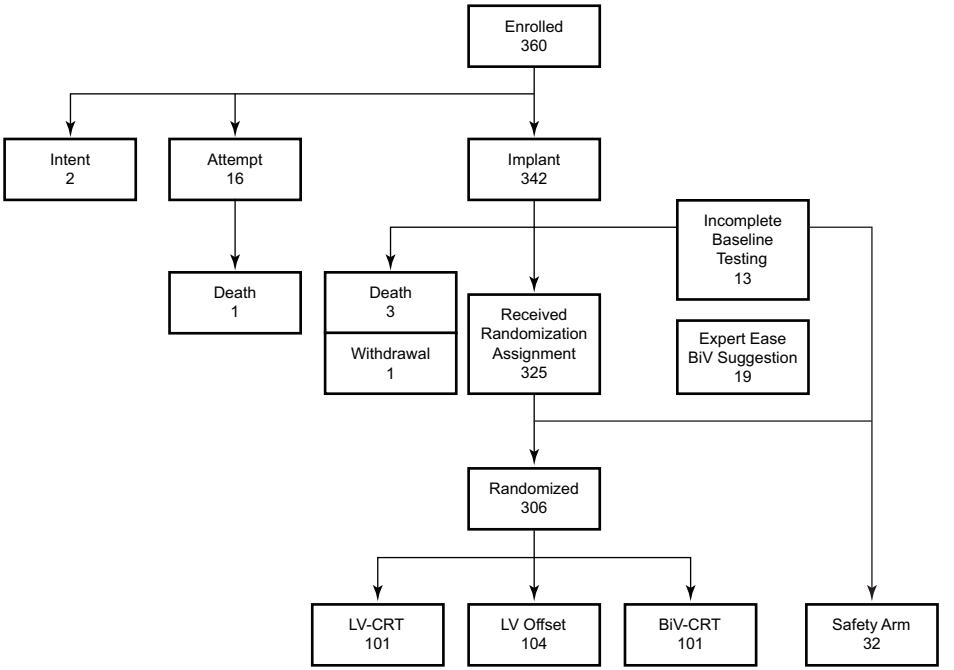

Figure C-1. DECREASE-HF Study Patient Enrollment and Randomization

Table C-2. 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)	

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Table C-2. DECREASE-HF study patient characteristics (continued)

Characteristic	Measurement	LV-CRT (N=101)	LV Offset (N=104)	BiV-CRT (N=101)	P-value[a]
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)	
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.

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STUDY RESULTS

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 (Figure C-2 on page C-6, Table C-3 on page C-7). 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.

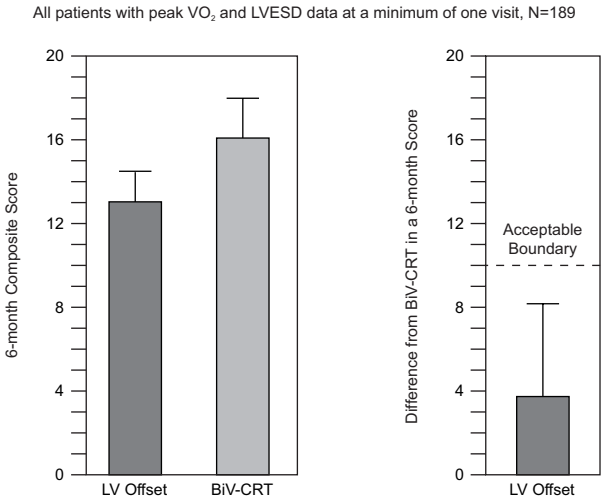

Figure C-2. Composite Score Equivalence to BiV-CRT at Six Months

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Table C-3. 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 C-3 on page C-8) and Table C-4 on page C-8, 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.

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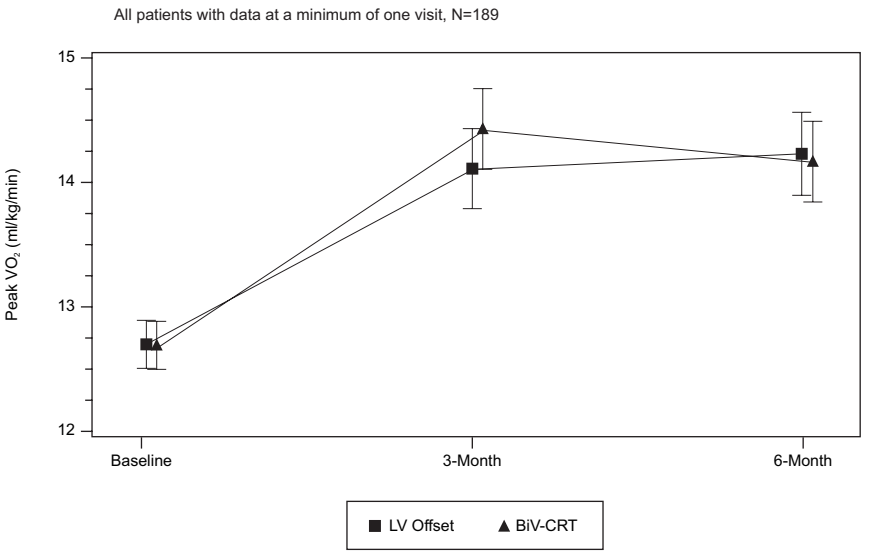

Figure C-3. Improvement in Peak V02 at Six Months

Table C-4. 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.

Both arms showed a statistically significant and clinically meaningful improvement (≤ -5 mm) in LVESD (Figure C-4 on page C-9, Table C-5 on page C-9). 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.

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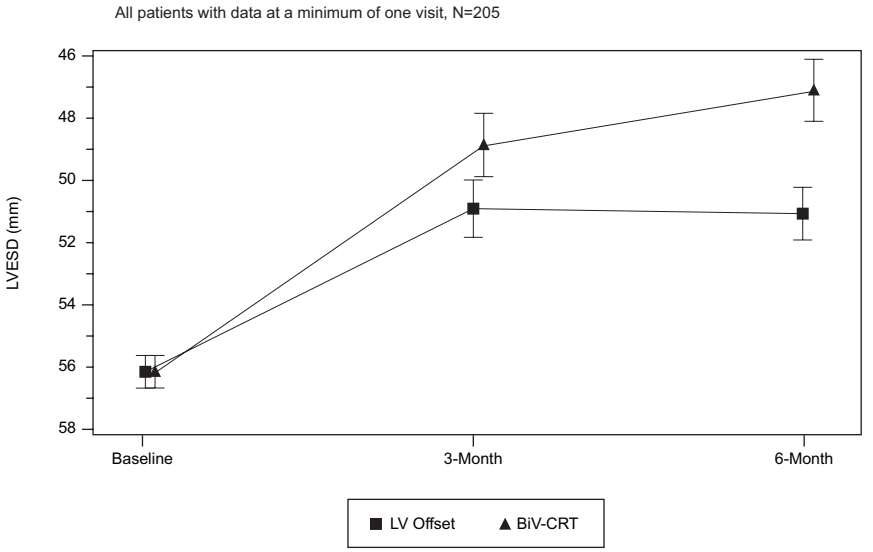

Figure C-4. Improvement in LVESD at Six Months

Table C-5. 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.

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 (Figure C-5 on page C-10, Table C-6 on page C-10). The null hypothesis was to be rejected if the

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

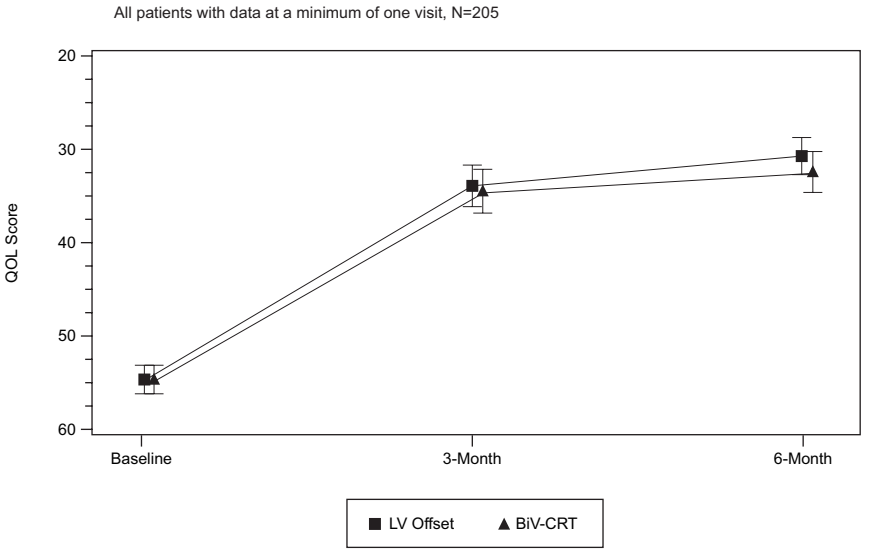

Figure C-5. Improvement in Quality of Life at Six months

Table C-6. Improvement in QOL at six months.

Statistic	LV Offset		BiV-CRT	
	N[a]	Estimate ± SE	N[a]	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

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

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 C-6 on page C-11 and Table C-7 on page C-11, 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

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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%.

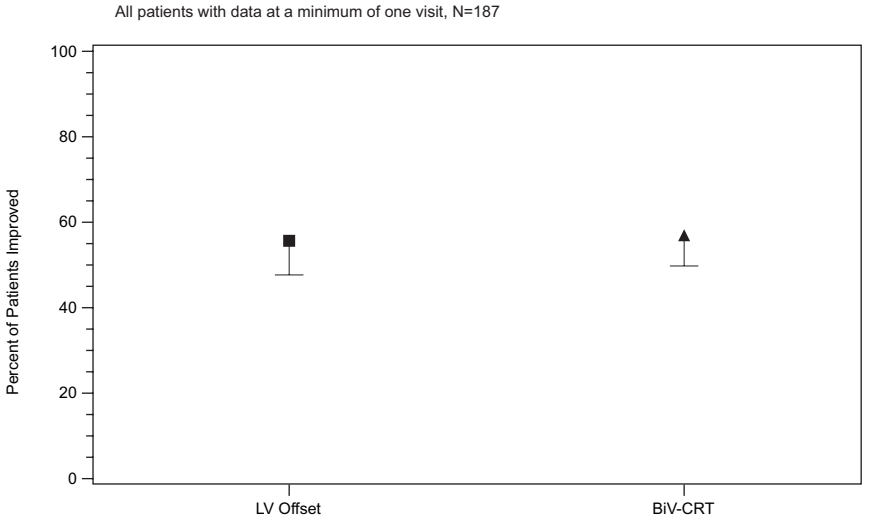

Figure C-6. Improvement in NYHA Class at Six Months

Table C-7. 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 C-8 on page C-11 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 C-8. Six-month change in NYHA by treatment group

6-Month Change in NYHA[a]	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)

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Table C-8. Six-month change in NYHA by treatment group (continued)

6-Month Change in NYHA[a]	LV Offset (N=95)	BiV-CRT (N=92)	Total (N=187)
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 C-9 on page C-12.

Table C-9. VT/VF detection time

Number of Patients[a]	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.

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Table C-10 on page C-13 summarizes the heart failure related adverse event rates through the six-month visit. A Kaplan-Meier analysis is also presented in Figure C-7 on page C-14 to show time to events.

Table C-10. Heart failure-related adverse event free rate at six months

Adverse Event[a]	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%.

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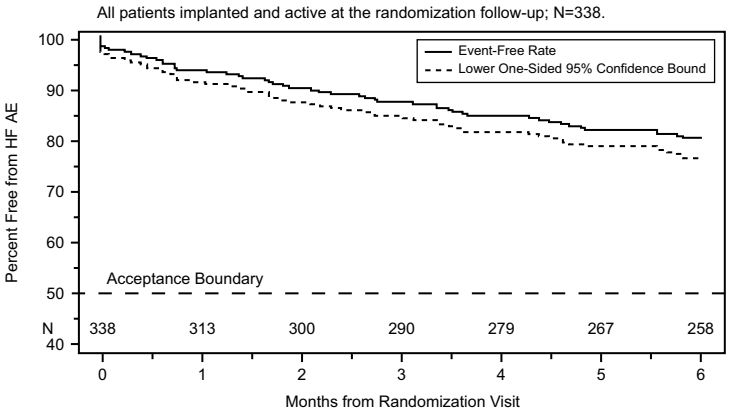

Figure C-7. Time to Heart Failure Related Adverse Event

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 C-11 on page C-14 shows the system related complication free rates by event type. A Kaplan-Meier analysis is also presented in (Figure C-8 on page C-15) to show time to events.

Table C-11. System-related complication free rate at six months

Complication[a]	Number ofEvents	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.

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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%.

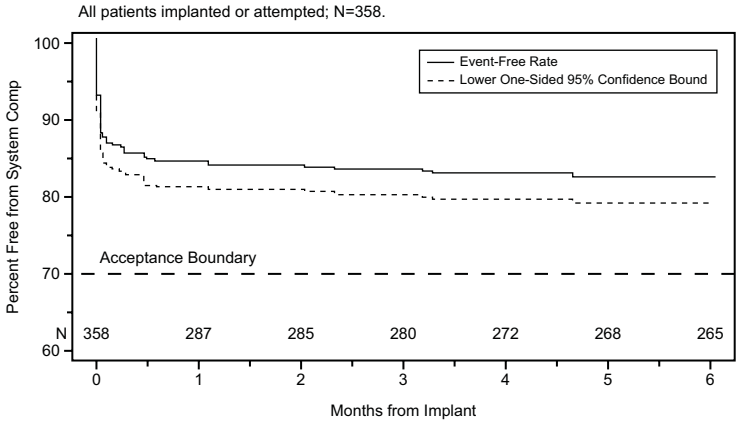

Figure C-8. Time to System Related Complication

The Holter Substudy

Ancillary Endpoints

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%.

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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 C-12 on page C-16).

Table C-12. Continuous appropriate pacing during activities of daily living

Statistic[a]	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%.

The mean percentage of appropriately paced beats during exercise was 99.4 ± 1.9 with a median of 100.0% (p < 0.01) (Table C-13 on page C-16).

Table C-13. Continuous appropriate pacing during exercise

Statistic[a]	Result
N	67
Mean ± SD	99.4 ± 1.9
Median	100.0

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Table C-13. Continuous appropriate pacing during exercise (continued)

Statistic[a]	Result
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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CLINICAL STUDY - CONTAK CD

APPENDIX D

CLINICAL STUDY POPULATIONS

Guidant CRT-Ds, when compared to OPT alone, have been demonstrated with reasonable assurance, to be safe and effective in significantly reducing: the risk of a composite of all-cause mortality or first hospitalization by 20%, the risk of all-cause mortality by 36%, and heart failure symptoms in patients who have moderate to severe heart failure (NYHA III/IV) including left ventricular dysfunction (EF ≤ 35%) and QRS duration ≥120 ms and remain symptomatic despite stable, optimal heart failure drug therapy, based on the Guidant sponsored COMPANION clinical study. (Guidant devices were the only devices studied in the COMPANION clinical trial.)

SUMMARY

Guidant conducted the CONTAK CD Study to demonstrate the safety and effectiveness of the CONTAK CD system and to demonstrate a reasonable assurance of the safety and effectiveness of biventricular stimulation, or cardiac resynchronization therapy (CRT), using the Guidant Model 1822 VENTAK CHF AICD and Model 1823 CONTAK CD CRT-D along with the EASYTRAK (Models 4510/4511/4512/4513) coronary venous, steroid-eluting, single-electrode pace/sense lead.

The CONTAK CD Study failed to prospectively demonstrate effectiveness of the CRT portion of the device. The CONTAK CD Study met the Lead and System Effectiveness endpoints as well as the Lead and System Safety endpoints. Subgroup analysis revealed a population of patients that had Class III/IV heart failure at the time of randomization that appeared to have improvements on certain functional endpoints, including the Peak VO_2 and the Six-Minute Hall walk. A second study was performed (Focused Confirmatory Study) using this subgroup of patients to confirm the effectiveness of CRT.

