SUMMARY OF SAFETY AND EFFECTIVENESS

I. General Information

Device Generic Name:	Dual Chamber Implantable Cardioverter Defibrillator (ICD) with Cardiac Resynchronization Therapy
Device Trade Name:	InSync® ICD Model 7272 Dual Chamber Implantable Cardioverter Defibrillator with Cardiac Resynchronization Therapy and the Model 9969 Application Software
Applicant's Name and Address:	Medtronic, Inc. 710 Medtronic Parkway Minneapolis, MN 55432-5604
PMA Number:	P010031
Date of Panel Recommendation:	March 5, 2002
Date of Notice of Approval to Applicant:	June 26, 2002

II. Indications for Use

InSync® ICD Model 7272 Device

The InSync® ICD Model 7272 is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias. The system is also indicated for the reduction of the symptoms of moderate to severe heart failure (NYHA Functional Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy (as defined in the clinical trials section), and have a left ventricular ejection fraction less than or equal to 35% and a QRS duration greater than or equal to 130 ms.

III. System Description

Description of InSync® ICD Model 7272

The InSync® ICD Model 7272 Dual Chamber Implantable Cardioverter Defibrillator (ICD) System is a multi-programmable, implantable cardioverter defibrillator with biventricular pacing for cardiac resynchronization therapy (CRT) that monitors and regulates a patient's heart rate by providing ventricular tachyarrhythmia therapy and single or dual chamber bradycardia pacing. Ventricular tachyarrhythmias therapies are for the treatment of ventricular tachycardia (VT) and ventricular fibrillation (VF), arrhythmias associated with sudden cardiac death (SCD). Cardiac resynchronization therapy uses simultaneous biventricular electrical stimulation to synchronize ventricular contractions.

The Model 7272 InSync® ICD System consists of:

- InSync® ICD Model 7272
- Model 9969 Application Software for use with the previously approved:
  - Model 9790C Programmer
  - Model 2090 Programmer
- Commercially Available Components
  - Attain LV Model 2187 Cardiac Vein Pacing Lead
  - Attain CS Model 2188 Coronary Sinus Pacing Lead
  - Attain Model 6215 Venogram Balloon
  - Attain Models 6216 and 6218 Left Heart Delivery Systems
  - Right Atrial, Right Ventricular and Cardioversion/Defibrillation leads, implant support instruments and accessories

IV. Contraindications

InSync® ICD Model 7272 Device

Do not use the InSync® ICD system in:

- Patients whose ventricular tachyarrhythmias may have transient or reversible causes, such as:
  - Acute myocardial infarction
  - Digitalis intoxication
  - Drowning
  - Electrocution
  - Electrolyte imbalance
  - Hypoxia
  - Sepsis
- Patients with incessant VT or VF
- Patients who have a unipolar pacemaker

V. Warnings and Precautions

See device labeling.

VI. Adverse Events

Per the investigational plan, an *adverse event* is defined as any undesirable experience (sign, symptom, illness, or other medical event) occurring to a patient whether it is considered to be device related or not. Adverse events were classified as complications or observations based on the following definitions:

- A *complication* is defined as an adverse event that results in invasive intervention, or directly results in the death or serious injury to the patient, the explant or repositioning of the ICD or lead, or the termination of significant device function regardless of other treatments.
- An *observation* is defined as an adverse event that does *not* result in invasive intervention, the death or serious injury to the patient, the explant or repositioning of the ICD or lead, or the termination of significant device function.

On the following pages, **Table 1** summarizes all reported adverse events in NYHA Class III and IV patients; and **Table 2** summarizes NYHA Class III and IV patient deaths.

The InSync® ICD study was a prospective, multi-center, randomized double-blind, parallel arm, controlled clinical trial to assess the safety and effectiveness of biventricular pacing for heart failure therapy in ICD patients.

A. Adverse Events

Table 1 provides a summary of all adverse events that occurred in NYHA Class III and IV patients from implant through the 6-month randomization period who had an implant attempt or were implanted with an InSync® ICD system. 1499 events were reported in 351 of 424 patients implanted or attempted with an InSync® ICD system (1861 total device months). Of the events, 459 were complications and 1040 were observations.

