

**Medtronic InSync® ICD
Cardiac Resynchronization System**

FDA Circulatory System Devices Panel
March 5, 2002

Clinicians in Attendance

- William T. Abraham, MD
University of Kentucky
- Bruce L. Wilkoff, MD
Cleveland Clinic Foundation
- Angel R. Leon, MD
Emory University
- James B. Young, MD
Cleveland Clinic Foundation
- Milton Packer, MD
Columbia University

Agenda

Background and Introduction	Dr. William Abraham	10 minutes
Study Design and Methodology	Dr. James Young	15 minutes
Safety and Lead Effectiveness Results	Dr. Angel Leon	30 minutes
Efficacy Results	Dr. James Young	15 minutes
Comparison to InSync and Conclusions	Dr. William Abraham	10 minutes

Introduction and Background

William T. Abraham, MD

4

Introduction

- Over a third of moderate to severe heart failure patients (in NYHA Functional Class III or IV) have ventricular dyssynchrony, evidenced by a QRS duration ≥ 130 ms¹
- Associated with
 - Limited exercise tolerance
 - Impaired quality of life and functional capacity
 - Poor left ventricular systolic function²

¹Aaronson KD, et al. *Circulation* 1997; 96:2660-2667
²Yu C-M, et al. *Circulation* 2002; 105:439-445

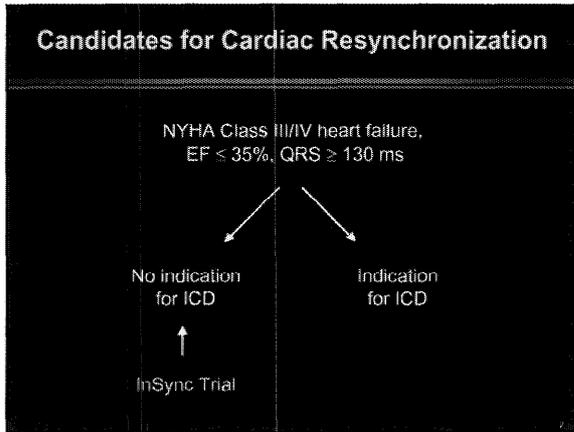
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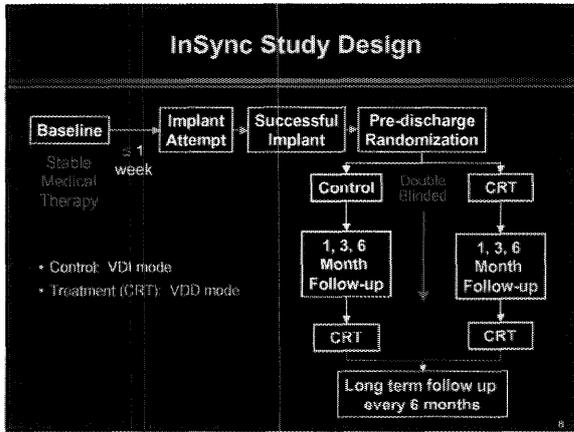
Candidates for Cardiac Resynchronization

NYHA Class III/IV heart failure,
EF $\leq 35\%$, QRS ≥ 130 ms

No indication for ICD Indication for ICD

6





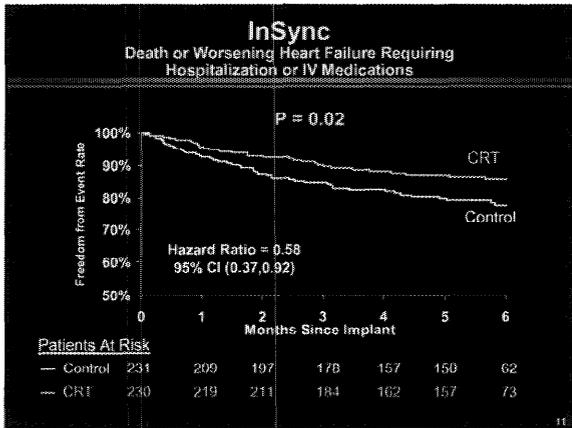
InSync Study Primary Endpoints*

Endpoint	Control	CRT	p value
Quality of Life (points)	- 9	- 18.5	0.003
NYHA Class (class)	0	- 1	<0.001
6-minute walk (meters)	10	40	0.003

* PMA# P010015, approved 8/28/01

InSync Study Secondary Clinical Endpoints

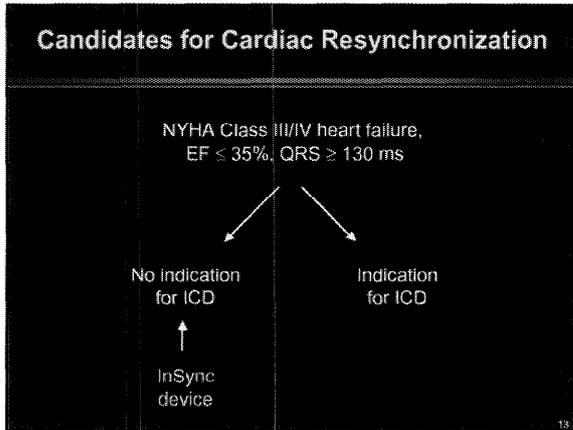
Endpoint	Control	CRT	p value
Peak VO ₂ (ml/kg/min)	0.1	1.0	0.038
Exercise Time (seconds)	12	85	<0.001
Composite Response (%)	↑42, ←→35, ↓23	↑66, ←→20, ↓14	<0.001