OBSERVED ADVERSE EVENTS

The VENTAK CHF/CONTAK CD/EASYTRAK Biventricular Pacing Study (hereafter referred to as the CONTAK CD Study) was a prospective, randomized, controlled, multicenter, double-blind study conducted at 47 sites in the United States and enrolled a total of 581 patients. Of these, 57 patients initially underwent a thoracotomy procedure to receive the Guidant Model 1822 VENTAK CHF AICD; 7 patients underwent a repeat procedure to receive an

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EASYTRAK lead. An additional 510 patients initially underwent an implant procedure to receive the Model 1823 CONTAK CD CRT-D along with the EASYTRAK (Models 4510/4511/4512/4513) coronary venous, single-electrode pace/sense lead for a total of 517 patients who underwent an EASYTRAK lead implant procedure. In 69 patients the EASYTRAK lead implant attempt was unsuccessful.

Table D-1 on page D-2 provides information on all adverse events reported from implant through the randomization period in patients attempted or implanted with the EASYTRAK lead. During this period, a total of 765 events were reported in 310 patients. Of these, 155 were classified as complications, and 610 were classified as observations.

Table D-1. Adverse events through randomization period

	# Of Events (# of pts)	% Complications (Patients)	Complications per 100 Device Months (Events)	% Observations (Patients)	Observations per 100 Device Months (Events)
Total Adverse Events	765 (310)	23.4 (121)	6.0 (155)	51.8 (268)	23.5 (610)
PG-Related Events					
Migration of device	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.0 (1)
Pacemaker-mediated tachycardia (PMT)	3 (3)	0.0 (0)	0.0 (0)	0.6 (3)	0.1 (3)
Telemetry difficulty	1 (1)	0.2 (1)	0.0 (1)	0.0 (0)	0.0 (0)
LV Lead-Related Events					
Loss of capture	43 (41)	5.6 (29)	1.1 (29)	2.5 (13)	0.5 (14)
Inappropriate shock due to oversensing	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.0 (1)
Insulation breach observed	1 (1)	0.2 (1)	0.0 (1)	0.0 (0)	0.0 (0)
Multiple counting	31 (22)	1.0 (5)	0.2 (5)	3.9 (20)	1.0 (26)
Phrenic nerve/diaphragm stimulation	15 (15)	0.4 (2)	0.1 (2)	2.5 (13)	0.5 (13)
RA Lead-Related Events					
Loss of capture	6 (6)	1.0 (5)	0.2 (5)	0.2 (1)	0.0 (1)
Oversensing	3 (3)	0.0 (0)	0.0 (0)	0.6 (3)	0.1 (3)
Undersensing	1 (1)	0.2 (1)	0.0 (1)	0.0 (0)	0.0 (0)
RV Lead-Related Events					

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Table D-1. Adverse events through randomization period (continued)

	# Of Events (# of pts)	% Complications (Patients)	Complications per 100 Device Months (Events)	% Observations (Patients)	Observations per 100 Device Months (Events)
Loss of capture	10 (9)	0.6 (3)	0.1 (3)	1.2 (6)	0.3 (7)
Elevated DFTs	6 (6)	0.4 (2)	0.1 (2)	0.8 (4)	0.2 (4)
Inappropriate shock above rate cutoff	49 (38)	0.4 (2)	0.1 (2)	7.2 (37)	1.8 (47)
Inappropriate shock due to oversensing	5 (4)	0.0 (0)	0.0 (0)	0.8 (4)	0.2 (5)
Nonconversion of VF	1 (1)	0.2 (1)	0.0 (1)	0.0 (0)	0.0 (0)
Oversensing	2 (2)	0.0 (0)	0.0 (0)	0.4 (2)	0.1 (2)
Phantom shock	2 (2)	0.0 (0)	0.0 (0)	0.4 (2)	0.1 (2)
Phrenic nerve/diaphragm stimulation	5 (5)	0.4 (2)	0.1 (2)	0.6 (3)	0.1 (3)
Subtotal Device-Related Events	**186 (135)**	**9.5 (49)**	**2.1 (54)**	**19.0 (98)**	**5.1 (132)**
Procedure-Related Events					
AV block	7 (7)	0.0 (0)	0.0 (0)	1.4 (7)	0.3 (7)
Coronary sinus dissection	5 (5)	0.0 (0)	0.0 (0)	1.0 (5)	0.2 (5)
Coronary venous perforation	5 (5)	0.2 (1)	0.0 (1)	0.8 (4)	0.2 (4)
Hematoma	11 (10)	0.8 (4)	0.2 (4)	1.2 (6)	0.3 (7)
Hypotension	7 (7)	0.0 (0)	0.0 (0)	1.4 (7)	0.3 (7)
Infection, post-operative wound	7 (7)	0.6 (3)	0.1 (3)	0.8 (4)	0.2 (4)
Pneumothorax	7 (7)	0.8 (4)	0.2 (4)	0.6 (3)	0.1 (3)
Post surgical wound discomfort	10 (9)	0.2 (1)	0.0 (1)	1.5 (8)	0.3 (9)
Renal failure	5 (5)	0.2 (1)	0.0 (1)	0.8 (4)	0.2 (4)
Other	18 (18)	1.2 (6)	0.2 (6)	2.3 (12)	0.5 (12)
Subtotal Procedure-Related Events	**79 (71)**	**3.9 (20)**	**0.7 (17)**	**10.0 (51)**	**2.2 (56)**

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Table D-1. Adverse events through randomization period (continued)

	# Of Events (# of pts)	% Complications (Patients)	Complications per 100 Device Months (Events)	% Observations (Patients)	Observations per 100 Device Months (Events)
Cardiovascular-Related Events					
AV Block	3 (3)	0.0 (0)	0.0 (0)	0.6 (3)	0.1 (3)
Arrhythmia - SVT	49 (42)	0.2 (1)	0.0 (1)	7.9 (41)	1.8 (48)
Arrhythmia - VT	20 (17)	1.0 (5)	0.2 (5)	2.7 (14)	0.6 (15)
Arrhythmia - brady	16 (14)	0.2 (1)	0.0 (1)	2.5 (13)	0.6 (15)
Cardiac arrest	2 (2)	0.4 (2)	0.1 (2)	0.0 (0)	0.0 (0)
Chest pain	30 (20)	1.0 (5)	0.2 (5)	3.1 (16)	1.0 (25)
Coagulopathy	3 (3)	0.2 (1)	0.0 (1)	0.4 (2)	0.1 (2)
Congestive heart failure	140 (91)	3.5 (18)	0.7 (18)	16.1 (83)	4.7 (122)
Distal thromboemboli	3 (2)	0.0 (0)	0.0 (0)	0.4 (2)	0.1 (3)
Dizziness	17 (17)	0.0 (0)	0.0 (0)	3.3 (17)	0.7 (17)
Dyspnea (shortness of breath)	16 (13)	0.0 (0)	0.0 (0)	2.5 (13)	0.6 (16)
Fatigue	10 (10)	0.0 (0)	0.0 (0)	1.9 (10)	0.4 (10)
Hypertension	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.0 (1)
Hypotension	11 (9)	0.2 (1)	0.0 (1)	1.7 (9)	0.4 (10)
Myocardial infarction	2 (2)	0.0 (0)	0.0 (0)	0.4 (2)	0.1 (2)
Pacemaker syndrome	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.0 (1)
Palpitations	2 (2)	0.0 (0)	0.0 (0)	0.4 (2)	0.1 (2)
Pulmonary edema	6 (6)	0.4 (2)	0.1 (2)	0.8 (4)	0.2 (4)
Shock	4 (4)	0.2 (1)	0.0 (1)	0.6 (3)	0.1 (3)
Stroke syndrome or CVA	4 (4)	0.0 (0)	0.0 (0)	0.8 (4)	0.2 (4)
Syncope	9 (9)	0.0 (0)	0.0 (0)	1.7 (9)	0.3 (9)
Thrombosis	3 (3)	0.0 (0)	0.0 (0)	0.6 (3)	0.1 (3)
Vascular related	6 (6)	1.0 (5)	0.2 (5)	0.2 (1)	0.0 (1)

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Table D-1. Adverse events through randomization period (continued)

	# Of Events (# of pts)	% Complications (Patients)	Complications per 100 Device Months (Events)	% Observations (Patients)	Observations per 100 Device Months (Events)
Subtotal Cardiovascular-Related Events	**358 (200)**	**7.7 (40)**	**1.6 (42)**	**35**.6 (184)	**12.2 (316)**
Total Noncardiovascular-Related Events	**142 (92)**	**6.2 (32)**	**1.5 (39)**	**13.5 (70)**	**4.0 (103)**

Deaths

A total of 109 deaths occurred during the study. These deaths occurred during the study periods as shown in Table D-2 on page D-5 along with the cause of death as adjudicated by an independent events committee.

Table D-2. Deaths that occurred during CONTAK CD study

Study Period[a]	# of pt deaths	Cause of Death				
		Cardiac: Pump Failure	Cardiac: Arrhythmic	Cardiac: Other	Non-cardiac	Unknown
After unsuccessful implant procedure	2	1	1	0	0	0
Peri-operative (≤ 30 days)	10	5	2	0	2	1
Randomized therapy phase: No CRT[b]	16	9	0	1	3	3
Randomized therapy phase: CRT[b]	11	4	1	2	2	2
Post-randomized therapy phase[c]	70	26	5	1	16	20
Total	109	47	9	4	23	26

a. All patients enrolled, N = 581.
b. Day 31 to 120 for Phase I patients, day 31 to 210 for Phase II patients.
c. Day 121 and beyond for Phase I patients, day 211 and beyond for Phase II patients.

STUDY DESIGN

The CONTAK CD Study was a prospective, randomized, controlled, multi-center, double-blind study conducted at 47 sites in the United States and enrolled a total of 581 patients. All patients enrolled were intended to be implanted with a device capable of delivering both CRT and treating ventricular tachyarrhythmias. Patients were randomized to CRT Off (VVI lower rate 40)

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or CRT On (VDD). The study began as a crossover design (called "Phase I") and enrolled 248 patients with a primary endpoint of functional status with three months of follow-up. The study was later modified to a parallel design (called "Phase II") and enrolled 333 patients with a longer, six-month follow-up. The data from the first three months of the crossover phase were pooled with data obtained from the six-month parallel phase. The visit schedule and testing requirements remained the same. Additionally, while the study originally used the VENTAK CHF ICD in conjunction with epicardial leads placed via thoracotomy, the CONTAK CD CRT-D and EASYTRAK lead (placed transvenously) were added to the protocol later in the study.

INCLUSION/EXCLUSION CRITERIA

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

- Meet the general indication for ICD implant
- Symptomatic heart failure despite optimal drug therapy (ACE inhibitors with diuretic and/or digoxin, as determined to be indicated and tolerated by the patient's physician-investigator)
- Left ventricular ejection fraction ≤ 35%
- QRS duration ≥ 120 ms
- Age ≥ 18 years
- Normal sinus node function

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

- Meet the general indications for permanent antibradycardia pacing, including pacemaker dependence
- Have chronic, medically refractory atrial tachyarrhythmias
- Require concomitant cardiac surgery
- Are unable to undergo device implant, including general anesthesia if required
- Are unable to comply with the protocol and follow-up requirements, including exercise testing
- Have a life expectancy of less than six months due to other medical conditions
- Have amyloid disease (amyloidosis)
- Have hypertrophic obstructive cardiomyopathy

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- Require in-hospital continuous intravenous inotropes
- Have pre-existing cardioversion/defibrillation leads other than those specified in this investigational plan (unless the investigator intends to replace them with permitted cardioversion/defibrillation leads)
- Women who are pregnant or not using medically accepted birth control
- Have a mechanical tricuspid prosthesis
- Involved in other cardiovascular clinical investigations of active therapy or treatment

FOLLOW-UP SCHEDULE

The follow-up schedule for the clinical study consisted of the following components:

- Pre-implant visit—initial assessment of patient eligibility; taking of patient history.

- Implant—implant of investigational devices and acute device testing. Randomization status (CRT or No CRT) was assigned for implementation after a 30-day recovery period.

- Recovery period—minimum 30-day period over which the patient recovered from the implant procedure and had his/her heart failure medications adjusted, but with no CRT, regardless of the randomization assignment.

- Post-recovery visit—first visit after the Recovery Period in which patients underwent Special Testing to establish their baseline condition, after which the randomization assignment was implemented (CRT or No CRT).

- Three- and six-month visit—evaluation of randomized therapy with Special Testing and device function at three- and six-months after the post-recovery visit.

- Quarterly visits—After the six-month visit, patients were seen for routine evaluation of device function and patient condition.

NOTE: *Special Testing included a Symptom-Limited Treadmill Test with measurement of oxygen uptake (Peak VO_2), a Six-Minute Walk, Echocardiography, Holter monitoring, blood chemistry testing, and a Quality of Life (QOL) questionnaire*

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DEMOGRAPHIC DATA

The CONTAK CD Study included patients with symptomatic heart failure despite optimal drug therapy as defined in the inclusion criteria. The population included patients who were NYHA Class II, III, or IV at the time of implant.

Based upon the clinical results from the covariate analyses in this study and the internal consistency of these clinical findings with those from other completed CRT studies, the patient subgroup with NYHA Class III/IV heart failure in this study was examined further.

- All Patients—all patients (NYHA Class II/III/IV at the time of implant) implanted with an investigational system (N = 501). Ten patients died and one withdrew before the post-recovery visit. Therefore, therapy effectiveness analyses used N = 490.

- NYHA Class III/IV (Advanced Heart Failure)—this subgroup was defined as those patients with moderate to severe heart failure at the time of the Post-Recovery Visit (N = 227). A percentage of patients either had an improvement or worsening of their NYHA Class during the post-implant recovery period. The patients in the Advanced Heart Failure subgroup were only those who remained in NYHA Class III/IV at the end of the post-recovery period. This subgroup was determined from interaction analysis of preselected covariates with the functional status endpoints.

ENDPOINTS

The CONTAK CD Study had three investigational elements consisting of the following components:

- CRT effectiveness
  - Primary—composite endpoint consisting of all-cause mortality, hospitalization for heart failure, and ventricular tachyarrhythmia requiring device intervention
  - Secondary–Peak VO_2 derived from a symptom-limited exercise test and Quality of Life as measured by the Minnesota Living with Heart Failure Questionnaire®
  - Additional—Six-Minute Walk, NYHA Class, Echocardiographic Analysis, Change in Norepinephrine, and Change in Heart Rate

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- Lead and System Effectiveness
  - Lead—left ventricular pacing thresholds, biventricular sensing, biventricular lead impedance, and lead placement success rate
  - System—VF detection time and biventricular ATP effectiveness
- Lead and System Safety
  - Lead—incidence of lead-related adverse events
  - System—incidence of severe, device-related adverse events and operative mortality

STUDY RESULTS

Patient Accountability (Figure D-1 on page D-10)

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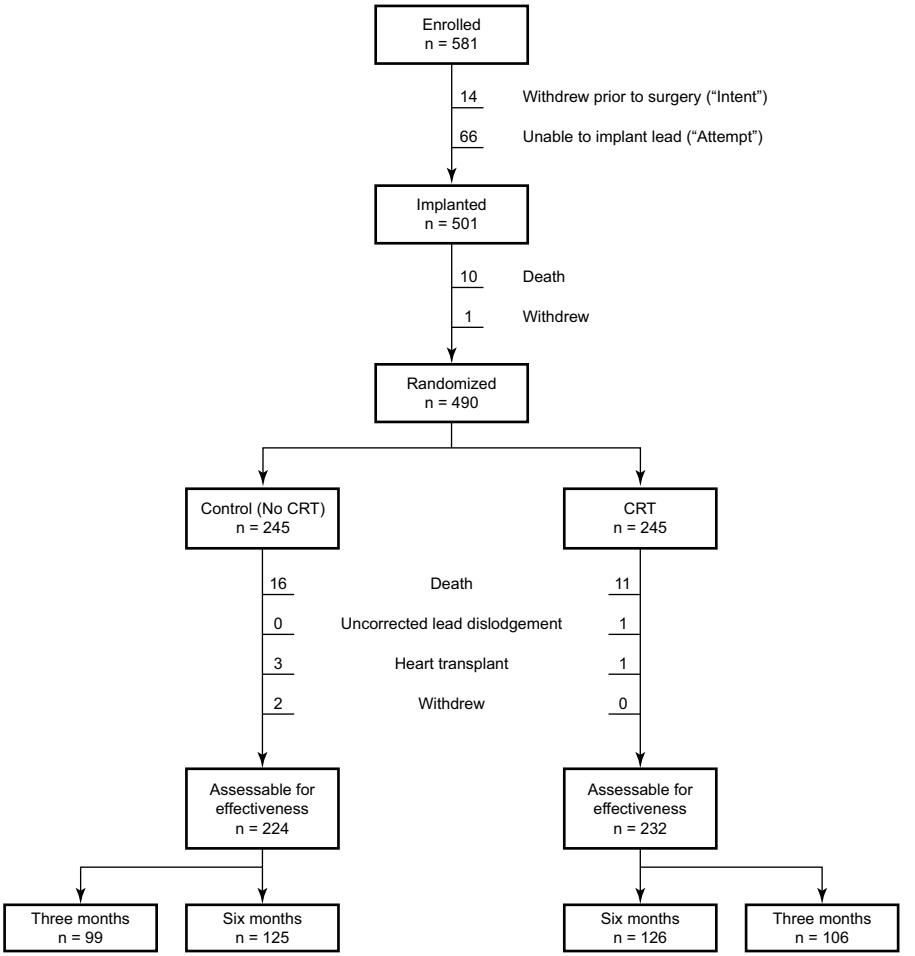

Figure D-1. Enrollment and follow-up of randomized patients

Baseline Characteristics—Includes all patients implanted; N = 501(Table D-3 on page D-11, Table D-4 on page D-12).