Table 1. Adverse Events During the Randomization Period

	# of Events (# of patients)	% Complications (# of patients)	Complications per 100 device-months (# of events)	% Observations (# of patients)	Observations per 100 device-months (# of events)
Total Adverse Events	**1499 (351)**	**49.4 (208)**	**24.7 (459)**	**75.8 (319)**	**55.9 (1040)**
ICD related events					
Abnormal impedance measurement	2 (2)	0.2 (1)	0.1 (1)	0.2 (1)	0.1 (1)
Atrial or ventricular arrhythmias	4 (4)	0.0 (0)	0.0 (0)	1.0 (4)	0.2 (4)
Electrical reset of ICD	1 (1)	0.2 (1)	0.1 (1)	0.0 (0)	0.0 (0)
ICD discharge	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Inappropriate VT/VF detection	5 (5)	0.0 (0)	0.0 (0)	1.2 (5)	0.3 (5)
Pacemaker mediated tachycardia	1 (1)	0.2 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Phantom shocks	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Pocket infection/ seroma/hematoma	2 (2)	0.2 (1)	0.1 (1)	0.2 (1)	0.1 (1)
Subtotal: ICD related events[1]	**19 (17)**	**1.0 (4)**	**0.2 (4)**	**3.3 (14)**	**0.8 (15)**
LV lead related events					
Cardiac perforation	2 (2)	0.5 (2)	0.1 (2)	0.0 (0)	0.0 (0)

	# of Events (# of patients)	% Complications (# of patients)	Complications per 100 device-months (# of events)	% Observations (# of patients)	Observations per 100 device-months (# of events)
Coronary Sinus dissection	5 (5)	0.7 (3)	0.2 (3)	0.5 (2)	0.1 (2)
Elevated pacing thresholds/ Failure to capture, loss of capture	12 (11)	2.1 (9)	0.5 (9)	0.7 (3)	0.2 (3)
Lead dislodgment	33 (31)	6.7 (28)	1.6 (30)	0.7 (3)	0.2 (3)
Muscle stimulation (diaphragm, chest wall, pectoral)	32 (29)	2.9 (12)	0.6 (12)	4.5 (19)	1.1 (20)
Pain (chest; neck)	2 (2)	0.0 (0)	0.0 (0)	0.5 (2)	0.1 (2)
Palpitations	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Pericardial effusion	2 (2)	0.2 (1)	0.1 (1)	0.2 (1)	0.1 (1)
Ventricular arrhythmias	1 (1)	0.2 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Subtotal: LV lead related events	**90 (77)**	**12.6 (53)**	**3.1 (58)**	**7.1 (30)**	**1.7 (32)**
RA lead related events					
Atrial arrhythmias	2 (2)	0.2 (1)	0.1 (1)	0.2 (1)	0.1 (1)
Atrial standstill	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Elevated pacing thresholds/ Failure to capture, loss of capture	7 (6)	1.0 (4)	0.2 (4)	0.7 (3)	0.2 (3)
Far-field R-wave sensing	1 (1)	0.2 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Lead dislodgment	6 (6)	1.4 (6)	0.3 (6)	0.0 (0)	0.0 (0)
Oversensing, undersensing	2 (2)	0.0 (0)	0.0 (0)	0.5 (2)	0.1 (2)
Subtotal: RA lead related events	**19 (18)**	**2.9 (12)**	**0.6 (12)**	**1.7 (7)**	**0.4 (7)**
RV lead related events					
Cardiac perforation	1 (1)	0.2 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Elevated pacing thresholds/ Failure to capture, loss of capture	2 (2)	0.5 (2)	0.1 (2)	0.0 (0)	0.0 (0)
Heart block	3 (3)	0.5 (2)	0.1 (2)	0.2 (1)	0.1 (1)
Lead dislodgment	1 (1)	0.2 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Muscle stimulation (diaphragm, pectoral)	2 (2)	0.5 (2)	0.1 (1)	0.2 (1)	0.1 (1)
Oversensing	4 (4)	0.0 (0)	0.0 (0)	1.0 (4)	0.2 (4)
PVCs	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Poor DFTs	1 (1)	0.2 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Subtotal: RV lead related events	**15 (15)**	**1.9 (8)**	**0.4 (8)**	**1.7 (7)**	**0.4 (7)**
System related events					
Elevated pacing thresholds/ Failure to capture, loss of capture	1 (1)	0.2 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Inappropriate VT/VF detection	2 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (2)
Muscle stimulation - diaphragm	2 (2)	0.0 (0)	0.0 (0)	0.5 (2)	0.1 (2)
Phantom shocks	2 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (2)
Programmer malfunction	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Twiddler's syndrome	1 (1)	0.2 (1)	0.1 (1)	0.0 (0)	0.0 (0)