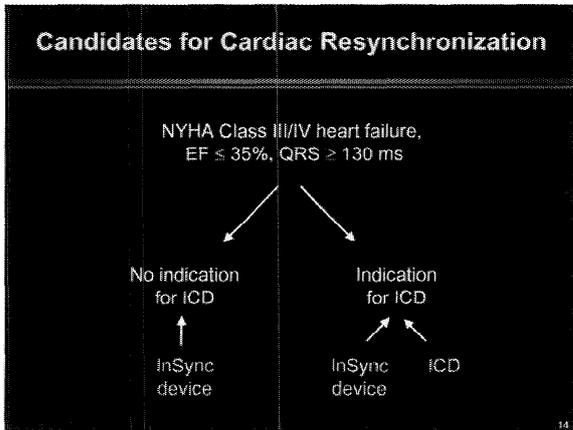


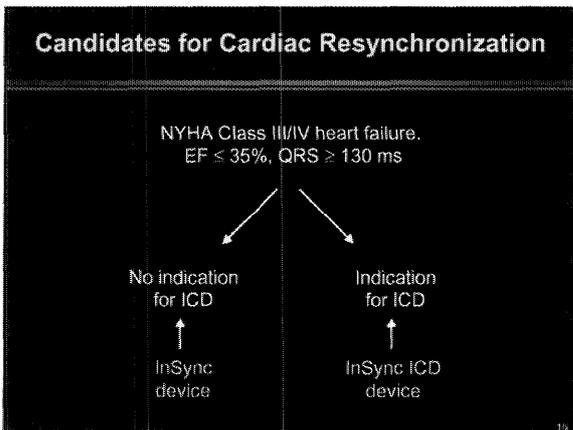
InSync Primary Safety Results Summary

Achieved all primary 6-month safety objectives including:

- ✓ Implant success
- 6-month device related complications attributed to:
 - ✓ InSync Model 8040
 - ✓ Attain Models 2187 and Model 2188 LV leads
 - ✓ InSync system
- ✓ Attain Models 2187 and 2188 LV lead 6-month pacing threshold







Combining Resynchronization and ICD Function in a Single Device

Model 7272 InSync ICD

- VT and VF detection
- Antitachycardia (ATP) pacing, cardioversion and defibrillation therapies
- Dual-chamber pacemaker
- Simultaneous bi-ventricular pacing
- RV sensing only



19

Combining Resynchronization and ICD Function in a Single Device

- Could an indication for an ICD influence the efficacy of resynchronization?
 - *Need to ensure that patients with an ICD indication respond favorably to resynchronization.*
- Could the presence of resynchronization therapy influence the efficacy of the ICD?
 - *Need to ensure that the coexistence of resynchronization function does not adversely affect ICD function.*

17

Study Design, Methodology and Patient Population

James B. Young, MD

18

Entry Criteria

- Chronic heart failure
- ≥ 18 years of age
- NYHA Functional Class II, III or IV
- QRS duration ≥ 130 ms
- LVEF $\leq 35\%$
- LVEDD ≥ 55 millimeters (echo measure)
- Stable HF medical regimen for ≥ 1 month
 - ACE-I or substitute, if tolerated
 - β -blocker - stable regimen for ≥ 3 months
- Indication for an ICD

19

Study Design

- Control: CRT off (DDI mode)
- Treatment: CRT on (DDD mode)
- ICD active in all patients

20

Timing of Baseline Tests

Test	InSync	InSync ICD
6-Minute Hall Walk	0-7 days pre-implant	0-7 days pre-implant
Cardiopulmonary Exercise Test	0-7 days pre-implant	0-7 days post-implant
QOL Questionnaire	0-7 days pre-implant	0-7 days pre-implant
NYHA	0-7 days pre-implant	0-7 days pre-implant

21

Study Features to Maintain the Blind

- **Blinded:**
 - Patients (study ID card)
 - Heart failure staff
 - Listed on study blinding log
 - Blinded to ECGs
 - Conducted QOL, 6 minute hall walk, patient global assessment, NYHA classification and HF exam
 - Events Classification Committee
- **Unblinded:**
 - EP staff
 - Listed on study blinding log
 - Viewed ECGs, device printouts, etc
 - Data placed into secure study envelopes

22

Primary Effectiveness Endpoints

- The change from baseline to 6-months for control and CRT groups for:
 - Quality of life (MLWHF Questionnaire)
 - NYHA class
 - 6-minute hall walk distance
- As pre-specified in the study protocol, all 3 endpoints must be met at $P \leq 0.05$, or 2 met at $P \leq 0.025$, or 1 met at $P \leq 0.0167$