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Table D-3. Pre-implant assessment

Characteristic		All Patients			NYHA Class III/IV		
		CRT (N = 248)	No CRT (N = 253)	P-value[a]	CRT (N = 117)	No CRT (N = 110)	P-value[a]
Age at Implant (years)	N	248	253		117	110	
	Mean ± SD	66.0 ± 10.5	66.3 ± 10.5	0.73	66.1 ± 10.5	65.8 ± 10.5	0.80
	Range	26.1 - 82.6	29.5 - 86.3		26.1 - 82.5	38.3 - 85.3	
Gender [N (%)]	Male	210 (84.7)	211 (83.4)	0.70	90 (76.9)	86 (78.2)	0.82
	Female	38 (15.3)	42 (16.6)		27 (23.1)	24 (21.8)	
NYHA Class [N (%)]	II	80 (32.3)	83 (32.8)	0.66	20 (17.1)	11 (10.0)	0.08
	III	148 (59.7)	144 (56.9)		85 (72.6)	78 (70.9)	
	IV	20 (8.1)	26 (10.3)		12 (10.3)	21 (19.1)	
Concomitant Medications [N (%)]	ACE or ARB	212 (85.5)	224 (88.5)	0.31	95 (81.2)	98 (89.1)	0.10
	Beta Blocker	119 (48.0)	117 (46.2)	0.70	53 (45.3)	44 (40.0)	0.42
	Digoxin	172 (69.4)	171 (67.6)	0.67	84 (71.8)	75 (68.2)	0.55
	Diuretic	217 (87.5)	210 (83.0)	0.16	108 (92.3)	95 (86.4)	0.15
Qualifying LVEF (%)	N	248	253		117	110	
	Mean ± SD	21.4 ± 6.6	21.5 ± 6.7	0.74	20.6 ± 6.4	21.1 ± 6.2	0.61
	Range	5.0 - 35.0	10.0 - 35.0		8.0 - 35.0	10.0 - 35.0	
PR Interval[b] (ms)	N	224	222		107	91	
	Mean ± SD	205± 42	202 ± 49	0.44	204 ± 41	200 ± 54	0.60
	Range	88 - 336	104 - 400		136 - 336	110 - 400	
Qualifying QRS Duration[b] (ms)	N	226	224		109	93	
	Mean ± SD	160 ± 27	156 ± 26	0.06	164 ± 27	152 ± 24	< 0.01
	Range	120 - 240	120 - 264		120 - 240	120 - 222	
Resting Heart Rate (bpm)	N	248	253		117	110	

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Table D-3. Pre-implant assessment (continued)

Characteristic		All Patients			NYHA Class III/IV		
		CRT (N = 248)	No CRT (N = 253)	P-value[a]	CRT (N = 117)	No CRT (N = 110)	P-value[a]
	Mean ± SD	73 ± 12	75 ± 14	0.37	75 ± 13	74 ± 15	0.61
	Range	43 - 108	48 - 120		43 - 108	50 - 120	
Systolic Blood Pressure (mmHg)	N	247	253		116	110	
	Mean ± SD	118 ± 21	118 ± 21	0.95	116 ± 20	117 ± 23	0.72
	Range	79 - 197	70 - 190		79 - 191	74 - 190	
Diastolic Blood Pressure (mmHg)	N	247	253		116	110	
	Mean ± SD	67 ± 12	69 ± 12	0.27	68 ± 12	67 ± 14	0.85
	Range	31 - 100	40 - 109		31 - 100	40 - 109	

a. P-values for comparing means were calculated with Student's t-test; p-values for comparing proportions were calculated with Pearson's chi-squared test.
b. PR interval and QRS duration were not obtained for thoracotomy patients.

Table D-4. Pre-implant history

Characteristic		All Patients			NYHA Class III/IV		
		CRT (N = 248)	No CRT (N = 253)	P-value[a]	CRT (N = 117)	No CRT (N = 110)	P-value[a]
Primary Tachyarrhythmia [N (%)]	Monomorphic VT (MVT)	148 (59.7)	136 (53.8)	0.44	72 (61.5)	48 (43.6)	0.03
	Polymorphic VT (PVT)	16 (6.5)	20 (7.9)		7 (6.0)	7 (6.4)	
	Nonsustained VT	58 (23.4)	63 (24.9)		30 (25.6)	35 (31.8)	
	Ventricular Fibrillation (VF)	26 (10.5)	32 (12.6)		8 (6.8)	18 (16.4)	
	Other	0 (0.0)	2 (0.8)		0 (0.0)	2 (1.8)	
Other Arrhythmias [N (%)]	Paroxysmal Atrial Fibrillation	43 (17.3)	62 (24.5)	0.05	21 (17.9)	29 (26.4)	0.13
	Atrial Flutter	10 (4.0)	13 (5.1)	0.55	3 (2.6)	7 (6.4)	0.16

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Table D-4. Pre-implant history (continued)

Characteristic		All Patients			NYHA Class III/IV		
		CRT (N = 248)	No CRT (N = 253)	P-value[a]	CRT (N = 117)	No CRT (N = 110)	P-value[a]
Arrhythmia/Conduction Disorder [N (%)]	LBBB	133 (53.6)	138 (54.5)	0.83	59 (50.4)	59 (53.6)	0.55
	RBBB	35 (14.1)	31 (12.3)		21 (17.9)	14 (12.7)	
	Non-Specific	80 (32.3)	84 (33.2)		37 (31.6)	37 (33.6)	
Etiology [N (%)]	Ischemic	167 (67.3)	178 (70.4)	0.47	76 (65.0)	78 (70.9)	0.34
	Non-Ischemic	81 (32.7)	75 (29.6)		41 (35.0)	32 (29.1)	

a. P-values were calculated with Pearson's chi-squared test.

CRT Effectiveness

Heart Failure Progression (Composite Index)—the Composite Index (primary endpoint) was a combination of three events: all-cause mortality, hospitalization for heart failure, and VT/VF event requiring therapy (Table D-5 on page D-13). A committee consisting of three heart failure specialists and an electrophysiologist reviewed and adjudicated all patient deaths and all hospitalizations, defined as an admission greater than 23 hours. Outpatient care, emergency room care, and clinic visits less than 23 hours were collected but not considered to be hospitalizations for the purposes of analysis.

Table D-5. Heart Failure Progression (Composite Index)

Group[a]	Heart Failure Mortality or Morbidity Event	CRT		No CRT		Relative Reduction with CRT
		N	%	N	%	
All Patients (N = 490)	Death from any cause	11	4.5	16	6.5	15% p = 0.35
	HF hospitalization	32	13.1	39	15.9	
	VT/VF	36	14.7	39	15.9	
NYHA Class III/IV (N = 227)	Death from any cause	11	9.4	11	10.0	22% p = 0.23
	HF hospitalization	23	19.7	27	24.5	
	VT/VF	21	17.9	22	20.0	

a. All patients implanted and active 31 days post-implant.

Twenty-seven patients died during the therapy phase. Mortality stratified by treatment group and cause, as adjudicated by the Events Committee, is shown

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inTable D-6 on page D-14. The Kaplan-Meier curve, showing total survival by treatment group, is shown in Figure D-2 on page D-14.

Table D-6. Mortality stratified by treatment group and cause

Deaths[a]	Patients with CRT (N = 245)	Patients with No CRT (N = 245)
Cardiac, pump failure	4 (1.6%)	9 (3.7%)
Cardiac, arrhythmic	1 (0.4%)	0 (0.0%)
Cardiac, other	2 (0.8%)	1 (0.4%)
Noncardiac	2 (0.8%)	3 (1.2%)
Unknown	2 (0.8%)	3 (1.2%)
Total	11 (4.5%)	16 (6.5%)

a. All patients implanted and active at 31 days post-implant; N = 490.

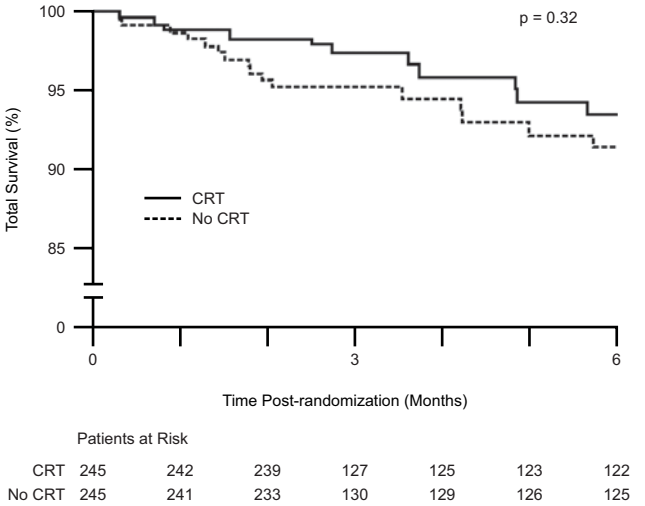

Figure D-2. Kaplan-Meier curve

Table D-7 on page D-15 presents the reasons for hospitalization within the treatment period as determined by the Events Committee. This table represents the number of patients with each category of hospitalization. Patients may have multiple hospitalizations that fall into different categories.

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Table D-7. Patients hospitalized during treatment period

Reason for Hospitalization[a]	All Patients			NYHA Class III/IV		
	CRT (N = 245)	No CRT (N = 245)	Total (N = 490)	CRT (N = 117)	No CRT (N = 110)	Total (N = 227)
Heart failure	32	39	71	23	27	50
Cardiac, other	20	25	45	14	14	28
Noncardiac	26	19	45	14	14	28
Total Hospitalizations	66	70	136	40	46	86

a. All patients implanted and active at 31 days post-implant; N = 490.

Peak VO_2—the Peak VO_2 was determined from a standardized protocol for exercise testing as a means of measuring a patient's capacity for performing physical activity. Figure D-3 on page D-15 and Table D-8 on page D-15 provide the change in Peak VO_2.

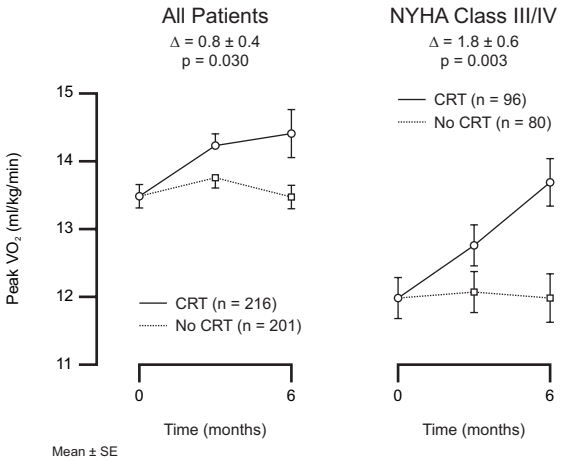

Figure D-3. Change in Peak VO2

Table D-8. Change in Peak VO2

Peak VO_2 (ml/kg/min)	All Patients			NYHA Class III/IV		
	CRT (N = 216)	No CRT (N = 201)	P-value[a]	CRT (N = 96)	No CRT (N = 80)	P-value[a]
Post-recovery Visit	13.5 ± 0.2	13.5 ± 0.2	– –	12.0 ± 0.3	12.0 ± 0.3	– –

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Table D-8. Change in Peak VO2 (continued)

Peak VO_2 (ml/kg/min)	All Patients			NYHA Class III/IV		
	CRT (N = 216)	No CRT (N = 201)	P-value[a]	CRT (N = 96)	No CRT (N = 80)	P-value[a]
3 Months	14.3 ± 0.2	13.9 ± 0.2	0.206	12.8 ± 0.4	12.1 ± 0.4	0.084
6 Months	14.4 ± 0.3	13.6 ± 0.3	0.030	13.8 ± 0.5	12.0 ± 0.5	0.003

a. P-values reflect the between-group differences with respect to baseline.

Six-Minute Walk—the Six-Minute Walk test is a measure of a patient's ability to sustain exercise during an activity similar to that which a patient may typically perform on a daily basis. For this test, patients are instructed to walk as far as possible in 6 minutes in a level corridor. Figure D-4 on page D-16 and Table D-9 on page D-16 provide the change in Six-Minute Walk.

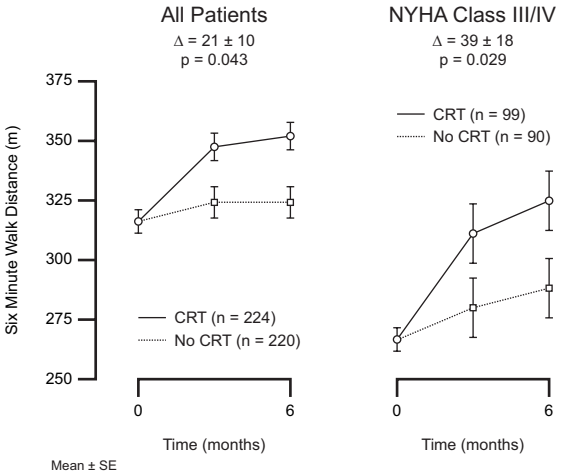

Figure D-4. Change in Six-Minute Walk

Table D-9. Change in Six-Minute Walk

Six Minute Walk Distance (meters)	All Patients			NYHA Class III/IV		
	CRT (N = 224)	No CRT (N = 200)	P-value[a]	CRT (N = 99)	No CRT (N = 90)	P-value[a]
Post-recovery Visit	317 ± 5	317 ± 5	– –	268 ± 9	268 ± 9	– –

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Table D-9. Change in Six-Minute Walk (continued)

Six Minute Walk Distance (meters)	All Patients			NYHA Class III/IV		
	CRT (N = 224)	No CRT (N = 200)	P-value[a]	CRT (N = 99)	No CRT (N = 90)	P-value[a]
3 Months	348 ± 7	331 ± 8	0.058	312 ± 12	280 ± 12	0.028
6 Months	353 ± 8	332 ± 8	0.043	327 ± 14	288 ± 15	0.029

a. P-values reflect the between-group differences with respect to baseline.

Quality of Life (QOL)—QOL was assessed using the 21-question Minnesota Living with Heart Failure Questionnaire®. Each question is answered by the patient, ranking each item on a scale ranging from 0 to 5. A lower total score indicates an improved quality of life. Figure D-5 on page D-17 and Table D-10 on page D-17 provide the change in QOL.