	# of Events (# of patients)	% Complications (# of patients)	Complications per 100 device-months (# of events)	% Observations (# of patients)	Observations per 100 device-months (# of events)
Subtotal: System related events[1]	**9 (7)**	**0.5 (2)**	**0.1 (2)**	**1.2 (5)**	**0.4 (7)**
Implant tools related events					
Cardiac perforation/pericardial effusion	4 (4)	0.7 (3)	0.2 (3)	0.2 (1)	0.1 (1)
Chest pressure/tightness	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Coronary Sinus dissection	8 (8)	1.4 (6)	0.3 (6)	0.5 (2)	0.1 (2)
Guide catheter damage	1 (1)	0.2 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Guidewire fracture	1 (1)	0.2 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Heart block	7 (7)	0.2 (1)	0.1 (1)	1.4 (6)	0.3 (6)
Hemo/Pneumothorax	1 (1)	0.2 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Lead stylet stuck	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Ventricular arrhythmias	1 (1)	0.2 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Subtotal: Implant tools related events	**25 (22)**	**3.1 (13)**	**0.8 (14)**	**2.4 (10)**	**0.6 (11)**
Possibly device related					
Atrial arrhythmias	12 (11)	0.5 (2)	0.1 (2)	2.1 (9)	0.5 (10)
Bradycardia/heart block/ junctional rhythm	3 (3)	0.0 (0)	0.0 (0)	0.7 (3)	0.2 (3)
Chest pain/angina pectoris	7 (7)	0.5 (2)	0.1 (2)	1.2 (5)	0.3 (5)
Dizziness	4 (4)	0.0 (0)	0.0 (0)	1.0 (4)	0.2 (4)
Fever	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Hypertension	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Hypotension	3 (3)	0.7 (3)	0.2 (3)	0.0 (0)	0.0 (0)
Ventricular arrhythmias	9 (8)	0.2 (1)	0.1 (1)	1.7 (7)	0.4 (8)
Subtotal: Possibly device related	**49 (36)**	**2.1 (9)**	**0.6 (11)**	**6.9 (29)**	**2.0 (38)**
Procedure related/Possibly procedure related					
Arm/hand numbness/ swelling	6 (6)	0.0 (0)	0.0 (0)	1.4 (6)	0.3 (6)
Atrial arrhythmias	6 (6)	0.5 (2)	0.1 (2)	1.0 (4)	0.2 (4)
Coronary Sinus dissection	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Dizziness	2 (2)	0.2 (1)	0.1 (1)	0.2 (1)	0.1 (1)
Drainage, pocket site	3 (3)	0.2 (1)	0.1 (1)	0.5 (2)	0.1 (2)
Eccymosis, groin	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Eccymosis, pocket site	2 (2)	0.0 (0)	0.0 (0)	0.5 (2)	0.1 (2)
Fatigue, tiredness	3 (3)	0.2 (1)	0.1 (1)	0.5 (2)	0.1 (2)
Fever	6 (5)	0.5 (2)	0.2 (3)	0.7 (3)	0.2 (3)
ICD migration	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Heart failure decompensation	5 (5)	1.2 (5)	0.3 (5)	0.0 (0)	0.0 (0)
Hematoma, groin	2 (2)	0.0 (0)	0.0 (0)	0.5 (2)	0.1 (2)
Hemo/Pneumothorax	3 (3)	0.5 (2)	0.1 (2)	0.2 (1)	0.1 (1)
Hypotension	8 (7)	1.7 (7)	0.4 (8)	0.0 (0)	0.0 (0)
Inadequate cardiac output	1 (1)	0.2 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Junctional rhythm	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Nausea/vomiting	11 (11)	1.4 (6)	0.3 (6)	1.2 (5)	0.3 (5)