23

Secondary Effectiveness Endpoints

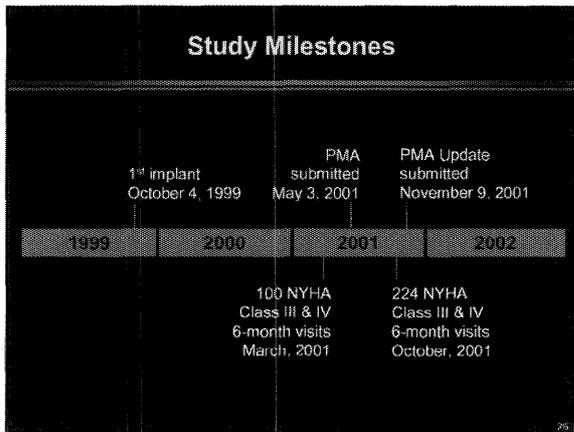
Clinical endpoints

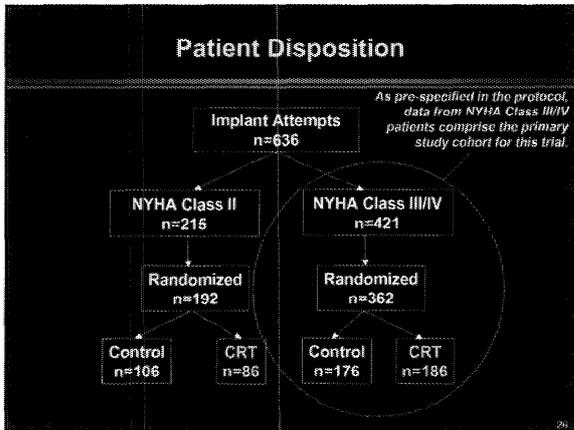
- Exercise performance
- Clinical composite response
- Health care utilization

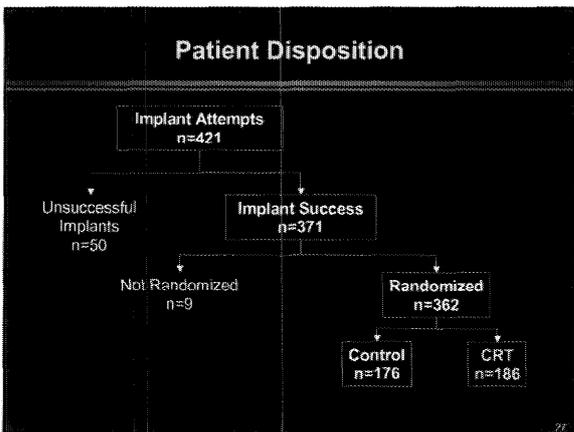
Physiological variables

- Echocardiographic variables
- QRS duration
- Neurohormonal variables

24







Patient Disposition

Control n = 176		CRT n = 186
124	6 Month Dataset	133
35	Still in DB F/U	36
15	Death	12
2	6 month F/U Visit Missed	5

Methodology Overview

Safety Data

- As pre-specified in the study protocol, data from NYHA Class II, III and IV patients were submitted to FDA for the primary safety objectives
- At FDA's request, safety data from NYHA Class III and IV patients only are included in the Panel Pack and in this presentation

Methodology Overview

Efficacy Data

- The study protocol pre-specified that the primary efficacy analysis was to be based on NYHA Class III and IV patients with paired data at baseline and 6 months, excluding crossovers
- However, results presented here are based on an intention-to-treat analysis for patients with paired data at baseline and 6 months, including crossovers
- In addition, a last-observation-carried-forward (LOCF) analysis (including crossovers) will be briefly summarized

Patient Baseline Demographics		
	Control n=176	CRT n=186
Age, years (mean ± sd)	68 ± 9	67 ± 11
Gender (% male)	77%	76%
NYHA (% Class III)	89%	88%
QRS duration, ms (mean ± sd)	162 ± 22	165 ± 22
LVEF, % (mean ± sd)	20 ± 6	21 ± 7
LVEDD, mm (mean ± sd)	71 ± 9	70 ± 9
Heart Failure Etiology (% ischemic)	74%	63%

Patient Baseline Demographics		
	Control n=176	CRT n=186
Peak VO ₂ , ml/kg/min (mean ± sd)	13.5 ± 4.1	13.5 ± 3.7
6-Min Walk Distance, meters (mean ± sd)	247 ± 118	245 ± 127
Heart Rate, bpm (mean ± sd)	72 ± 13	71 ± 12
SBP, mmHg (mean ± sd)	111 ± 17	112 ± 20
DBP, mmHg (mean ± sd)	67 ± 13	66 ± 11
Diuretic Use	94%	93%
ACE-I or ARB Use	88%	91%
Beta-blocker Use	57%	63%

Safety Results		
Angel R. Leon, MD		

Primary Safety Objectives

- InSync ICD-related complication-free survival at 3 months
- Attain Model 4189 LV lead-related complication-free survival at 6 months
- Attain Model 2187/2188 LV lead-related complication-free survival at 6 months
- InSync ICD system-related complication-free survival at 6 months

34

Secondary Safety Objectives

- Characterize patient survival
- Characterize complication events
- Characterize observation events

35

Adverse Event Definitions

- **Complication:** An adverse event requiring invasive intervention or that results in the death of or serious injury to the patient or in the termination of a significant device function
- **Observation:** An adverse event not requiring invasive intervention or resolves spontaneously
- **System-related complication:** A device-related complication that occurs after the initially implanted functioning system, comprised of: Model 7272 InSync ICD, a Model 4189, 2187 or 2188 LV lead, and RA and RV leads

36

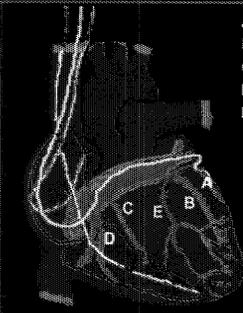
Lead Effectiveness Objectives

- Implant success
- Evaluate the electrical performance of the Model 4189 LV lead
- Evaluate the electrical performance of the Model 2187 and Model 2188 LV leads