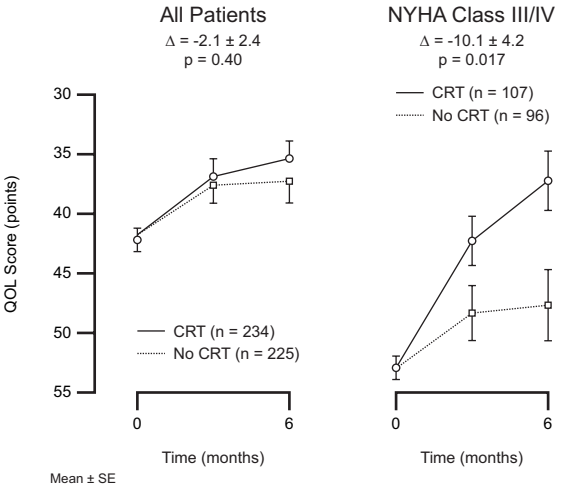

Figure D-5. Change in Quality of Life

Table D-10. Change in Quality of Life

QOL (points)	All Patients			NYHA Class III/IV		
	CRT (N = 234)	No CRT (N = 225)	P-value[a]	CRT (N = 107)	No CRT (N = 96)	P-value[a]
Post-recovery Visit	41.8 ± 1.1	41.8 ± 1.1	– –	52.7 ± 1.5	52.7 ± 1.5	– –

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Table D-10. Change in Quality of Life (continued)

QOL (points)	All Patients			NYHA Class III/IV		
	CRT (N = 234)	No CRT (N = 225)	P-value[a]	CRT (N = 107)	No CRT (N = 96)	P-value[a]
3 Months	36.6 ± 1.5	37.3 ± 1.6	0.711	41.9 ± 2.4	47.5 ± 2.6	0.078
6 Months	34.8 ± 1.8	36.9 ± 1.8	0.395	37.2 ±- 3.1	47.3 ± 3.2	0.017

a. P-values reflect the between-group differences with respect to baseline.

NYHA Class—the determination of New York Heart Association (NYHA) Class is based on mutual assessment by the patient and the patient's physician of the patient's heart failure symptoms both at rest and while performing ordinary physical activity. NYHA Class was determined at each follow-up visit by a physician who was blinded to the patient's randomized therapy. Figure D-6 on page D-18 and Table D-11 on page D-18 provide the change in NYHA Class results.

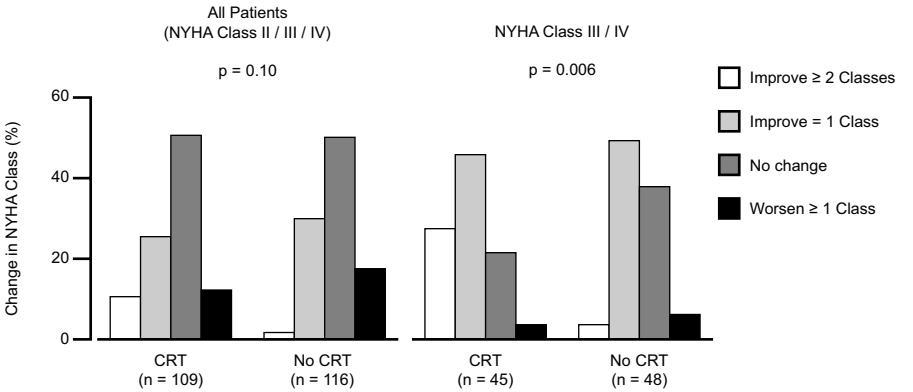

Figure D-6. Change in NYHA Class

Table D-11. Change in NYHA Class

Change in NYHA Class	All Patients					NYHA Class III/IV				
	CRT (N = 109)		No CRT (N = 116)		P-value[a]	CRT (N = 45)		No CRT (N = 48)		P-value[a]
	N	%	N	%		N	%	N	%	
Improve 2 or More Classes	12	11.0	2	1.7	0.10	12	26.7	2	4.2	0.006
Improve 1 Class	27	24.8	35	30.2		21	46.7	24	50.0	
No Change	56	51.4	59	50.9		10	22.2	18	37.5	

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Table D-11. Change in NYHA Class (continued)

Change in NYHA Class	All Patients					NYHA Class III/IV				
	CRT (N = 109)		No CRT (N = 116)		P-value[a]	CRT (N = 45)		No CRT (N = 48)		P-value[a]
	N	%	N	%		N	%	N	%	
Worsen 1 Class	13	11.9	19	16.4		2	4.4	4	8.3	
Worsen 2 or More Classes	1	0.9	1	0.9		0	0.0	0	0.0	

a. P-value was calculated from Mantel-Haenszel test and reflects the between-group differences with respect to baseline.

Echocardiography—several echocardiography (echo) variables were identified to assist in measuring the possible hemodynamic impact of CRT (Table D-12 on page D-19). The limitation of this data is that patients are measured while at rest, and therefore, the data may not reflect any hemodynamic benefit that may be observed when patients are exercising and performing their daily activities.

Table D-12. Echocardiography results

Parameter	Timepoint	CRT		No CRT		Between Groups	
		N	Mean ± SE	N	Mean ± SE	Mean ± SE	P-value
All Patients							
LVIDd (mm)	Post-recovery Visit	228	70.4 ± 0.5	219	70.4 ± 0.5	0	– –
	Change at 6 Months	228	-3.4 ± 0.6	219	-0.3 ± 0.6	-3.1 ± 0.9	< 0.001
LVIDs (mm)	Post-recovery Visit	228	58.3 ± 0.5	219	58.3 ± 0.5	0	– –
	Change at 6 Months	228	-4.0 ± 0.7	219	-0.7 ± 0.7	-3.3 ± 0.9	< 0.001
LVEF (%)	Post-recovery Visit	222	27.8 ± 0.3	216	27.8 ± 0.3	0	– –
	Change at 6 Month	222	5.1 ± 0.7	216	2.8 ± 0.7	2.4 ± 1.0	0.020
NYHA Class III/IV							
LVIDd (mm)	Post-recovery Visit	104	71.2 ± 0.7	92	71.2 ± 0.7	0	– –
	Change at 6 Months	104	-4.9 ± 1.0	92	-0.2 ± 1.1	-4.7 ± 1.5	0.001
LVIDs (mm)	Post-recovery Visit	104	59.2 ± 0.7	92	59.2 ± 0.7	0	– –

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Table D-12. Echocardiography results (continued)

Parameter	Timepoint	CRT		No CRT		Between Groups	
		N	Mean ± SE	N	Mean ± SE	Mean ± SE	P-value
	Change at 6 Months	104	-5.4 ± 1.1	92	-0.6 ± 1.1	-4.8 ± 1.5	0.002
LVEF (%)	Post-recovery Visit	99	26.9 ± 0.5	91	26.9 ± 0.5	0	– –
	Change at 6 Months	99	6.0 ± 1.1	91	2.3 ± 1.2	3.7 ± 1.7	0.029

Measures of Sympathetic Tone—Mean Norepinephrine levels (Table D-13 on page D-20) and Mean Heart Rate (Table D-14 on page D-20) were examined as markers of how CRT may influence the excessive sympathetic drive associated with chronic heart failure.

Table D-13. Mean Norepinephrine results

Norepinephrine (pg/mL)	All Patients			NYHA Class III/IV		
	CRT (N = 228)	No CRT (N = 217)	P-value	CRT (N = 104)	No CRT (N = 90)	P-value
Post-recovery Visit	663 ± 19	663 ± 19	– –	720 ± 31	720 ± 31	– –
3 Months	651 ± 31	681 ± 32	0.479	685 ± 55	743 ± 60	0.463
6 Months	658 ± 40	738 ± 41	0.143	681 ± 75	827 ± 79	0.163

Table D-14. Mean heart rate results

Heart Rate (bpm)	All Patients			NYHA Class III/IV		
	CRT (N = 240)	No CRT (N = 233)	P-value	CRT (N = 113)	No CRT (N = 101)	P-value
Post-recovery Visit	72.3 ± 0.6	72.3 ± 0.6	– –	74.5 ± 1.0	74.5 ± 1.0	– –
3 Months	70.8 ± 0.8	72.1 ± 0.8	0.20	74.1 ± 1.2	73.9 ± 1.3	0.94
6 Months	69.4 ± 1.0	70.2 ± 1.0	0.58	70.6 ± 1.6	72.5 ± 1.6	0.40

EASYTRAK Lead and System Effectiveness

It was hypothesized that the upper tolerance limit of the chronic left ventricular pacing threshold of the EASYTRAK lead be less than 5.5 V to ensure that an adequate safety margin exists. Chronic left ventricular pacing thresholds

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shown in Figure D-7 on page D-21 and Table D-15 on page D-21 are well within this limit.

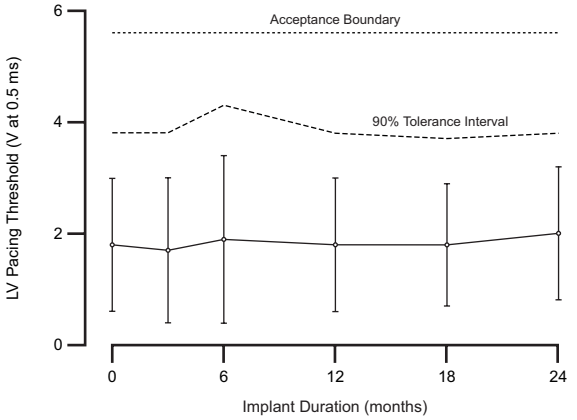

Figure D-7. EASYTRAK lead threshold measurements

Table D-15. EASYTRAK lead threshold measurements

Statistic[a]	Implant	3 Months	6 Months	12 Months	18 Months	24 Months
N	435	347	330	233	103	25
Mean ± SD	1.8 ± 1.2	1.7 ± 1.3	1.9 ± 1.5	1.8 ± 1.2	1.8 ± 1.1	2.0 ± 1.2
Range	0.2 - 7.5	0.2 - 7.5	0.2 - 7.5	0.4 - 7.5	0.6 - 7.5	0.6 - 5.0
Upper Tolerance Limit	3.8	3.8	4.3	3.8	3.7	3.9

a. EASYTRAK lead models: 4511, 4512, and 4513

Mean chronic biventricular R-wave amplitudes are measured as a combination of the R-waves from both the right ventricle (commercially available ENDOTAK lead) and left ventricle (EASYTRAK lead). It was hypothesized that the mean biventricular R-wave amplitude be greater than 5 mV to ensure proper sensing. In Figure D-8 on page D-22 and Table D-16 on page D-22, the performance of the EASYTRAK lead system was significantly above this value ($p < 0.01$).

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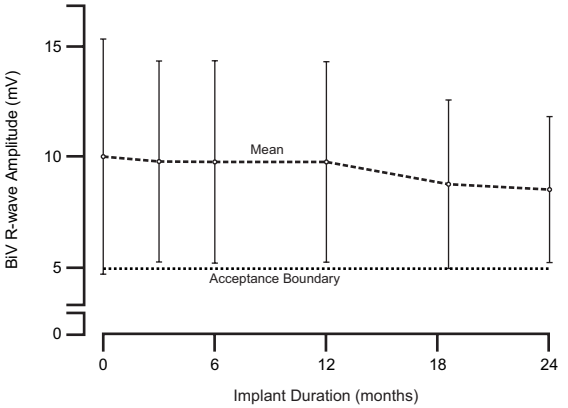

Figure D-8. EASYTRAK biventricular-sensed R-wave amplitude

Table D-16. EASYTRAK biventricular-sensed R-wave amplitude

Statistic[a]	Implant	3 Months	6 Months	12 Months	18 Months	24 Months
N	433	346	326	220	99	23
Mean ± SD	10.0 ± 5.2	9.9 ± 4.4	9.9 ± 4.5	9.8 ± 4.4	8.9 ± 3.5	8.5 ± 3.3
Upper Tolerance Limit	1.9 - 25.0	1.4 - 25.0	1.7 - 25.0	1.2 - 25.0	2.6 - 20.4	2.2 - 13.6

The impedance measured by the CONTAK CD device is the parallel combination of the left ventricular (EASYTRAK) and right ventricular (ENDOTAK) leads simultaneously. Therefore, the biventricular lead impedance will be substantially less than that of either lead alone. It was hypothesized that the lower limit of the 95% confidence interval of the mean chronic biventricular lead impedance would be greater than 200 Ω to ensure proper pulse generator function. The lower limit of the 95% confidence interval of the chronic biventricular lead impedance exceeds this value (Figure D-9 on page D-23, Table D-17 on page D-23).

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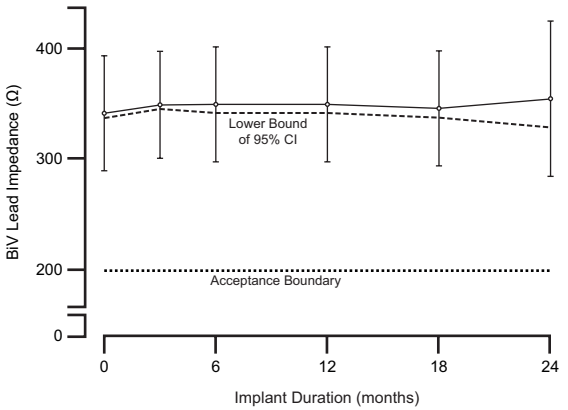

Figure D-9. EASYTRAK biventricular pacing impedance

Table D-17. EASYTRAK biventricular pacing impedance

Statistic[a]	Implant	3 Months	6 Months	12 Months	18 Months	24 Months
N	436	355	336	237	107	26
Mean ± SD	340 ± 46	352 ± 47	349 ± 50	351 ± 51	347 ± 46	356 ± 67
Range	243 - 550	248 - 519	186 - 534	237 - 513	254 - 507	267 - 520
95% CI	(336, 344)	(347, 357)	(344, 355)	(345, 358)	(338, 356)	(329, 383)

EASYTRAK Lead Placement Success Rate—the EASYTRAK lead was implanted in 448/517 (87%) of patients who underwent the implant procedure. Table D-18 on page D-23 shows the reasons for inability to place the EASYTRAK lead. Table D-19 on page D-24 provides the EASYTRAK lead implant success rate.

Table D-18. Reasons for unsuccessful EASYTRAK lead implant

Reason	# of pts[a]	%
Inability to locate or cannulate the coronary sinus	29	42
Dislodgment of EASYTRAK lead while removing guide catheter	13	18.8
Inability to advance the lead to a stable position	11	15.9
Inability to obtain adequate pacing thresholds	6	8.7
Procedure stopped due to coronary sinus dissection or perforation	5	7.2
Procedure stopped due to transient AV block	1	1.4
Procedure stopped due to venous perforation during subclavian stick	1	1.4
Reason not stated	1	1.4

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Table D-18. Reasons for unsuccessful EASYTRAK lead implant (continued)

Reason	# of pts[a]	%
Extracardiac stimulation	1	1.4
Inability to place an atrial pace/sense lead	1	1.4
Total	69	100

a. Patients with unsuccessful attempt to implant EASYTRAK lead; N = 69.

Table D-19. EASYTRAK lead placement success rate

Measurement	All Procedures[a]
Number of patients implanted or attempted	517
Number of placements of the EASYTRAK Lead[b]	448
Rate	87%
95% CI	(84%, 90%)

a. All patients implanted or attempted with EASYTRAK lead; N = 517.
b. Defined as an EASYTRAK implant procedure that is concluded with the implant of the investigational cardiac resynchronization system.

Although some situations such as patient anatomy and poor thresholds cannot be avoided, increased investigator experience with the EASYTRAK lead and accessories was associated with improved success, decreased total procedure time (measured skin-to-skin), and decreased fluoroscopy exposure time (Figure D-10 on page D-24).

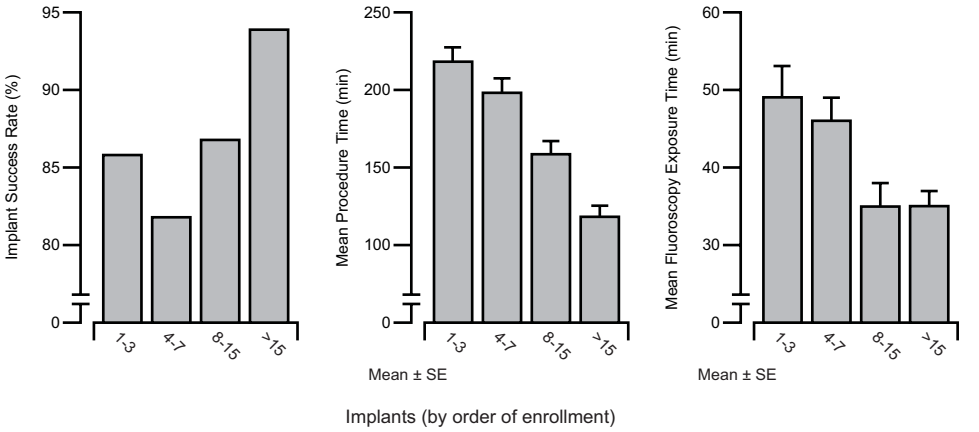

Figure D-10. EASYTRAK success rate, procedure time, and fluoroscopy exposure time

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Biventricular ATP Conversion Effectiveness Performance—the conversion rate of induced monomorphic ventricular tachycardia (MVT) was 64% and that of spontaneous MVT was 88%.