	# of Events (# of patients)	% Complications (# of patients)	Complications per 100 device-months (# of events)	% Observations (# of patients)	Observations per 100 device-months (# of events)
Pain pocket site	101 (96)	1.7 (7)	0.5 (9)	21.4 (90)	4.9 (92)
Pain (arm, back, chest, groin, head, shoulder)	62 (61)	1.0 (4)	0.1 (2)	13.5 (57)	3.1 (58)
Pericardial effusion/Pericarditis	4 (4)	0.2 (1)	0.2 (1)	0.7 (3)	0.2 (3)
Phlebitis	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Pleural effusion	6 (6)	0.2 (1)	0.1 (1)	1.2 (5)	0.3 (5)
Pocket infection/seroma/ hematoma/swelling	38 (38)	2.4 (10)	0.5 (10)	6.7 (28)	1.5 (28)
Rash	3 (3)	0.2 (1)	0.1 (1)	0.5 (2)	0.1 (2)
Renal insufficiency/failure	4 (4)	0.7 (3)	0.2 (3)	0.2 (1)	0.1 (1)
Respiratory arrest/ failure	2 (2)	0.5 (2)	0.1 (2)	0.0 (0)	0.0 (0)
Thrombosis	2 (2)	0.5 (2)	0.1 (2)	0.0 (0)	0.0 (0)
Atrial or ventricular arrhythmias	6 (6)	1.0 (4)	0.2 (4)	0.5 (2)	0.1 (2)
Subtotal: Procedure related/Possibly procedure related[1]	**317 (208)**	**13.3 (56)**	**4.0 (74)**	**42.5 (179)**	**13.1 (243)**
Heart failure decompensation					
Atrial arrhythmias	3 (3)	0.7 (3)	0.2 (3)	0.0 (0)	0.0 (0)
Cardiac related[2]	12 (12)	1.9 (8)	0.4 (8)	1.0 (4)	0.2 (4)
Edema	6 (5)	0.2 (1)	0.1 (1)	1.2 (5)	0.3 (5)
Electrolyte imbalance[3]	3 (3)	0.2 (1)	0.1 (1)	0.5 (2)	0.1 (2)
Elevated liver enzymes	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Heart failure decompensation	127 (88)	14.3 (60)	4.4 (82)	9.7 (41)	2.4 (45)
Pleural effusion	2 (2)	0.5 (2)	0.1 (2)	0.0 (0)	0.0 (0)
Renal insufficiency/failure; elevated creatinine	13 (12)	1.4 (6)	0.4 (7)	1.4 (6)	0.3 (6)
Respiratory related[4]	26 (25)	1.9 (8)	0.5 (9)	4.0 (17)	0.9 (17)
Subtotal: Heart failure decompensation[1]	**202 (120)**	**17.1 (72)**	**6.3 (118)**	**16.2 (68)**	**4.5 (84)**
Not device or procedure related	**754 (259)**	**21.9 (92)**	**8.5 (158)**	**56.3 (237)**	**32.0 (596)**

[1]The following adverse events were reported in three or fewer patients: ICD related: Pain pocket site, shoulder pain/discomfort. Possibly device related: Back pain/discomfort, diaphoresis, dyspnea/shortness of breath, palpitations, peripheral edema, renal insufficiency/failure, shoulder pain/discomfort. Procedure related/possibly procedure related: Adrenal insufficiency, anemia, anxiety, bloody sputum, COPD, confusion, decreased oxygen saturation, density on chest x-ray, drainage of old device pocket site, dysphagia, electromechanical dissociation (transient), elevated white blood cell count, eye abrasion, headache, nose bleed, occluded brachiocephalic vein, palpitations, sinus tachycardia, sleep problems, subclavian vein collapse, urinary problems. Heart failure decompensation: Anxiety, decreased appetite, fatigue, heart block, heart transplant, syncope, ventricular arrhythmias, weight gain.

[2] Reported cardiac related events: cardiac arrest, cardiogenic shock, cardiomyopathy, chest pain/angina pectoris, inadequate cardiac output.

[3] Reported electrolyte imbalances: hyperkalemia, hyponatremia.

[4] Reported respiratory events: Bloody sputum, dyspnea/shortness of breath, COPD, respiratory failure.

A total of 82 deaths were reported in the 434 enrolled NYHA Class III and IV patients. Of these deaths, 59 occurred in 364 patients who were implanted with an InSync® ICD system and randomized to either the control (CRT OFF) or treatment group (CRT ON) **Table 2** summarizes the investigator's death classifications.