Evaluation of Integrity of ICD Function

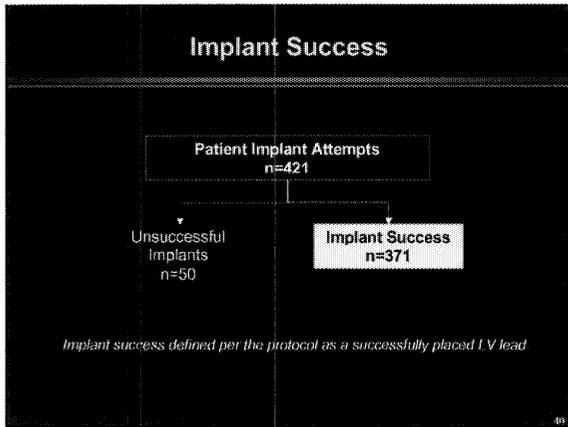
- Spontaneous VT/VF therapy effectiveness
- Comparison of VT/VF event rates in the control and treatment arms
- Bi-ventricular ATP therapy effectiveness

Lead Placement and LV Venous Anatomy



- A. Lateral (marginal) cardiac vein
- B. Postero-lateral cardiac vein
- C. Posterior cardiac vein
- D. Middle cardiac vein
- E. Great cardiac vein

Attain SD Model 4189
• Transvenous, 4 French
• Stylet/catheter Delivered
• Unipolar



Unsuccessful Implants (n=50)

Reason	n
Dislodgement/unstable position	24
Unable to obtain distal location	18
Unable to cannulate coronary sinus ostium	16
Unacceptable pacing thresholds	13
Dissection/perforation	13
Unable to access coronary vein	8
Coronary vein too small	3
Patient decompensation during implant	3
Delivery system/tool problems	3
Patient venous anatomy	2
Diaphragmatic stimulation	2
Complete heart block	1

Not mutually exclusive

41

Adverse Events During the Implant Procedure

	371 Successful Implants (53 Events)	50 Unsuccessful Implants (26 Events)
Coronary Sinus Dissection	4 (4)	9 (8)
Heart Block	9 (8)	3 (3)
Pericardial Effusion	2 (2)	3 (2)
Ventricular Tachycardia	2 (2)	3 (3)
Atrial Fibrillation	4 (4)	
Cardiac Perforation	2 (2)	2 (2)
Heart Failure Decompensation	3 (3)	
Hypotension	2 (2)	1 (0)
Atrial Flutter	2 (2)	
Other Events	23 (21)	5 (4)

Number in () = events resolved

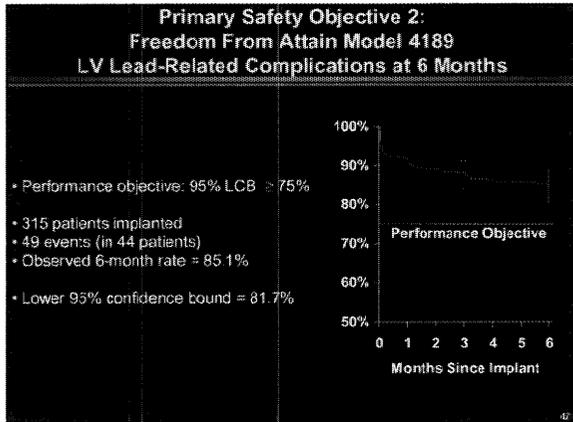
42

**Freedom From InSync ICD
Related Complications at 3 Months**

371 patients implanted
7 events in 7 patients

	Events	Patients
Pocket seroma/hematoma	2 (2)	2
Pain at pocket site	1 (1)	1
Abnormal impedance measurement	1 (1)	1
Dizziness	1 (1)	1
Electrical reset of ICD	1 (1)	1
Pocket infection	1 (1)	1

Number in () = events resolved.

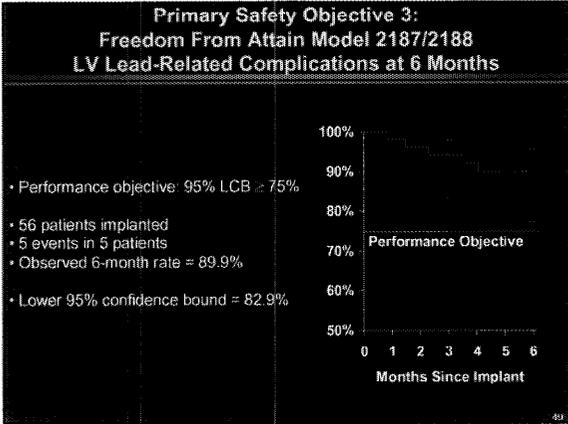


**Freedom From Attain Model 4189
LV Lead-Related Complications at 6 Months**

315 patients implanted
49 events in 44 patients

	Events	Patients*
Lead dislodgment	28 (25)	26
Extra cardiac stimulation	12 (11)	11
Elevated pacing thresholds	4 (3)	4
Failure to capture	3 (3)	3
Muscle stimulation -- pectoral	1 (0)	1
Pericardial effusion	1 (1)	1

** Not mutually exclusive* *Number in () = events resolved.*



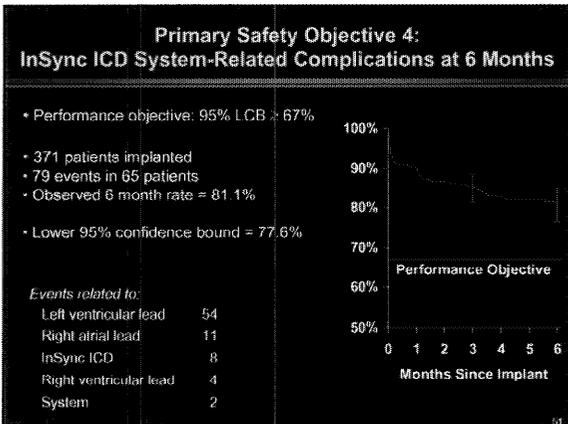
**Freedom From Attain Model 2187/2188
LV Lead-Related Complications at 6 Months**

56 patients implanted
5 events in 5 patients

	Events	Patients
Lead dislodgment	3 (2)	3
Failure to capture	1 (0)	1
Elevated pacing thresholds	1 (1)	1

Number in () = events resolved.