Ventricular Tachyarrhythmia Detection Time—the VENTAK CHF and CONTAK CD devices sense events from both ventricles simultaneously. Ventricular tachyarrhythmia detection time was analyzed to determine if the additional lead had an adverse effect on sensing VT/VF. Guidant's ICDs typically have a detection time of two seconds. The VF detection time of 2.1 ± 0.6 seconds was statistically significantly lower than 6 seconds ($p < 0.01$), demonstrating that there was no statistically significant prolongation of induced VF detection times with the additional left ventricular lead[1]. There were also no adverse events reported in which a VENTAK CHF or CONTAK CD failed to detect a spontaneous ventricular tachyarrhythmia.

EASYTRAK Lead and System Safety

EASYTRAK Lead Safety—safety was established using the rate of adverse events that are either related to the EASYTRAK lead or to the implant procedure necessary to place the EASYTRAK lead.

An EASYTRAK lead implant procedure was performed in 517 patients with 448 patients (86.7%) being successfully implanted with the EASYTRAK lead. The upper boundary of the 95% confidence interval was hypothesized to be less than 23% at six months (Table D-20 on page D-25).

Table D-20. Lead-related adverse events at six months

Patient Population	N	Event Rate (%)	95% CI
All Patients	517	12.2	(9.4, 15.0)
NYHA Class III/IV	201	17.4	(12.7, 22.7)

Fifty-three lead-related adverse events were reported during the clinical investigation of the EASYTRAK lead among the 448 patients who were implanted with an EASYTRAK lead. Twenty-seven procedure-related adverse events were reported among the 517 patients who underwent the implant procedure for an EASYTRAK lead.[2] The overall lead-related adverse event

1. Detection time at implant with legally marketed Guidant ICD devices is typically two seconds, and investigators have stated that an additional delay of 3 to 5 seconds would be a clinically significant event. The expected detection time is 2 seconds (95% CI: [0, 6 sec]).
2. For purposes of defining event rates, a denominator of 448 will be used for those adverse events that pertain to chronically implanted EASYTRAK leads, and a denominator of 517 will be used for those adverse events that pertain to the implant procedure of the EASYTRAK lead.

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rate was 14.5% (95% CI [11.5–17.5%]). Table D-21 on page D-26 reports lead-related adverse events observed during the CONTAK CD Study.

Table D-21. EASYTRAK lead-related adverse events

Adverse Events[a]	Total	% of pts (95% CI)
Lead-Related, N = 448		
Loss of capture/lead dislodgment	31[b]	6.9 (4.6–9.3)
Ventricular oversensing	11	2.5 (1.0–3.9)
Extracardiac stimulation	9	2.0 (0.7–3.3)
Insulation breach	2	0.4 (0.0–1.1)
Procedure-Related, N = 517		
Transient AV block	6	1.2 (0.2–2.1)
Coronary venous dissection	5	1.0 (0.1–1.8)
Coronary venous perforation	5	1.0 (0.1–1.8)
Transient renal failure	5	1.0 (0.1–1.8)
Pericardial effusion	2	0.4 (0.0–0.9)
Finishing wire left in lead	1	0.2 (0.0–0.6)
Right ventricular lead dislodgment	1	0.2 (0.0–0.6)
Guide wire fracture	1	0.2 (0.0–0.6)
Hypotension due to blood loss	1	0.2 (0.0–0.6)
Total (unique patients)	75	14.5 (11.5–17.5)

a. All patients implanted, N = 448; All patients attempted, N = 517.
b. Twenty-six events were successfully corrected in a repeat procedure.

The most common of the 53 lead-related adverse events (>1% incidence) included the following:

- Loss of left ventricular capture (31 patients, 6.9%)
- Ventricular oversensing (11 patients, 2.5%)
- Extracardiac stimulation (9 patients, 2.0%)

These events were typically resolved with surgical intervention.

The most common of the 27 procedure-related adverse events (> 1% incidence) included the following:

- Coronary venous trauma (10 patients, 2.0%)
- Transient atrioventricular block (6 patients, 1.2%)

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- Transient renal failure (5 patients, 1.0%)

These events were typically resolved without intervention and no permanent long-term sequelae were reported.

Severe, Device-Related Adverse Events and Operative Mortality—the incidence of severe, device-related events was reported in 7 of 567 patients (1.2%); this was significantly less than the hypothesized rate of 20% ($p < 0.01$) (Table D-22 on page D-27). Table D-23 on page D-27 reports system, device-related, severe adverse events observed during the CONTAK CD Study.

Table D-22. Adverse events and operative mortality

Measurement[a]	N	%	95% CI
Severe, Device-Related Adverse Events (Type I)[b]	7	1.2	(0.3, 2.1)
All-Cause Operative Mortality (< = 30 Days Post Implant)	12	2.1	(0.9, 3.3)

a. All patients attempted or implanted, N = 567
b. Percent is of patients with at least one event.

Table D-23. System, device-related, severe adverse events

Adverse Event[a]	# of pts	% of pts (95% CI)
Telemetry difficulty; device explanted	2	0.4 (0.0–0.9)
Ventricular tachycardia during CPX testing	1	0.2 (0.0–0.5)
Coronary sinus perforation	1	0.2 (0.0–0.5)
Inappropriate shock due to oversensing	1	0.2 (0.0–0.5)
Lead dislodgment	1	0.2 (0.0–0.5)
Anaphylaxis in association with use of a pulmonary artery catheter	1	0.2 (0.0–0.5)

a. All patients attempted or implanted, N = 567

Operative mortality, defined as death from any cause within 30 days of implant, was reported in 12 of 567 patients (2.1%) undergoing the implant procedure. The outcome is significantly less than the hypothesized rate of 9% ($p < 0.01$). Table D-24 on page D-28 reports the cause of death for operative mortality.

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Table D-24. Cause of death for operative mortality

Cause of Death	Implants N = 501	Attempts N = 66	Total[a] N = 567
Cardiac: pump failure	5	1	6
Cardiac: arrhythmic	2	1	3
Noncardiac	2	0	2
Unknown	1	0	1
Total	10	2	12

a. All patients attempted or implanted, N = 567.

System Safety Profile—analysis of system safety was performed on the complication-free rate of device-related adverse events, regardless of whether or not they were related to the investigational device (Figure D-11 on page D-29). Table D-25 on page D-28 outlines the device related complications. This study used an acceptance criterion such that the lower boundary of the 95% confidence interval could not be less than 70%.

Table D-25. Device-related complications

Complication[a]	# of pts	% of pts
All patients implanted (N = 448)		
Loss of LV capture	31	6.9
Loss of right atrial capture	7	1.6
Ventricular oversensing	6	1.3
Extracardiac stimulation	5	1.1
All patients attempted or implanted (N = 517)		
Infections	7	1.4

a. This table represents patients attempted or implanted with the EASYTRAK lead; most common (> 1%) device-related complications reported.

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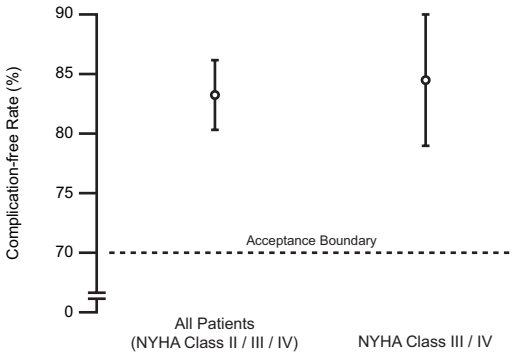

Figure D-11. System safety

Verification of CRT Delivery

The delivery of biventricular pacing throughout the CONTAK CD Study was confirmed by comparing the programmed device output to the biventricular pacing threshold and demonstrating that capture was maintained in daily activities and during exercise.

The investigational plan recommended programming the device output to at least twice the biventricular pacing voltage threshold. Electrocardiograms (ECGs) from Holter Monitors during daily activities were received and analyzed to verify that total capture was maintained at the 3-month and 6-month visits and to ensure that the safety margin was adequate. Cardiopulmonary exercise tests (CPX) were performed on patients who were randomized to receive CRT therapy at 3- and 6- month visits.

- In 623 evaluations of safety margin at baseline, three-, and six-months, the device output was programmed to deliver a voltage approximately three times that necessary to stimulate both ventricles.

- A total of 1139 Holter monitors were placed throughout the study at baseline, three-, and six-months. The tests indicated only 4 instances (0.4%) of inappropriate pacing or sensing that were all corrected with device programming.

- A total of 316 CPX tests at the three- and six-month follow-up visits were performed in patients with CRT who also had interpretable ECG results. Of these, 277 (88%) had continuous CRT delivery throughout exercise. The remaining 39 patients (12%) had continuous CRT delivery until the sinus rate exceeded the maximum tracking rate (MTR).

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FOCUSED CONFIRMATORY STUDY

Study Design

The Focused Confirmatory Study (FCS) was a prospective, multicenter study conducted in the United States in 127 patients who participated in an exercise performance study. The purpose of the FCS was to confirm effectiveness results related to functional capacity measures, specifically the Peak VO_2 and 6-Minute Hall Walk, previously reported in the NYHA Class III/IV subgroup of the CONTAK CD Study.

CRT was provided in the same manner for the FCS as for the CONTAK CD Study. The EASYTRAK lead, along with market approved right atrial and right ventricular leads were used to provide biventricular stimulation.

Demographic Data

The patients in the FCS had the same heart failure indications as the patients in the NYHA Class III/IV subgroup of the CONTAK CD Study; i.e., patient inclusion criteria included NYHA Class III or IV while on drug therapy, QRS duration ≥ 120 ms, and Left Ventricular Ejection Fraction (LVEF) ≤ 35%.

A baseline physical assessment and functional measures were performed prior to CRT system implant. Patients were eligible for participation in the study if they were capable of walking between 150 and 425 meters. In addition to a Six-Minute Walk test, other special tests were performed prior to implant consisting of a symptom-limited treadmill test and completion of the Minnesota Living with Heart Failure Questionnaire® to assess Quality of Life. CRT therapy was enabled immediately upon device implant. Patients were followed at one week, one month, three months, six months and every three months thereafter for a routine physical assessment and device evaluation. Special testing as defined above was repeated at three months and six months post-implant.

Prior to study entry, patients were stable on optimal heart failure medications (ACE inhibitors or substitute > 1 month and beta blockers > 3 months). Patients were excluded if they were indicated for either a pacemaker or ICD or if they were hospitalized for heart failure in the month prior to enrollment.

The patient characteristics at study entry are summarized in Table D-26 on page D-31.

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Table D-26. Pre-implant characteristics of study patients

Characteristics	All Patients Receiving CRT
Age (years)	61 ± 12
Male Gender (%)	69
NYHA Class III (%)	94
Ischemic Etiology (%)	49
Resting heart rate (bpm)	73 ± 12
QRS width (ms)	159 ± 27
LBBB/NSIVCD (%)	91
Heart failure medications (%)	
ACE inhibitor or ARB	91
Beta blockers	77
Digoxin	76
Diuretics	98

Inclusion Criteria

Inclusion criteria included:

- Moderate or severe heart failure, defined as symptomatic heart failure for at least six months with NYHA Class III or IV symptoms at the time of enrollment, AND at least one of the following events in the previous 12 months:
  - Hospitalization for heart failure management
  - Outpatient visit in which intravenous (IV) inotropes or vasoactive infusion were administered continuously for at least 4 hours
  - Emergency room visit of at least twelve hours duration in which IV heart failure medications were administered (including diuretics)
- QRS ≥ 120 ms and PR interval > 150 ms from any two leads of a 12-lead ECG
- Left ventricular ejection fraction ≤ 35%
- Left ventricular end diastolic dimension ≥ 60 mm (required only if LVEF measured by echo)

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- Age ≥ 18 years
- Optimal pharmacologic therapy for heart failure
- Able to walk between 150 and 425 m in a Six-Minute Walk test

Major Differences Between CONTAK CD and Focused Confirmatory Study Patients

The CONTAK RENEWAL 3, CONTAK RENEWAL, and CONTAK CD devices provide the same cardiac resynchronization therapy (biventricular pacing) and have the same Indications for Use. Therefore, the CONTAK CD clinical trial data used to support CONTAK CD is also applicable to CONTAK RENEWAL and CONTAK RENEWAL 3. The primary difference between CONTAK CD devices and CONTAK RENEWAL and CONTAK RENEWAL 3 devices is that CONTAK CD utilizes an electrically common RV and LV sensing/pacing circuit whereas CONTAK RENEWAL and CONTAK RENEWAL 3 incorporate an independent RV and LV sensing/pacing circuit. Additional clinical analysis was also conducted with CONTAK RENEWAL to provide confirmation that the independent sensing and pacing capability did not adversely affect the ability of the device to detect ventricular tachyarrhythmias or provide continuous biventricular pacing therapy.

Some of the major differences between the study populations included:

- Patients were excluded from the FCS if they were indicated for either a pacemaker or implantable cardioverter defibrillator (ICD). Patients in the CONTAK CD Study were excluded if they met the indications for a pacemaker; however, they were required to meet the general indications for an ICD.
- Patients were excluded from the FCS if they were hospitalized for heart failure in the month prior to enrollment; whereas, there was no exclusion for hospitalization for heart failure in the month prior to enrollment for the CONTAK CD patients.
- Patients in the FCS must have been on stable, optimal heart failure medications, including beta blocker therapy for three months, prior to study entry. Patients in the CONTAK CD Study could be optimized on drug therapy between the time from device implant until the treatment phase (either CRT or No CRT) began.

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- Patients in the FCS had baseline measurements performed prior to implant. Patients in the CONTAK CD Study had baseline measurements performed post-implant, but before programming of the randomized therapy.

- Seventy-seven percent of patients in the FCS (98 of N = 127) were on beta blockers compared to 42% in the CONTAK CD Study (95 of N = 227).

- Forty-nine percent of patients in the FCS (62 of N = 127) had ischemic etiology compared to 68% in the CONTAK CD Study (154 of N = 227).

Endpoints

The primary endpoints of the study were Peak VO_2 and Six-Minute Walk distance. The study was designed to show a mean change of at least 1ml/kg/min and a 95% lower confidence bound (LCB) at least 0.5 ml/kg/min. The study was also designed to detect a statistically significant improvement in the Six-Minute Walk distance at a one-sided significance level of 0.10. Additionally, two ancillary analyses of Quality of Life Score and NYHA Class had to demonstrate a change that was directionally favorable towards CRT using descriptive statistics.

Study Results

Study results for the Focused Confirmatory Study include the following:

- Peak VO_2—a statistically significant improvement from baseline of 0.94 ± 0.30 ml/kg/min with a 95% LCB of 0.45 was observed in Peak VO_2 after six months of CRT

- Six-Minute Walk—statistically significant improvements versus baseline were observed in Six-Minute Walk distance after six months of CRT with an observed mean improvement of 50.9 ± 10.4 m with a 95% LCB of 37.6 m

- Quality of Life—consistent with the other analyses, a statistically significant improvement of 23.9 ± 2.6 points was observed in the Quality of Life score after six months of CRT with a 95% LCB of 19.7 points

- New York Heart Association Class—after six months of CRT, a statistically significant improvement in NYHA Class was observed with 60.4% of patients improving one or more NYHA Class

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CLINICAL STUDY - CONTAK RENEWAL

APPENDIX E

CLINICAL STUDY POPULATIONS

Guidant CRT-Ds, when compared to OPT alone, have been demonstrated with reasonable assurance, to be safe and effective in significantly reducing: the risk of a composite of all-cause mortality or first hospitalization by 20%, the risk of all-cause mortality by 36%, and heart failure symptoms in patients who have moderate to severe heart failure (NYHA III/IV) including left ventricular dysfunction (EF ≤ 35%) and QRS duration ≥120 ms and remain symptomatic despite stable, optimal heart failure drug therapy, based on the Guidant sponsored COMPANION clinical study. (Guidant devices were the only devices studied in the COMPANION clinical trial.)