Table 2. Summary of Death Classifications for Randomized NYHA Class III and IV Patients

Investigator Classification	Control	Treatment
Sudden Cardiac	5	4
Non-sudden Cardiac	17	20
Non-Cardiac	7	3
Unknown	1	2
Total	**30**	**29**

In addition, 23 deaths occurred in patients who were not randomized: 3 deaths in patients in whom an implant was not attempted; 14 deaths in patients in whom an implant attempt was unsuccessful; and 6 deaths in patients who were implanted with an InSync® ICD system but were not randomized. Of these 23 deaths, 4 were classified by the investigator as sudden cardiac, 12 as non-sudden cardiac, 3 as non-cardiac and 4 as unknown.

B. Possible Adverse Events

Possible adverse events associated with ICD systems with Cardiac Resynchronization Therapy include (in alphabetical order):

- acceleration of arrhythmias (caused by ICD)
- air embolism
- bleeding
- chronic nerve damage
- erosion
- exacerbation of heart failure
- excessive fibrotic tissue growth
- extrusion
- fluid accumulation
- formation of hematomas or cysts
- inappropriate shocks
- infection
- keloid formation
- lead abrasion and discontinuity
- lead migration / dislodgment
- myocardial damage
- pneumothorax
- potential mortality due to inability to defibrillate or pace
- shunting current or insulating myocardium during defibrillation; thromboemboli
- venous occlusion
- venous or cardiac perforation.

The adverse events related to the use of transvenous leads include, but are not limited to, the follow patient-related conditions when the lead is being inserted and/or repositioned

- cardiac dissection
- cardiac perforation
- cardiac tamponade
- coronary sinus dissection
- endocarditis
- fibrillation or other arrhythmias
- heart block
- heart wall or vein wall rupture
- infection, muscle or nerve stimulation
- myocardial irritability
- pericardial effusion
- pericardial rub
- pneumothorax
- thrombolytic and air embolism
- thrombosis
- valve damage (particularly in fragile hearts).

VII. Alternative Practices and Procedures

The present established therapies for the treatment of heart failure and sudden cardiac death and the associated signs and symptoms include pharmacological therapy, heart transplantation, other approved biventricular ICDs or other surgical procedures.

VIII. Marketing History

The InSync® ICD device and Attain Models 2187/2188/4189* leads are currently distributed commercially outside the United States. Specifically, these devices are approved for sale in the European Community, Australia, Canada, and Latin America (Argentina, Uruguay).

Neither the device nor leads have been withdrawn from the market in any country for any reason related to the safety and effectiveness of the device.

IX. Summary of Pre-clinical Studies InSync® ICD System

A. Safety and Risk Analysis

A safety and risk analysis of the InSync® ICD system was conducted to identify potential system hazards and to identify appropriate mitigating actions. This analysis included:

Hazard Analysis

Hazard analysis identifies possible hazards from use of the InSync® ICD system, determines the probability of occurrence and documents mitigating actions to minimize risk. Hazard analysis was performed on the InSync® ICD system, including review of all hazards and mitigating actions, and the remaining risk was determined to be acceptable.

Failure Modes Effects Analysis (FMEA)

FMEA was performed on the InSync® ICD system to identify and mitigate any potential design, test, or process issues that could adversely influence the safety and/or performance of the device.

Reliability Prediction Analysis

An analysis of the expected field performance on the InSync® ICD was performed based on the field performance of similar Medtronic devices. The predicted field performance of the InSync® ICD is a failure rate of 0.035% per month at a 90% confidence level.

* These data are included for completeness in reporting the results of the clinical study. The 4189 lead is not currently market approved in the U.S.

B. Non-clinical Laboratory Studies – InSync® ICD Model 7272

Major Components

The InSync® ICD Model 7272 is a derivation of the GEM DR Model 7271 and GEM II DR Model 7273 systems with biventricular pacing capability added for cardiac resynchronization. The InSync® ICD Model 7272 components are identical or similar to those used in the GEM DR Model 7271.