50



Primary Safety Results: Summary

- All primary safety objectives satisfied
- ✓ Device-related complications attributed to:
 - ✓ InSync ICD Model 7272
 - ✓ Attain Models 4189, 2187 and 2188 leads
 - ✓ InSync ICD system

52

Secondary Safety Objectives

- Characterize patient survival
- Characterize complication events
- Characterize observation events

53

Complications During the Randomization Period

	Control 137 events	CRT 134 events
Not device or therapy related	64	65
HF decompensation	38	31
System related	24	28
Procedure related	5	5
Other	6	5

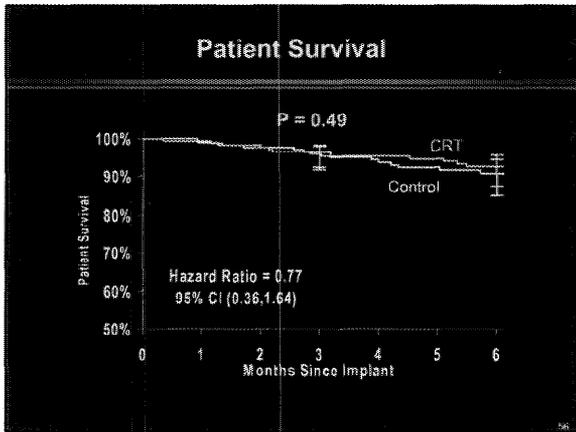
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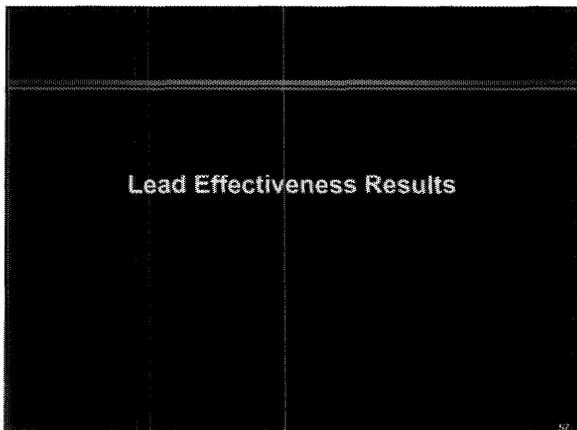
54

Observations During the Randomization Period

	Control 294 events	CRT 401 events
Not device or therapy related	208	277
HF decompensation	27	33
System related	36	54
Procedure related	16	23
Other	7	14

Not mutually exclusive





**Lead Effectiveness Objective 1:
Implant Success Results**

- Performance Objective:
 - Lower 95% Confidence Limit \geq 83%
- Results:
 - Observed rate: 371 successes / 421 attempts = 88.1%
 - Lower Limit of 2-Sided 95% C.I. = 84.6%

Implant success defined per the protocol as a successfully placed LV lead.

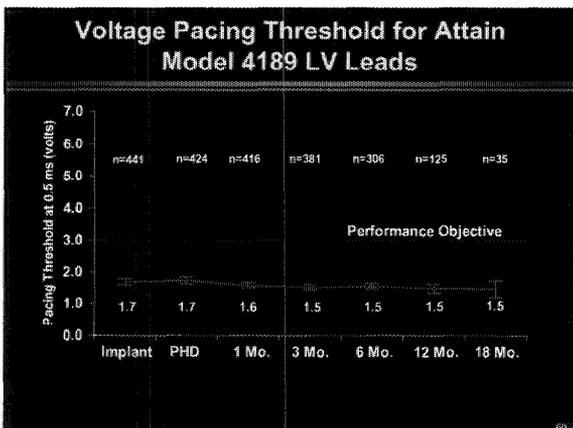
**Lead Effectiveness Objective 2:
Attain Model 4189
LV Lead Pacing Threshold Performance**

Performance Objective:

- The upper 95% confidence bound for the mean pacing voltage threshold is \leq 3.0 Volts

Results:

- Mean 6-month pacing threshold = 1.5 Volts \pm 0.9 Volts
- Upper limit of 2-sided 95% confidence interval = 1.7 Volts



**Lead Effectiveness Objective 3:
Attain Model 2187/2188
LV Lead Pacing Threshold Performance**

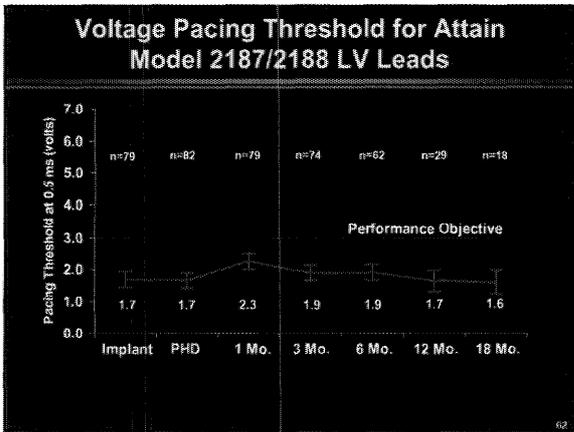
Performance Objective:

- The upper 95% confidence bound for the mean pacing voltage threshold is ≤ 3.0 Volts

Results:

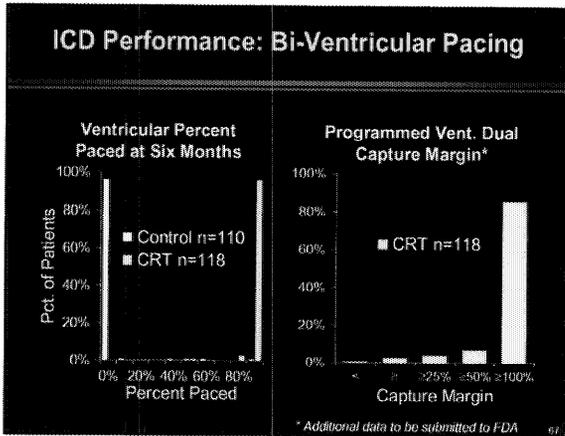
- Mean 6-month pacing threshold = 1.9 Volts ± 1.0 Volts
- Upper limit of 2-sided 95% confidence interval = 2.2 Volts

61



Evaluation of Integrity of ICD Function

63



ICD Performance: Inappropriate VT/VF Episodes*

	GEM DR ¹	InSync ICD
Total Episodes in VT/VF Log	933 pts. 3945 (278 pts.)	371 pts. 950 (100 pts.)
Inappropriate VT/VF Episodes	457 (11.6%) (in 86 pts.)	135 (14.2%) (in 31 pts.)
GEE adjusted rates	21.9%	21.3%
Average Follow-up Time	3.9 months	7.9 months

¹ PMA P880016 approved 10/3/98
* Additional data to be submitted to FDA

ICD Performance: VF Detection Time

- VF Detection Time
- There is no difference in VF detection times between CRT and control patients

	VF NID = 12/16			VF NID = 18/24		
	N	Mean V. Cycle Length	Mean Detection Time	N	Mean V. Cycle Length	Mean Detection Time
OFF	51	272	3.4 sec	14	278 ms	5.3 sec
CRT	42	283	3.8 sec	26	256 ms	4.9 sec
P-value			0.07			0.84

Effectiveness Results

James Young, MD

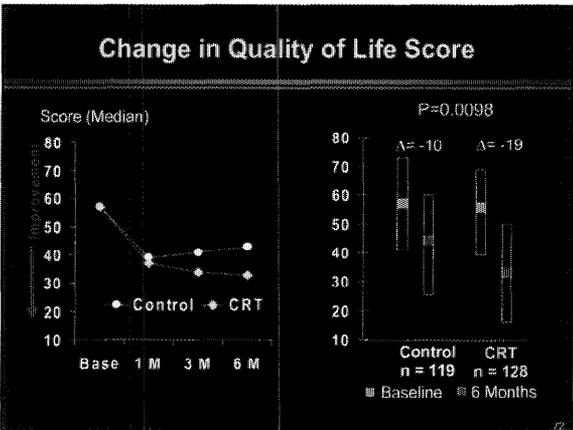
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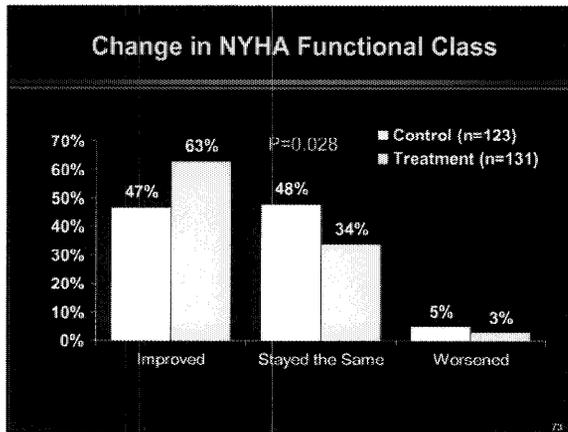
Primary Effectiveness Endpoints

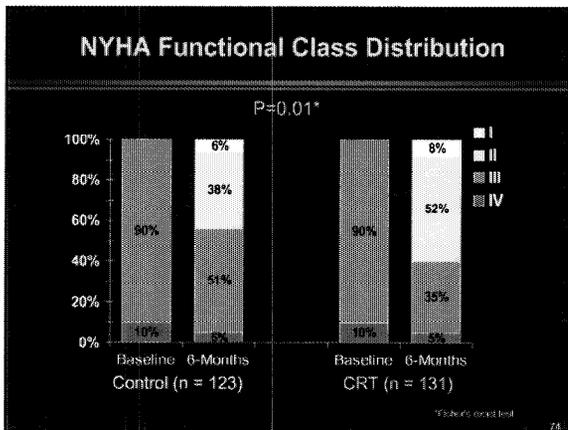
Change from baseline to 6-month follow up between control and treatment groups in:

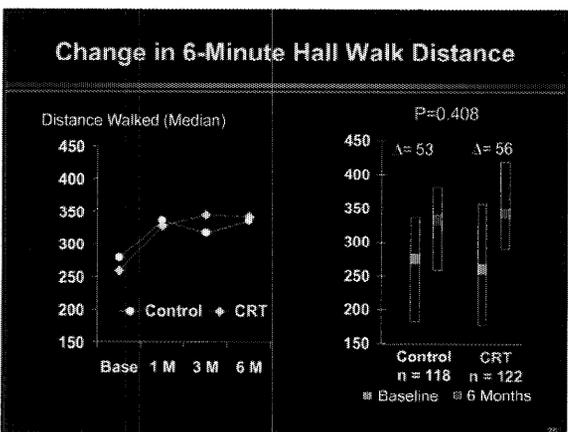
- QOL score (MLWHF Questionnaire)
- NYHA class
- 6 minute hall walk distance

71





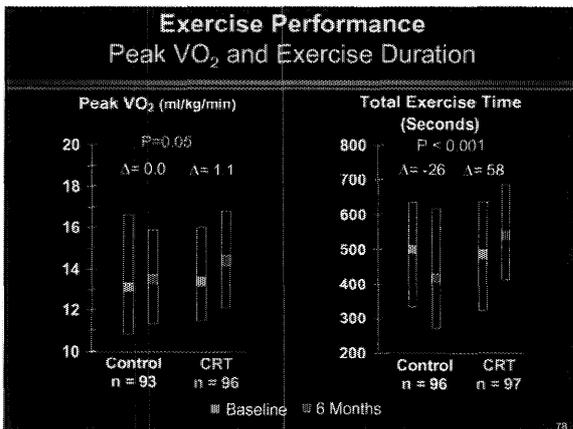




Summary of Effect on Primary Endpoints

Endpoint	Intention-to-Treat	P-Values	
		Per Protocol	Last Observation Carried Forward
QOL	0.0098	0.0044	0.002
NYHA	0.028	0.0145	0.02
6 Minute Hall Walk	0.408	0.4993	0.23

- ### Secondary Effectiveness Endpoints
- Clinical endpoints
 - Exercise performance
 - Clinical composite response
 - Healthcare utilization
 - Physiological variables
 - Echocardiographic variables
 - QRS duration
 - Plasma neurohormones

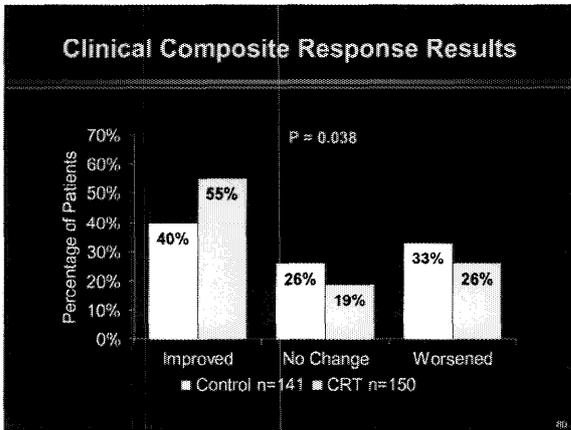


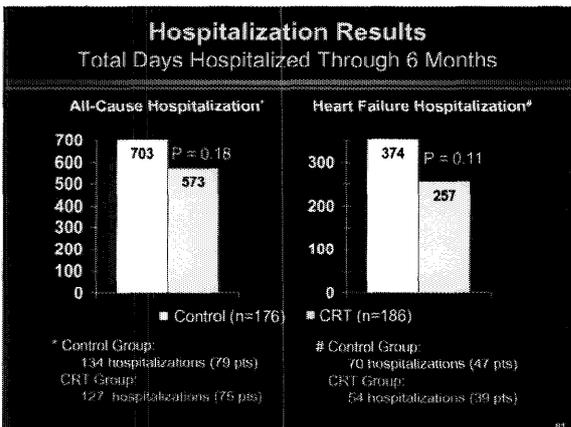
Clinical Composite Response - Definition

- Improved
Improved NYHA class or global assessment
- Worsened
Death; worsening heart failure leading to hospitalization or permanent withdrawal of therapy; or worsening of NYHA class or global assessment
- No Change

Packer et al. J Cardiac Failure 2001;7:176-182

79





Change in Echo Parameters			
	Control	CRT	P-value
LV End Diastolic Volume	-5	-25	0.046
LV End Systolic Volume	-8	-26	0.04
LV Ejection Fraction	1.6	3.0	0.06
Cardiac Index	-0.02	0.03	0.89
Mitral regurgitation	-0.5	-0.4	0.98
LV Inflow E Wave Max Velocity	0.5	-10.0	0.03
LV Inflow A Wave Max Velocity	6.5	-4.0	0.04

Change in Echo/ECG Parameters			
	Control	CRT	P-value
LV E-Wave/A-Wave Ratio	-0.03	-0.06	0.82
Normalized LV Filling Time	0.01	0.05	0.001
LV Mass	-6	-3	0.97
LV Diameter in Systole	-0.3	-0.2	0.98
LV Diameter in Diastole	-0.1	-0.3	0.85
Interventricular Mechanical Delay	-2	-18	0.12
QRS Width	-6	-20	0.01

Change in Neurohormone Levels			
	Control	CRT	P-value
Brain Natriuretic Peptide (BNP)	-3	-38	0.41
Dopamine	0.0	0.0	0.56
Norepinephrine	-38.0	10.5	0.24
Epinephrine	-4.0	0.0	0.03
Big Endothelin	-0.5	-0.5	0.88