SUMMARY

Guidant conducted the CONTAK RENEWAL Study, which demonstrated the device's ability to appropriately detect ventricular tachyarrhythmias with an independent sensing configuration. Finally, the CONTAK RENEWAL Holter Study was conducted to provide confirmation of the device's ability to provide continuous biventricular pacing on both a daily basis and during exercise.

STUDY DESIGN

The CONTAK RENEWAL Study was a prospective, multi-center, non-randomized evaluation conducted in Europe and enrolled a total of 45 patients. The purpose of the study was to verify that the CONTAK RENEWAL device performs according to specification.

INCLUSION/EXCLUSION CRITERIA

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

- Symptomatic heart failure
- Left ventricular dysfunction
- Wide QRS
- At risk for sudden cardiac death
- 18 years or of legal age in order to give informed consent according to national laws

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- Able to understand the nature of the procedure
- Available for follow-up on a regular basis at an approved investigational center

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

- Life expectancy of less than six months due to other medical conditions
- For women: Pregnancy or absence of medically accepted birth control
- Inability or refusal to sign the Patient Informed Consent
- Inability or refusal to comply with the follow up schedule or protocol requirements
- Mechanical tricuspid prosthesis
- Currently enrolled in another investigational study, including drug investigations
- Hypertrophic Obstructive Cardiomyopathy
- Are unable to undergo device implant, including general anesthesia if required
- Have pre-existing leads other than those specified in the investigational plan (unless the investigator intended to replace them with the permitted leads)

DEMOGRAPHIC DATA

The patient characteristics at study entry are summarized in Table E-1 on page E-2.

Table E-1. Pre-implant characteristics of study patient

Characteristics[a]	Patient Data
N patients implanted	44
Gender	Male (91%), Female (9%)
Age (years)	65 ± 9
NYHA	II (14%), III (77%), IV (9%)
LVEF (%)	22 ± 6
BBB	LBBB/NSIVCD (86%),RBBB (14%)
Etiology	Ischemic (56%), Non-ischemic (44%)
QRS Width	172 ± 24 ms

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Table E-1. Pre-implant characteristics of study patient (continued)

Characteristics[a]	Patient Data
PR Interval	211 ± 49 ms
Resting HR	70 ± 12 bpm

a. Continuous measures are reported as means ± standard deviations.

VENTRICULAR TACHYARRHYTHMIA DETECTION TIME

The CONTAK RENEWAL device has independent Left Ventricular and Right Ventricular Sensing. Ventricular tachyarrhythmia detection time was analyzed to determine if the sensing configuration had any effect on sensing VT/VF. Based on previous clinical studies of the VENTAK AV family, upon which the ICD function of CONTAK CD and CONTAK RENEWAL are built, Guidant's ICDs typically have a VF detection time of approximately two seconds. The VF detection time of 2.4 ± 0.5 seconds in the RENEWAL study was statistically lower than 6 seconds ($p < 0.01$), demonstrating that there was no statistically significant prolongation of induced VF detection times with the independent sensing configuration.[1] There were no adverse events reported in which a CONTAK RENEWAL device failed to detect a spontaneous ventricular tachyarrhythmia.

HOLTER STUDY - CONTAK RENEWAL

Study Design

The CONTAK RENEWAL Holter Study was a prospective, multi-center, non-randomized evaluation conducted in Europe, in which 46 patients completed testing. The purpose of the study was to demonstrate continuous appropriate biventricular (BiV) pacing over a 24 hour period and during exercise using Holter monitor recordings. All patients had been implanted with a CONTAK RENEWAL for a minimum of one month at the time of the study initiation.

1. Detection time at implant with legally marketed Guidant ICD devices is typically two seconds, and investigators have stated than an additional delay of 3 to 5 seconds would be a clinically significant event. The expected detection time is 2 seconds (95% CI: [0, 6 sec]).

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Inclusion/Exclusion Criteria

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

- Availability for 24 hours follow-up at an approved study center
- Willingness and ability to participate in all testing associated with this study
- Age 18 or above, or of legal age to give informed consent as specified by national law
- Implanted with the CONTAK RENEWAL system for at least 1 month
- Stable when programmed according to labeled recommendations for continuous BV pacing
- Sinus rhythm at follow-up
- Active atrial lead implanted

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

- Life expectancy of less than six months due to other medical conditions
- Concurrent participation in any other clinical study, including drug study
- In atrial fibrillation at follow-up
- Inability or refusal to sign the Patient Informed Consent
- Inability or refusal to comply with the follow-up schedule
- Known pregnancy

Demographic Data

The patient characteristics at study entry are summarized in Table E-2 on page E-4.

Table E-2. Pre-implant characteristics of study patients

Characteristics		Patient Data
N patients		46
Gender		Male: 40 (87%), Female: 6 (13%)
Age (years)		60.9 ± 9.0
NYHA at implant [N (%)]	I	0 (0%)
	II	5 (10.9%)
	III	34 (73.9%)

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Table E-2. Pre-implant characteristics of study patients (continued)

Characteristics		Patient Data
	IV	7 (15.2)%
NYHA current [N (%)]	I	9 (19.6%)
	II	25 (54.3%)
	III	11 (23.9%)
	IV	1 (2.2%)
Duration implanted (months)	Mean ± SD	8.3 ± 4.1
	Range	1.5 – 15.0
	Median	9.0

Programming Parameters

Refer to the Pacing Therapies chapter for information about programming to maintain CRT. Programming recommendations in this study were consistent with the recommendations in that chapter.

Endpoints

The study had the following primary endpoints:

- Continuous appropriate BiV pacing during activities of daily living
- Continuous appropriate BiV pacing during exercise

The mean percentage of sinus beats appropriately BiV paced was measured by a Holter monitor over a 24 hour period and during exercise. Exercise intensity was measured using the Borg rating of perceived exertion (RPE) 6-20 scale. Patients were asked to exercise to a Borg level of 15 (difficult). The exercise protocol used was left to the discretion of the physician based on the patients' functional status. The type of exercise performed, duration and intensity of exercise testing is listed in Table E-3 on page E-5 and Table E-4 on page E-6.

Table E-3. Type of exercise testing performed

Exercise Performed	Number of Patients
Bicycle Ergometry	24 (52.2%)
Hall Walk	8 (17.4%)

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Table E-3. Type of exercise testing performed (continued)

Exercise Performed	Number of Patients
Stair Climbing	14 (30.4%)
Total	46

Table E-4. Duration and intensity of exercise testing

		Results (N = 46)
Borg RPE Rating Obtained	Mean ± SD	15 ± 1
	Median	15
	Range	7 – 18
Duration of Exercise (minutes)	Mean ± SD	6.6 ± 3.3
	Median	6.0
	Range	1 – 17
Maximum HR Obtained (bpm)	Mean ± SD	103 ± 20
	Median	105
	Range	60 – 156

Study Results

Pacing during activities of daily living

The mean percentage of appropriately continuously paced beats during daily living was calculated as 99.6 ± 1.3% with a median of 100% and is summarized in Table E-5 on page E-6. Continuous appropriate BiV pacing is defined as pacing provided between the lower rate limit and the MTR, excluding PVCs.

Table E-5. Activities of daily living: continuous appropriate BiV pacing

	Statistic	P-value[a]
Mean ± SD	99.6 ± 1.3	–
Range	91.4 – 100	–
Median[b]	100	<0.01

a. The p-value is based on the sign-rank test.
b. Due to the non-normality of the data a non-parametric test of the median was performed comparing the median to 90%.

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Pacing During Exercise

The mean percentage of appropriately continuously paced beats during exercise was calculated as 98.3 ± 5.6% with a median of 100% and is summarized in Table E-6 on page E-7. Continuous appropriate BiV pacing is defined as pacing provided between the lower rate limit and the MTR, excluding PVCs.

Table E-6. Exercise: continuous appropriate BiV pacing

	Statistic	P-value
Mean ± SD	98.3 ± 5.6	–
Range	68.1 – 100	–
Median	100	<0.01

Device Counters

Finally, during the study CONTAK RENEWAL device counters were found to correlate highly to the data collected on the independent Holter monitors (Table E-7 on page E-7).

Table E-7. Correlation between holter and device

	Mean ± SD	Correlation (P-value)
Holter	97,536 ± 13,307	0.97 (<0.01)
Device	100,143 ± 13,373	–

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CLINICAL STUDY - SUMMARY OF CRT OPTIMIZATION ALGORITHM VALIDATION STUDY

APPENDIX F

CLINICAL STUDY DESIGN

NOTE: *The SmartDelay optimization feature was previously known as Expert Ease for Heart Failure (EEHF+).*

This clinical investigation was a 50 patient, multi-center, acute hemodynamic study at 5 centers in the United States to validate the performance of Expert Ease for Heart Failure AV delay optimization algorithm (EEHF+[1]).

The main purposes of this clinical investigation were: (A) to test prospectively the effectiveness of EEHF+ in optimizing LV dP/dt_{max} (maximum rate of LV pressure change) for biventricular (BV) CRT in atrial sensing and pacing modes; and (B) to evaluate and compare LV dP/dt_{max} and stroke volume as measured by AoVTI[2] at AV delays determined by a CRT optimization method (EEHF+, Echo) and also by a series of population fixed values, for BV CRT in atrial sensing and pacing modes.

The study consisted of three phases in the following order: an acute test (during implant), a device implant, and an echocardiography study. In the acute test the LV pressure data was collected invasively at various stimulation mode/site/AV delay combinations. After the implant of a CRT/CRT-D device using standard procedures, a standard non-invasive Doppler echo procedure was performed, in which Doppler flow-velocity profiles from aortic, mitral, and pulmonary valves were collected during BV CRT at various stimulation mode/AV delay combinations.

Inclusion/Exclusion Criteria

Patients enrolled in this study were required to meet the criteria for a CRT/CRT-D device implant at the time of implant (Sept 2003 - Oct 2004).

Patients were excluded from the study if they met any of the following criteria:

1. From this point on, Expert Ease for Heart Failure AV delay optimization algorithm is referred as EEHF+.
2. Otto CM, Pearlman AS, Comess K, Reamer R, Janko C, Huntsman L. Determination of the stenotic aortic valve area in adults using Doppler echocardiography. J Am Coll Cardiol 1986;7:509-17.

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- Patients in AF that can not be cardioverted for the study
- Sustained, uncontrolled ventricular tachycardia
- Frequent ectopic activity that makes stable hemodynamic measurements infeasible
- Sinus rhythm < 30 bpm or > 100 bpm
- Complete AV node block
- Acute severe heart failure exacerbation
- Severe aortic valvular stenosis (valve area < 1.0 square cm)
- Hypertrophic obstructive cardiomyopathy
- CABG within 2 weeks
- Congenital heart disease
- Pregnancy
- Patient involved in other clinical investigations of active therapy or treatment
- Patient at unacceptably high risk for catheterization (a patient who would not medically be indicated for an EP study or diagnostic catheterization)

STUDY RESULTS

Patient Accountability

Fifty patients were enrolled in the study. Forty-one patients had valid acute hemodynamic tests completed and thirty-eight patients had valid echo tests completed. Among the 9 patients with invalid acute hemodynamic tests, 7 were attempts, and 2 completed the acute test but with invalid results (one of them had an unstable atrial rate and the other had 2:1 AV conduction). A valid echo was defined as a subject who had a valid acute hemodynamic test and also completed the echo test.

Patient Characteristics

The subject demographics are shown below (Table F-1 on page F-3).

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Table F-1. Subject Demographics

Characteristic	Measurement	Result
Age at Implant	Number of subjects	50
	Mean ± SD	68.1 ± 10.5
	Range	[47.0, 85.0]
Gender [N (%)]	Female	12 (24.0)
	Male	38 (76.0)
NYHA Class [N (%)]	II	1 (2.0)
	III	49 (98.0)
LVEF	Number of subjects	50
	Mean ± SD	26.6 ± 6.6
	Range	[5.0, 35.0]
Conduction Disorder	LBBB	38 (86.4)
	RBBB	12 (27.3)

LV DP/dt$_{max}$ Results

Correlation between the LV dP/dt$_{max}$ at the EEHF+ recommended AV delay and maximum achievable LV dP/dt$_{max}$

- For the regression analysis, the 95% confidence intervals of the regression slope were [0.98, 1.07] and [0.94, 1.10] for atrial sensing and pacing. The corresponding intercept values were [-2.07, -0.86] and [-3.73, -0.76] for atrial sensing and pacing (Figure F-1 on page F-4). The ability of EEHF+ to suggest an AV delay that maximizes %LV dP/dt$_{max}$ for both atrial sensing and atrial pacing is demonstrated in the regression plots. For patients with a near-zero maximum improvement in %LV dP/ dt$_{max}$ from baseline, the %LV dP/dt$_{max}$ at the AV delay estimated by EEHF+ was close to the maximum achievable %LV dP/dt$_{max}$ as indicated by the small intercept (-1.47 for atrial sensing and -2.25 for atrial pacing).

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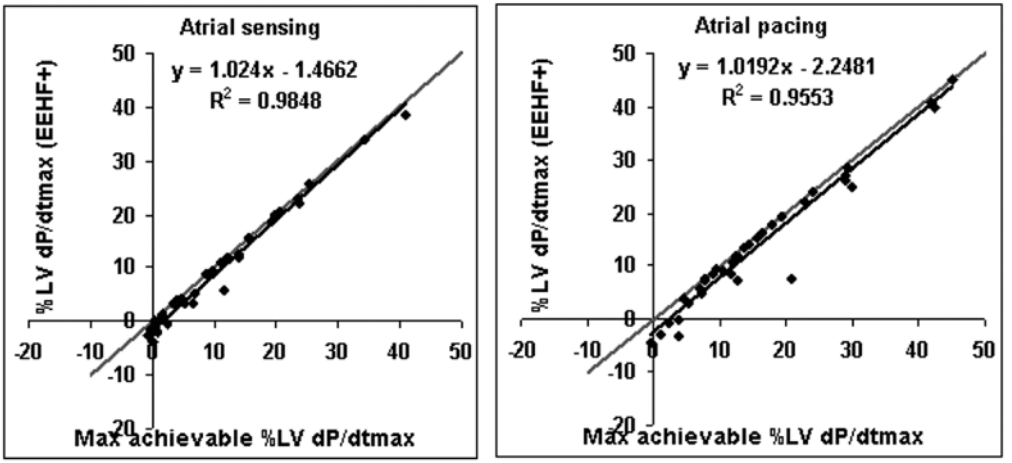

Correlation between maximum achievable %LV dP/dt_{max} and the %LV dP/dt_{max} achieved with the EEHF+ delay for both atrial sensing (left, n=38) and atrial pacing (right, n=36).

Figure F-1. Correlation between achievable and achieved

Comparison of EEHF+ recommended AV delay to fixed AV delays of 100 ms, 120 ms, 140 ms or 160 ms in achieving LV dP/dt_{max}

- Differences between the %LV dP/dt_{max} achieved with EEHF+ and the %LV dP/dt_{max} achieved with fixed AV delays were plotted for each fixed AV delay (Figure F-2 on page F-5). A negative value indicated that the %LV dP/dt_{max} achieved with EEHF+ was higher. See the tables below for further details about the number of subjects, mean, standard deviation, p-value, and confidence interval for each comparison (Table F-2 on page F-5, Table F-3 on page F-6).

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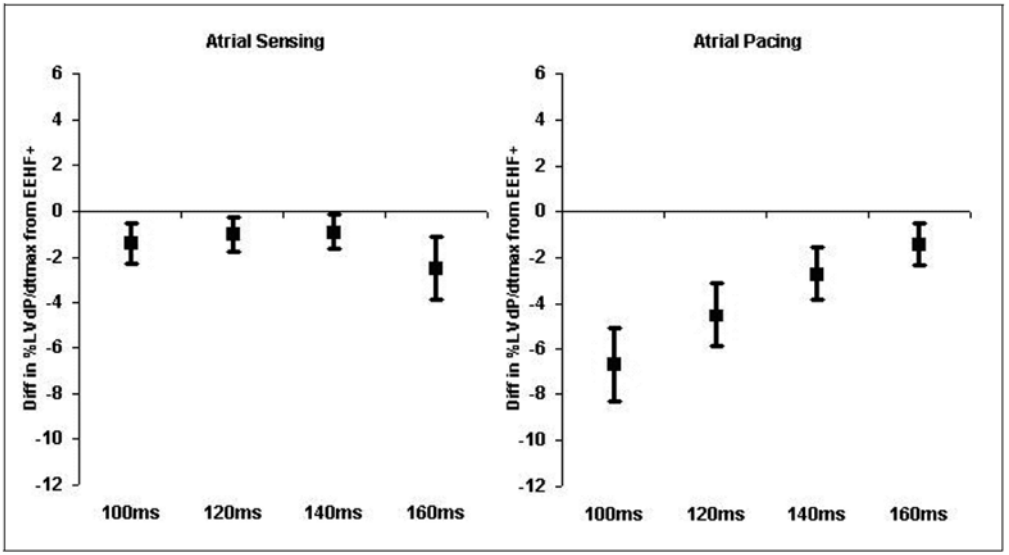

Differences between %LV dP/dt_{max} achieved with EEHF+ and with fixed AV delays of 100 ms, 120 ms, 140 ms or 160 ms for atrial sensing (left) and atrial pacing (right). A negative value indicates that the EEHF+ algorithm is better. The box represents the mean and error bars represent 95% CI of mean.