Table 3. Major Components of the InSync® ICD Model 7272

Component	Comparison to Model 7271 GEM DR	Qualification
Connector Module	• Polyurethane module that contains lead ports. The module is bonded to device can • Similar to Model 7271 GEM DR. LV lead port added to the connector module	• InSync® ICD Model 7272 Connector Qualification Testing
Battery (2)	• Same lithium-silver vanadium oxide cells (Li/SVO) developed by the Promeon Division of Medtronic	• Qualified with Model 7271 GEM DR
High Voltage Capacitors (2)	• Two HV output capacitors provide energy for cardioversion and defibrillation therapies. Same as Model 7271	• Qualified with Model 7271 GEM DR
Antenna	• The antenna sends/receives device communications through bi-directional telemetry • Same component used in Model 7271 GEM DR	• Qualified with Model 7271 GEM DR
Transformer	• The transformer converts low voltage from the battery to high voltage for the HV capacitors • Same component used in Model 7271 GEM DR	• Qualified with Model 7271 GEM DR
Reedswitch	• The reedswitch is a magnetically controlled mechanical switch that, once closed, signals the device that telemetry communications with the external programmer can occur • Same component used in Model 7271 GEM DR	• Qualified with Model 7271 GEM DR
Biocompatibility	• The materials used in the InSync® ICD device are identical to those used in the Medtronic GEM DR Model 7271. These materials include: titanium, silicone adhesive, silicone rubber, and polyurethane. No new materials or processes were introduced with the InSync® ICD Model 7272 that would introduce new issues of biocompatibility.	• Qualified with Model 7271 GEM DR

Connector Module

Qualification activities performed on the InSync® ICD Model 7272 tested the electrical and physical integrity of the connector module, adhesive interfaces, and block / MBC-to-feedthrough welds (qualified by similarity to GEM Model 7227Cx). The connector design met all connector-specific requirements specified in the InSync® ICD product specification and the IS-1 and DF-1 international standards for connectors (ISO 5841-3 and ISO 11318, respectively). Qualification demonstrated that the connector module met these requirements with 90% reliability at a 90% confidence level.

Table 4. Connector Test

Connector Test	Sample Size	Acceptance Criteria	Result
1. Insertion / Withdrawal (Go Gauge & Lead Connector)	22	≤ 2.0 lbf, Go Gauge), ≤ 13.15 lbf, Lead Connector)	Passed Passed
2. IS-1 Electrical Leakage Impedance	22	≥ 50 K ohms	Passed
3. DF-1 Electrical Isolation	22	≤ 50 mA	Passed
4. DF-1 Current Carrying	NA	≤ 65 V	Qualified by Similarity
5. Suture Hole Pull Force	22	≥ 6 lbs	Passed

Device Qualification

Device qualification testing was performed to ensure that the InSync® ICD Model 7272 performs acceptably in typical shipping, handling and operating environments. The device qualification testing is summarized below. The results demonstrated that the InSync® ICD Model 7272 will perform acceptably in typical shipping, handling, and operating environments and is qualified for its intended use.

Table 5. Device Qualification Testing

Test	Sample Size	Acceptance Criteria	Results
Environmental	10	**Temperature Storage:** Meets Section 26.2 of European Standard prEN45502-2-2 **Mechanical Vibration:** Meets Section 23.2 of European Standard prEN45502-2-2. **Mechanical Shock:** Show no visible signs of damage which affects function of device after a shock having a change in velocity (dV) of 118 inches per second and a duration of 1ms in each of six axes. Simulates a drop of 45cm (18") to a hard surface.	Meets Acceptance Criteria
Electromagnetic Compatibility	22	**Electromagnetic Interference:** Meets requirements of the 1975 AAMI Pacemaker Standard. Also meets requirements at additional frequencies, including radiated continuous wave and pulsed electromagnetic fields and conducted continuous wave sinusoidal currents.	Meets Acceptance Criteria
	3	**Cellular Phone:** Not susceptible to interference from analog or digital cellular telephones at distances >=8 cm, including the following systems: AMPS, TDMA-50 (NADC), GSM, DCS, and CDMA.	
	22	**X-ray:** Testing waived based on similarity to GEM DR Model 7271.	
	22	**Electrosurgical Cautery:** Must withstand spark cutting, spark coagulating, and sine cutting modes and energies.	
	22	**Transthoracic Defibrillation:** must withstand 1000V and 1500V.	
Design Verification Testing	3	Because of hardware similarity between InSync® ICD and GEM DR, verification testing was conducted only on hardware components (tests on the CRT therapy, unmodified circuits and device immunity to noise and ESD). Testing confirmed conformance with product specifications.	Meets Acceptance Criteria

C. Non-clinical Laboratory Testing – Firmware/Software

1. Firmware Verification Testing

Firmware verification testing functionally verifies that each firmware requirement for the Model 7272 InSync® ICD is met. The verification test plan is developed in parallel with the firmware design and firmware implementation phases.