Conclusions

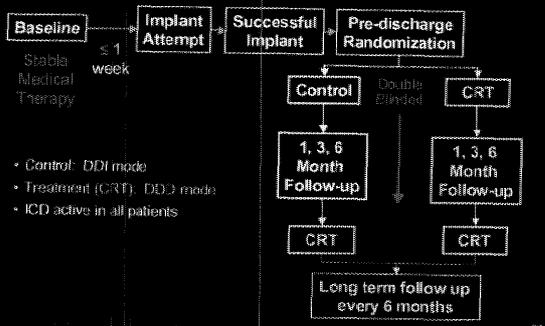
In NYHA Class III and IV systolic heart failure patients with an intraventricular conduction delay and an indication for an ICD, cardiac resynchronization:

- Improves quality of life, functional capacity and exercise tolerance
- Has an acceptable safety profile

Comparison of InSync and InSync ICD

William T. Abraham, MD

Study Design



Timing of Baseline Tests

Test	InSync	InSync ICD
6-Minute Hall Walk	0-7 days pre-implant	0-7 days pre-implant
Cardiopulmonary Exercise Test	0-7 days pre-implant	0-7 days post-implant
QOL Questionnaire	0-7 days pre-implant	0-7 days pre-implant
NYHA	0-7 days pre-implant	0-7 days pre-implant

Comparison of Patient Demographics – InSync and InSync ICD

	InSync ICD n=362	InSync n=532
Age, years (mean ± sd)	67 ± 10	64 ± 11
Gender (% male)	77%	70%
QRS duration, ms (mean ± sd)	164 ± 22	166 ± 21
LVEF, % (mean ± sd)	20 ± 7	22 ± 6
LVEDD, mm (mean ± sd)	71 ± 9	69 ± 10
Heart Failure Etiology (% ischemic)	69%	55%

Comparison of Patient Demographics – InSync and InSync ICD

	InSync ICD n=362	InSync n=532
Peak VO ₂ , ml/kg/min (mean ± sd)	13.5 ± 3.9	13.8 ± 3.7
6-MW Distance, meters (mean ± sd)	246 ± 123	298 ± 97
NYHA (% Class III)	88%	90%
Quality of Life (mean ± sd)	56 ± 23	59 ± 20
Diuretic Use	93%	93%
ACE-I or ARB Use	90%	91%
Beta-blocker Use	60%	56%

**InSync and InSync ICD Studies:
Primary Endpoints**

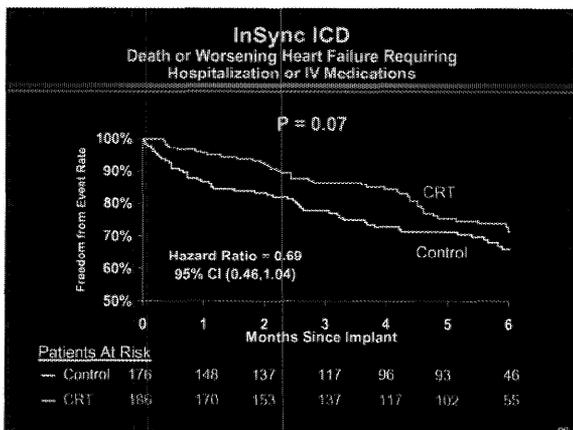
Endpoint	Control	CRT	P-value
Quality of Life (points)	-9	-18.5	0.003
	-10	-19	0.010
NYHA Class (class)	0	-1	<0.001
	0	-1	0.028
6-minute walk (meters)	+10	+40	0.003
	+53	+56	0.408

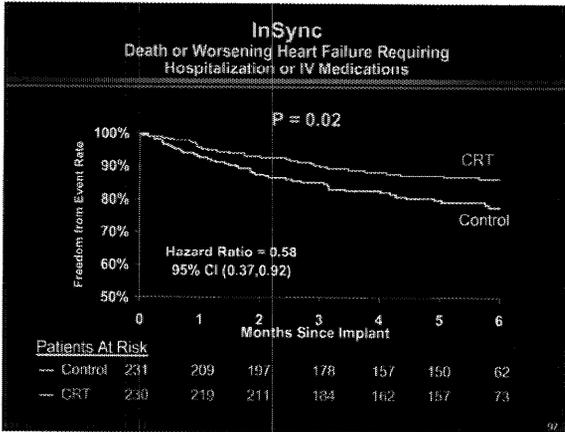
White = InSync Study, Yellow = InSync ICD Study

**InSync and InSync ICD Studies:
Secondary Clinical Endpoints**

Endpoint	Control	CRT	P-value
Peak VO2 (ml/kg/min)	0.1	1.0	0.038
	0.0	1.1	0.050
Exercise Time (sec)	12	85	<0.001
	-26	58	<0.001
Composite Response (%)	↑42, ↔35, ↓23	↑66, ↔20, ↓14	<0.001
	↑40, ↔26, ↓33	↑55, ↔19, ↓26	0.038

White = InSync Study, Yellow = InSync ICD Study





Conclusions

In NYHA Class III and IV systolic heart failure patients with ventricular dyssynchrony and an indication for an ICD, cardiac resynchronization:

- Improves quality of life, functional capacity and exercise tolerance and
- Has an acceptable safety profile

The benefits of resynchronization in patients with an ICD indication are similar in both direction and magnitude to the effects seen in patients without an ICD indication.

98

The End

99