Figure F-2. Differences, achieved with EEHF+ and fixed AV delays

Table F-2. Differences between maximal achievable %LV dP/dt max and that achieved using EEHF+ and a fixed AV delay of 100 ms, 120 ms, 140 ms and 160 ms, during atrial sensing

n, mean ± std, 95% CI	n, mean ± std, 95% CI	n, mean ± std, 95% CI	Paired t-test
EEHF+	100 ms	Paired difference	P-value
38, -1.2 ± 1.3, (-1.6, -0.8)	38, -2.7 ± 2.9, (-3.6, -1.8)	38, -1.4 ± 2.8, (-2.3, -0.6)	0.0025
EEHF+	120 ms	Paired difference	P-value
38, -1.2 ± 1.3, (-1.6, -0.8)	38, -2.2 ± 2.2, (-2.9, -1.5)	38, -1.0 ± 2.3, (-1.7, -0.2)	0.0130
EEHF+	140 ms	Paired difference	P-value
36, -1.3 ± 1.3, (-1.7, -0.8)	36, -2.1 ± 2.0, (-2.8, -1.5)	36, -0.9 ± 2.3, (-1.6, -0.1)	0.0279

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Table F-2. Differences between maximal achievable %LV dP/dt max and that achieved using EEHF+ and a fixed AV delay of 100 ms, 120 ms, 140 ms and 160 ms, during atrial sensing (continued)

n, mean ± std, 95% CI	n, mean ± std, 95% CI	n, mean ± std, 95% CI	Paired t-test
EEHF+	160 ms	Paired difference	P-value
33, -1.1 ± 1.3, (-1.6, -0.7)	33, -3.6 ± 3.8, (-4.9, -2.3)	33, -2.5 ± 4.0, (-3.8, -1.1)	0.0013

Table F-3. Differences between maximal achievable %LV dP/dt max and that achieved using EEHF+ and a fixed AV delay of 100 ms, 120 ms, 140 ms and 160 ms, during atrial pacing

n, mean ± std, 95% CI	n, mean ± std, 95% CI	n, mean ± std, 95% CI	Paired t-test
EEHF+	100 ms	Paired difference	P-value
36, -2.0 ± 2.6, (-2.8, -1.1)	36, -8.7 ± 5.1, (-10.3, -7.0)	36, -6.7 ± 4.8, (-8.3, -5.2)	< 0.0001
EEHF+	120 ms	Paired difference	P-value
36, -2.0 ± 2.6, (-2.8, -1.1)	36, -6.5 ± 4.7, (-8.0, -4.9)	36, -4.5 ± 4.2, (-5.9, -3.2)	< 0.0001
EEHF+	140 ms	Paired difference	P-value
36, -2.0 ± 2.6, (-2.8, -1.1)	36, -4.7 ± 4.2, (-6.1, -3.3)	36, -2.7 ± 3.5, (-3.9, -1.6)	< 0.0001
EEHF+	160 ms	Paired difference	P-value
36, -2.0 ± 2.6, (-2.8, -1.1)	36, -3.4 ± 3.6, (-4.5, -2.2)	36, -1.4 ± 2.8, (-2.3, -0.5)	0.0049

Comparison of EEHF+ recommended AV delay to the echo-based Ritter and AoVTI methods in achieving LV dP/dt$_{max}$

- Differences between the %LV dP/dt$_{max}$ achieved with EEHF+ and the %LV dP/dt$_{max}$ achieved with the Ritter and AoVTI echo methods were plotted for the two echo methods (Figure F-3 on page F-7). A negative value indicated that the LV dP/dt$_{max}$ achieved with EEHF+ was higher. See the tables below for further details about the number of subjects, mean, standard deviation, p-value, and confidence interval for each comparison (Table F-4 on page F-7, Table F-5 on page F-7).

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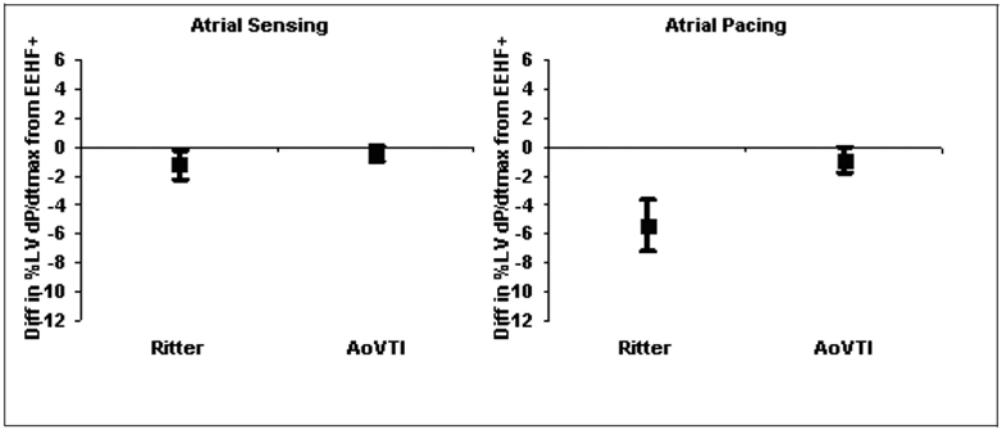

Differences between %LV dP/dt_{max} achieved with EEHF+ and with two echo-based methods: the Ritter method and the AoVTI method for atrial sensing (left) and atrial pacing (right). A negative value indicates that EEHF+ was better. The box represents the mean and error bars represent 95% CI of mean.

Figure F-3. Differences, achieved with EEHF+ and echo-based methods

Table F-4. Differences between maximal achievable %LV dP/dt max and that achieved from the EEHF+, the Ritter method, and the AoVTI method during atrial sensing

n, mean ± std, 95% CI	n, mean ± std, 95% CI	n, mean ± std, 95% CI	Paired t-test
EEHF+	Ritter method	Paired difference	P-value
35, -1.3 ± 1.3, (-1.7, -0.8)	35, -2.5 ± 2.7, (-3.3, -1.6)	35, -1.2 ± 3.0, (-2.1, -0.2)	0.0259
EEHF+	AoVTI method	Paired difference	P-value
33, -1.3 ± 1.3, (-1.8, -0.8)	33, -1.7 ± 1.9, (-2.3, -1.0)	33, -0.4 ± 1.6, (-0.9, 0.2)	0.2036

Table F-5. Differences between maximal achievable %LV dP/dt max and that achieved from the EEHF+, the Ritter method, and the AoVTI method during atrial pacing

n, mean ± std, 95% CI	n, mean ± std, 95% CI	n, mean ± std, 95% CI	Paired t-test
EEHF+	Ritter method	Paired difference	P-value
33, -2.0 ± 2.7, (-2.9, -1.1)	33, -7.4 ± 5.5, (-9.3, -5.5)	33, -5.4 ± 5.1, (-7.2, -3.7)	< 0.0001

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Table F-5. Differences between maximal achievable %LV dP/dt max and that achieved from the EEHF+, the Ritter method, and the AoVTI method during atrial pacing (continued)

n, mean ± std, 95% CI	n, mean ± std, 95% CI	n, mean ± std, 95% CI	Paired t-test
EEHF+	AoVTI method	Paired difference	P-value
34, -2.0 ± 2.6, (-2.8, -1.1)	34, -2.8 ± 2.9, (-3.8, -1.8)	34, -0.9 ± 2.6, (-1.8, 0.0)	0.0617

AoVTI Results

There was a large variance in the difference in %AoVTI$_{max}$ achieved by all the methods evaluated in this study, which is consistent with the inherent variability of the AoVTI measurements[3].

Comparison of EEHF+ recommended AV delay to fixed AV delays of 100 ms, 120 ms, 140 ms, and 160 ms in achieving AoVTI$_{max}$

- As shown in the tables below, there was a large variance in the difference in %AoVTI$_{max}$ achieved by EEHF+ and the fixed AV delays for both atrial sensing and pacing; the tables also provide further details about the number of subjects, mean, standard deviation, p-value, and confidence interval (Table F-6 on page F-8, Table F-7 on page F-9).

Table F-6. Differences between maximal achievable %AoVTI and that achieved using the EEHF+ and a fixed AV delay of 100 ms, 120 ms, 140 ms, and 160 ms during atrial sensing.

n, mean ± std, 95% CI	n, mean ± std, 95% CI	n, mean ± std, 95% CI	Paired t-test
EEHF+	100 ms	Paired difference	P-value
36, -8.5 ± 8.3, (-11.2, -5.8)	36, -6.6 ± 5.7, (-8.4, -4.7)	36, 1.9 ± 9.5, (-1.2, 5.0)	0.2323
EEHF+	120 ms	Paired difference	P-value
35, -7.7 ± 7.0, (-10.0, -5.4)	35, -5.1 ± 6.9, (-7.3, -2.8)	35, 2.7 ± 8.9, (-0.3, 5.6)	0.0837
EEHF+	140 ms	Paired difference	P-value
36, -8.5 ± 8.3, (-11.2, -5.8)	36, -6.1 ± 4.4, (-7.5, -4.6)	36, 2.4 ± 9.3, (-0.6, 5.5)	0.1296

3. Otto CM, Pearlman AS, Comess K, Reamer R, Janko C, Huntsman L. Determination of the stenotic aortic valve area in adults using Doppler echocardiography. J Am Coll Cardiol 1986;7:509-17.

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Table F-6. Differences between maximal achievable %AoVTI and that achieved using the EEHF+ and a fixed AV delay of 100 ms, 120 ms, 140 ms, and 160 ms during atrial sensing. (continued)

n, mean ± std, 95% CI	n, mean ± std, 95% CI	n, mean ± std, 95% CI	Paired t-test
EEHF+	160 ms	Paired difference	P-value
36, -8.5 ± 8.3, (-11.2, -5.8)	36, -7.3 ± 6.4, (-9.4, -5.2)	36, 1.2 ± 9.8, (-2.0, 4.4)	0.4769

Table F-7. Differences between maximal achievable %AoVTI and that achieved using the EEHF+ and a fixed AV delay of 100 ms, 120 ms, 140 ms, and 160 ms during atrial pacing

n, mean ± std, 95% CI	n, mean ± std, 95% CI	n, mean ± std, 95% CI	Paired t-test
EEHF+	100 ms	Paired difference	P-value
35, -6.6 ± 5.2, (-8.3, -4.8)	35, -11.9 ± 6.4, (-14.0, -9.8)	35, -5.4 ± 9.3, (-8.4, -2.3)	0.0017
EEHF+	120 ms	Paired difference	P-value
34, -6.4 ± 5.3, (-8.2, -4.7)	34, -9.3 ± 7.1, (-11.7, -6.9)	34, -2.8 ± 9.9, (-6.2, 0.5)	0.1046
EEHF+	140 ms	Paired difference	P-value
35, -6.6 ± 5.2, (-8.3, -4.8)	35, -7.9 ± 5.3, (-9.7, -6.2)	35, -1.4 ± 7.7, (-3.9, 1.2)	0.2977
EEHF+	160 ms	Paired difference	P-value
35, -6.6 ± 5.2, (-8.3, -4.8)	35, -7.1 ± 5.4, (-8.9, -5.3)	35, -0.5 ± 7.7, (-3.1, 2.0)	0.6896

Comparison of EEHF+ recommended AV delay to echo-based Ritter method in achieving $AoVTI_{max}$

- As shown in the tables below, there was a large variance in the difference in %AoVTI obtained with EEHF+ and that obtained with Ritter method in atrial sensing mode and atrial pacing mode; the tables also provide further details about the number of subjects, mean, standard deviation, p-value, and confidence interval (Table F-8 on page F-10, Table F-9 on page F-10).

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Table F-8. Differences between maximum achievable %AoVTI and that achieved with EEHF+ and Ritter during atrial sensing

n, mean ± std, 95% CI	n, mean ± std, 95% CI	n, mean ± std, 95% CI	Paired t-test
EEHF+	Ritter method	Paired difference	P-value
36, -8.5 ± 8.3, (-11.2, -5.8)	36, -6.5 ± 5.6, (-8.3, -4.6)	36, 2.0 ± 9.1, (-0.9, -5.0)	0.1895

Table F-9. Differences between maximum achievable %AoVTI and that achieved with EEHF+ and Ritter during atrial pacing

n, mean ± std, 95% CI	n, mean ± std, 95% CI	n, mean ± std, 95% CI	Paired t-test
EEHF+	Ritter method	Paired difference	P-value
34, -6.8 ± 5.2, (-8.5, -5.0)	34, -10.4 ± 6.6, (-12.6, -8.1)	34, -3.6 ± 9.0, (-6.7, -0.6)	0.0255

CONCLUSIONS

The results of the CRTAVO study are summarized as follows:

- The algorithm recommended AV delays that maximized global contractile function as measured by LV dP/dt.
- The EEHF+ algorithm recommended an AV delay that increased acute hemodynamic responses in terms of %LV dP/dt_{max}, as compared to fixed AV delays of 100 ms, 120 ms, 140 ms or 160 ms.
- The EEHF+ algorithm recommended an AV delay that increased acute hemodynamic responses in terms of %LV dP/dt_{max}, as compared to AV delay recommended by Ritter method.

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CLINICAL STUDY - VITALITY

APPENDIX G

CLINICAL STUDY POPULATIONS

Guidant CRT-Ds, when compared to OPT alone, have been demonstrated with reasonable assurance, to be safe and effective in significantly reducing: the risk of a composite of all-cause mortality or first hospitalization by 20%, the risk of all-cause mortality by 36%, and heart failure symptoms in patients who have moderate to severe heart failure (NYHA III/IV) including left ventricular dysfunction (EF ≤ 35%) and QRS duration ≥120 ms and remain symptomatic despite stable, optimal heart failure drug therapy, based on the Guidant sponsored COMPANION clinical study. (Guidant devices were the only devices studied in the COMPANION clinical trial.)

CHRONIC IMPLANT STUDY - VITALITY

The purpose of this study was to evaluate the safety and effectiveness of Guidant VITALITY family devices with Automatic Intrinsic Rhythm ID. This clinical study was a single-arm, prospective, multi-center study. There were a total of 100 patients enrolled at 21 US investigational centers between December 3, 2002 and January 10, 2003.

Patient Population

One hundred patients were enrolled in this study and 96 patients received investigational devices. The mean age of the patients implanted with the VITALITY device was 67.3 ± 10.8 years old. The mean left ventricular ejection fraction was 30.4% (range 11.0% - 71.0%). Seventy-eight (78) patients (81.3%) were male. The primary cardiovascular disease (42.1%) was coronary artery disease (CAD) and the primary tachyarrhythmia (38.5%) was monomorphic ventricular tachycardia (MVT).

Methods

A prospective, multi-center, nonrandomized clinical study evaluated the safety and effectiveness of the VITALITY device in humans. Ninety-six patients selected from the investigator's general patient population who met the indications for use of the VITALITY device were followed through pre-discharge, 2-week and 1-month follow-ups and continued every 3 months thereafter until study closure.

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Results

A total of 100 patients were enrolled in this study. Of these, 96 patients were successfully implanted, with 4 intents. Ninety-three (93) patients finished their 1-month follow-up per the study protocol. All primary and secondary endpoints of this study were met. The results from this study provide evidence of the safety and effectiveness of the VITALITY with Automatic Intrinsic Rhythm ID algorithm (Table G-1 on page G-2).

Table G-1. VITALITY Chronic Study Results

Safety Endpoints			
VT/VF Detection Time			3.43 seconds
Primary Endpoints			
Sensitivity			
Induced VT/VF			100%
Spontaneous VT/VF			100%
Specificity—Induced			
Rhythm	**Physician/Annotation**	**Device Decision–SVT**	**Specificity**
Atrial Fibrillation	71	68	95.8%
Atrial Flutter	94	88	93.6%
Sinus Tachycardia	7	5	71.4%
Total Induced	172	161	93.6%
Specificity–Spontaneous			
Rhythm	**Physician/Annotation**	**Device Decision–SVT**	**Specificity**
Atrial Fibrillation	65	65	100%
Atrial Flutter	31	28	90.3%
Sinus Tachycardia	37	32	86.5%
Other	7	7	100%
Total Spontaneous	140	132	94.3%[a]
Combined Specificity[b]	**312**	**293**	**93.9%**
Secondary Endpoints			
Acute Automatic Rhythm ID Accuracy (2 weeks)			100%

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Table G-1. VITALITY Chronic Study Results (continued)

Automatic Rhythm ID Accuracy (1 month)	97.7%
Manual Rhythm ID Accuracy (1 month)	100%

a. GEE adjusted specificity = 93.7%
b. Combined specificity includes both Induced and Spontaneous data.

ACUTE STUDY - VITALITY

The VITALITY ICD was compared to a commercially available ICD (VENTAK PRIZM, or VENTAK PRIZM 2 ICD) in an acute (nonimplant) paired study of 50 patients enrolled at nine investigating centers between March 8, 2001 and July 24, 2001. A total of 47 patients were tested with the study device, followed by a control device at the time of a Guidant commercially approved (VENTAK PRIZM, model 1851 or VENTAK PRIZM 2, model 1861) implantation.

The purpose of the acute study was to demonstrate that the addition of an SVT detection enhancement and brady features did not adversely impact normal ICD sensing and detection functionality. A total of 50 patients were tested in nine U.S. centers.

Patients studied

The patients (38 M/9 F) had a mean age of 66 years (range 37 to 90) and a left ventricular ejection fraction of 32% (range 10% to 62%). Most (40%) presented with monomorphic ventricular tachycardia (MVT) and nonsustained VT as their primary arrhythmia. Of the patients studied, 87 percent presented with coronary artery disease or ischemic cardiomyopathy.

Methods and statistics

The acute study was done in the operating room or electrophysiology laboratory without implantation of the study device. The primary endpoint was to determine that VT/VF detection time for induced episodes is within two seconds of the VENTAK PRIZM or VENTAK PRIZM 2 detection time.

Results

A total of 50 patients were enrolled in the acute study. Of those, 47 patients were successfully tested with the system per study protocol; there were two attempted procedures and one intent. There was one clinical complication and two observations reported in the acute study, all of which were non-investigational device related. No patient deaths were reported.

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The VT/VF detection time of the VITALITY ICD was found to be within two seconds of the VENTAK PRIZM 2 detection time, leading to the conclusion that activating the additional VITALITY features does not have a negative effect on the existing ICD sensing and detection functionality (Table G-2 on page G-4).

Table G-2. Acute study results

Study Endpoint	VITALITY (Mean ± std) N	VENTAK PRIZM 2 DR (Mean ± std) N
VT/VF Detection Time (seconds)	3.60 ± 0.60 N = 47	3.52 ± .057 N = 47
p-value: <0.001		

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CLINICAL STUDY - SUMMARY OF GDT1000 SENSING ACUTE STUDY

APPENDIX H

CLINICAL STUDY POPULATIONS

GDT1000 study included patients indicated for a CRT-D device. Excluded from the study were patients meeting any of the following criteria:

- Having no intrinsic P and/or R waves at implant
- Having a pre-existing unipolar pacemaker that was not to be explanted/abandoned
- Enrolled in a concurrent study that would confound the study results
- Having ventricular tachyarrhythmias associated with a reversible cause (e.g., digitalis toxicity, hypoxia, sepsis, transient electrolyte imbalance, acute myocardial infarction, electrocution, or drowning)
- Women who were pregnant or planned to become pregnant
- Having a prosthetic mechanical tricuspid heart valve

STUDY METHODS

This clinical investigation was a 50 patient, multi-center, acute study conducted at seven (7) centers in the United States. The main purpose of this clinical investigation was to characterize the performance of the new Automatic Gain Control (AGC) sensing platform, with the Dynamic Noise Adjustment (DNA) feature, that is used in both COGNIS and TELIGEN devices. The AGC sensing platform was studied using a Guidant Acute Sensing Device (GASD) system, a non-implantable device containing the COGNIS/TELIGEN system board, hardware, and firmware required for sensing intracardiac signals. The study enrolled a total of 50 patients and was conducted in two phases. In the first phase, 28 of 30 patients completed protocol testing. The algorithm was modified after the first phase, and it was re-evaluated in the second phase, in which 17 of 20 patients completed protocol testing. Of the five patients who did not complete testing in the two phases, three were attempts, and two were intents.

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Protocol Testing

Four scenarios were tested, including different combinations of sensed atrial signals (AS), paced atrial signals (AP), sensed ventricular signals (VS), and paced ventricular signals (VP), i.e., AS/VS, AS/VP, AP/VS, and AP/VP. Sensing algorithm performance was analyzed from patients' real-time electrograms (EGM) and electronic signals. Primary analysis was performed by visually reviewing the EGM and markers of the printed strips for proper sensing, as well as for instances of undersensing and oversensing.

Additional analysis included tabulating the sensed and paced events stored in the patient data files from the patient CD-ROM. During this tabulation, unexpected events were noted. An example of an unexpected event is a sensed event during an AP/VP testing scenario. The sensed event could be a real event, such as a PVC, or an oversensed event. These unexpected events were evaluated by viewing the electronic signals stored in the patient data files and correlating these signals to the printed strips.

Statistical Analysis

The sensitivity, specificity, positive predictive value, rate of oversensing, and rate of undersensing of the sensing algorithm were analyzed for each chamber. A true positive (TP) is the number of intrinsic/paced signals appropriately sensed, a false positive (FP) is the number of intrinsic/paced signals from the opposite chamber oversensed, a false negative (FN) is the number of intrinsic/paced signals undersensed, and a true negative (TN) is the number of intrinsic/paced signals from the opposite chamber appropriately not sensed. The sensing sensitivity was calculated as TP/(TP+FN), specificity as TN/(TN+FP), positive predictive value (PPV) as TP/(TP+FP), rate of oversensing as FP/(TP+FP), and rate of undersensing as FN/(TP+FN).

The sensing performance results from the first phase of the study are provided and compared to the results from the second phase in order to demonstrate the improvement in the operation of the updated sensing algorithm following the between-phase changes. Results from the second phase of the study are the most clinically relevant, as they reflect the performance of the final sensing algorithm implemented in the COGNIS/TELIGEN devices.

The GDT1000 protocol did not pre-specify acceptable sensitivities, specificities, PPV, rates of oversensing, or rates of undersensing for the RA, RV, and LV channels.

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STUDY RESULTS

Patient Characteristics

The table below shows the characteristics of the patients implanted or attempted (Table H-1 on page H-3).

Table H-1. All patients implanted or attempted, Phase 1 and Phase 2

Characteristic	Measurement	Phase 1 Result (N=29)	Phase 2 Result (N=19)
Age at implant	Mean ± SD	65.8 ± 12.2	68.1 ± 9.6
	Range	[44.6, 85.5]	[51.3, 81.8]
Gender [N (%)]	Female	14 (48.0)	14 (74.0)
	Male	15 (52.0)	5 (26.0)
NYHA Class [N (%)]	III	27 (93)	19 (100)
	IV	2 (7)	0 (0)
LVEF (%)	Mean ± SD	22.4 ± 7.7	23.5 ± 6.4
	Range	[10.0, 35.0]	[15.0, 35.0]
QRS Duration	Mean ± SD	161± 29	149± 30
	Range	[124, 248]	[106, 220]
Cardiac Disease [N (%)]	Nonischemic Cardiomyopathy	14 (48)	7 (37)
	Ischemic Cardiomyopathy, CAD	10 (34)	9 (47)
	Hypertension	3 (10)	0 (0)
	Coronary Artery Disease (CAD)	1 (3)	0 (0)
	Ischemic Cardiomyopathy, no CAD	1 (3)	3 (16)
	Valvular Heart Disease	0 (0)	1 (5)
	Other	0 (0)	1 (5)

Lead Position

In this study, the position of each lead was per physician's discretion. A majority of the atrial leads in the first/second phase of the study were placed in the right atrial appendage (19/12) with the remaining placed in the lateral wall (5/2), septal wall (2/3), and unspecified location (1/0). A majority of the right ventricular leads were implanted in the right ventricular apex, with the remaining

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placed in the septal wall (0/1) and unspecified location (1/0). A majority of the left ventricular leads were implanted in the lateral, postero-lateral, or posterior wall (21/15), with the remaining placed in an antero-lateral, anterior, or postero-septal location (4/3).

Lead Configurations

In this study, both RA and RV leads used a bipolar configuration, which was not programmable. The LV lead configuration programming was per physician's discretion. In the first phase, 20 patients had LV sensing programmed to the LVtip>>LVring configuration, four to LVtip>>RVcoil, and one to LVtip>>Can. In the second phase, 13 patients had LV sensing programmed to the LVtip>>LVring configuration, and four to LVtip>>RVcoil.

Lead Performance

The lead performance, including pacing threshold, pacing impedance and sensing amplitude, were measured at implant by a commercially available Pacing System Analyzer (PSA). The results are provided in the table below (Table H-2 on page H-4).

Table H-2. Lead performance

Measurement	Lead Location	Number of Leads: Phase 1	Mean ± SD: Phase 1	Number of Leads: Phase 2	Mean ± SD: Phase 2
Pacing Impedance (Ω)	Left Ventricle	25	1034 ± 394	18	779 ± 227
	Right Atrium	28	520 ± 161	17	519 ± 112
	Right Ventricle	29	816 ± 263	18	649 ± 206
Pacing Threshold (V)	Left Ventricle	25	1.9 ± 1.4	18	1.3 ± 1.0
	Right Atrium	28	1.1 ± 0.7	16	1.2 ± 0.6
	Right Ventricle	29	1.0 ± 0.4	18	0.8 ± 0.3
Sensing Amplitude (mV)	Left Ventricle	25	14.1 ± 7.6	18	13.2 ± 7.3
	Right Atrium	28	2.9 ± 1.5	16	3.7 ± 3.3
	Right Ventricle	29	12.3 ± 6.2	18	13.4 ± 7.0

Sensing Performance

In the first phase of the study, a total of 55,207 signals were recorded, including 54,151 appropriate sensed intrinsic and paced beats and 1,056 inappropriate

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sensed events (223 undersense and 833 oversense events). The sensing algorithm used in the first phase achieved the sensitivities, specificities, positive predictive values (PPV), rates of undersensing (1-sensitivity), and rates of oversensing (1-PPV) are summarized in the table below (Table H-3 on page H-5).

Table H-3. Summary of Sensing Performance - First Phase

	Sensitivity (Rate of Undersensing)	Specificity	Positive Predictive Value (Rate of Oversensing)	Appropriate Sensed Beats	Inappropriate Sensed Beats: Undersense	Inappropriate Sensed Beats: Oversense
Right Atrial Channel	100% (0%)	96.81%	97.03% (2.97%)	19,478	0	615
Right Ventricular Channel	100% (0%)	98.94%	98.86% (1.14%)	18,439	0	216
Left Ventricular Channel	98.63% (1.37%)	99.99%	99.99% (0.01%)	16,054	223	2
Totals				54,151	223	833

In the second phase of the study, a total of 35,998 signals were recorded including 35,831 appropriate sensed intrinsic and paced beats and 171 inappropriate sensed events (2 undersense and 169 oversense events). The upgraded sensing algorithm used in the second phase achieved the sensitivities, specificities, positive predictive values (PPV), rates of undersensing (1-sensitivity), and rates of oversensing (1-PPV) summarized in the table below; the table also summarizes the results of the analysis from the second phase (Table H-4 on page H-5).

Table H-4. Summary of Sensing Performance - Second Phase

	Sensitivity (Rate of Undersensing)	Specificity	Positive Predictive Value (Rate of Oversensing)	Appropriate Sensed Beats	Inappropriate Sensed Beats: Undersense	Inappropriate Sensed Beats: Oversense
Right Atrial Channel	100% (0%)	98.64%	98.54% (1.46%)	11,372	0	168
Right Ventricular Channel	100% (0%)	100%	100% (0%)	12,230	0	0

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Table H-4. Summary of Sensing Performance - Second Phase (continued)

	Sensitivity (Rate of Undersensing)	Specificity	Positive Predictive Value (Rate of Oversensing)	Appropriate Sensed Beats	Inappropriate Sensed Beats: Undersense	Inappropriate Sensed Beats: Oversense
Left Ventricular Channel	99.98% (0.016%)	99.99%	99.99% (0.008%)	12,227	2	1
Totals				35,831	2	169

Comparing the performance between the two phases, there were 1,056 inappropriate sensing events out of 55,027 signals (1.919%) in the first phase of the study, and a total of 171 inappropriate sensing events out of 35,998 signals (0.475%) in the second phase of the study, reflecting a 75.2% reduction in inappropriate sensing events from phase one to two.

Oversense Events

During the analysis of the first phase data, some unexpected oversense events were identified. There were a total of 831 oversense events in the RA (615) and RV (216) channels in phase one. The majority of the RA and RV oversense events were attributed to an artificial event introduced while pacing. This type of oversense was observed in 6 patients in the RA channel and 7 patients in the RV channel. The results for the second phase of the study demonstrated that oversensing artificial events observed in the first phase of the study were successfully eliminated by using the upgraded GASD system. There were no artificial events introduced in the second phase of the study.

In the second phase, a total of 168 oversense events in the RA channel were observed in one patient. This patient had an intrinsic P-R interval greater than 300 ms. In order to complete the AP/VS test scenario, the device was programmed with a LRL = 80 bpm and AV Delay = 300 ms, which is the maximum allowable AV Delay in a CRT-D device. At the end of the AV Delay, no intrinsic activity occurred and the device paced both ventricles. These paced beats were oversensed by the atrial channel. If the atrial blanking period were programmed to a larger value, atrial oversensing would have been eliminated. Therefore, excluding this patient's AP/VS test scenario from the analysis, there were no undersensing or oversensing events in the RA channel.

In one patient, the single oversense event in the LV channel was caused by noise.

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Undersense Events

LV undersense events (223) in the first phase of the study primarily occurred in one patient whose LV intrinsic amplitude was less than 1.0 mV, which is much smaller than the clinically acceptable threshold. This small LV intrinsic amplitude resulted in undersensing some LV events.

Two LV undersense events occurred in the second phase of the study. A potential cause for the LV undersense events was premature ventricular contractions while atrial pacing.

CONCLUSIONS

This acute study demonstrated excellent sensitivity (100% in the RA, 100% in the RV, and 99.98% in the LV channels), specificity (98.64% in the RA, 100% in the RV, and 99.99% in the LV channels), and positive predictive values (98.54% in the RA, 100% in the RV, and 99.99% in the LV channels). In conclusion, the new sensing platform evaluated in the GDT1000 study will be implemented in COGNIS/TELIGEN devices.

By excluding one patient's oversensed events that could be eliminated by programming a longer atrial blanking period, the modified specificity and positive predictive values in the RA channel are 100% and 100% (oversensing eliminated). While the GDT1000 protocol did not pre-specify acceptable sensitivities, specificities, or PPV values, a Sensing Tape Testing DAT report for COGNIS/TELIGEN on file at Boston Scientific CRM[1] reported a 99.96% sensitivity (0.04% Undersensing) and a 99.97% positive predictive value (0.03% Oversensing) for the RV channel in normal sinus rhythm. Using the RV values as a benchmark (RA and LV values were not calculated), the results of this study compare favorably.

1. Sensing Tape Testing Design Analysis Test report 100019-687 Revision A describes testing performed in which the COGNIS/TELIGEN sensing platform is modeled and compared to a previous Guidant device, CONTAK RENEWAL TR. The analysis was performed using 219 patient rhythms from the Gold Development Database, including normal sinus rhythm and atrial and ventricular arrhythmias.

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