Table 6. Summary of Firmware Verification Testing

Summary of Firmware Verification Testing	Sample Tested	Result
Firmware verification testing was performed as defined by the Verification Test Plan Rev. 003	Firmware	Passed

2. Software Verification Testing

Software verification testing was performed on the Model 9969 Application Software on both the Model 9790 and 2090 Programmers.

Table 7. Summary of Software Verification Testing

Summary of Software Verification Testing	Sample Tested	Result
Software verification testing was performed as defined by the Verification Test Plan. Testing consisted of functional testing, Software Install testing, stress testing, and regression testing.	Software	Passed

3. System Testing

System testing of the InSync® ICD system (InSync® ICD Model 7272, Model 9969 Software, Model 9790 and 2090 programmers, and accessories) was performed to ensure that all system components work together appropriately under simulated clinical situations.

Table 8. Summary of System Testing

Summary of System Testing	Sample Tested	Result
System testing evaluates the compatibility, interaction and functional operation of the InSync® ICD system components when used together as a system.	InSync® ICD System Components	Passed

D. Biocompatibility Testing

All blood-contacting materials used in the InSync® ICD pulse generator are identical to those used in PMA-approved Medtronic pulse generators. These currently-marketed pulse generators have previously been subject to standard biocompatibility evaluations which conform to FDA Tripartite Biocompatibility Guidance (4/87), FDA Blue Book Memorandum #95-1 (5/95), and the International Standard ISO-10993.

All biocompatibility testing was conducted in compliance with Good Laboratory Practices (GLP).

E. Sterilization Information

The 100% ethylene oxide (EtO) sterilization process used to sterilize the implantable pulse generator has been previously approved in other PMA applications. All processes used to sterilize a product are validated and qualified according to the major guidelines and standards. Package qualification testing was performed on both the device to ensure suitability for their intended purpose.

F. Animal Studies

GLP studies were conducted in 3 canines with the InSync® ICD Model 7272. The purpose of the Model 7272 InSync® ICD study was to determine that the device provided acceptable performance for sensing and detection of cardiac rhythms, appropriate rejection of sinus arrhythmias, and correct delivery of appropriate programmed therapy. In each of the studies, appropriate pacing, sensing, and thresholds were documented.

G. Conclusion Concerning Non-clinical Laboratory Testing

Medtronic conducted a hazard analysis on all new features and critical components and then conducted testing to evaluate these and other device features. All test results were found to be acceptable.

H. Shelf Life

Based on battery longevity testing, the shelf life for the InSync® ICD pulse generator was established and approved at 18 months from battery attachment date.

X. Summary of Clinical Study

A. Study Design

The InSync® ICD study was a prospective, multi-center, randomized, double-blind, parallel arm, controlled clinical trial to assess the safety and effectiveness of transvenous atrial-based synchronous biventricular pacing for heart failure therapy (cardiac resynchronization therapy – CRT) in patients who are indicated for an ICD. Patients in NYHA Classes II, III and IV were enrolled in the clinical study (for the purposes of FDA approval, only data from NYHA Class III and IV patients are presented unless otherwise noted). The products being evaluated include the Model 7272 InSync® ICD and the Model 9969 application software for use with the Model 9790C and 2090 programmers and the commercially available Models 2187 and 2188 Attain LV leads and the Model 4189* Attain LV Lead.

Note: The 4189 Attain Lead is not currently market approved in the U.S. Lead performance data in the clinical trial did not support reasonable assurance of the safety and effectiveness of the 4189 Lead. However, the data obtained with the 4189 Lead are presented for completeness here. Based on similarities in the design and function of the 4189 and 2187/2188, these two sets of leads are equally compatible with the Model 7272 InSync® ICD to deliver biventricular pacing.

Figure 1 depicts the InSync® ICD study design. Patients were randomized within 7 days of a successful implant and were in double-blind follow-up for 6 months. After the six-month follow up, all patients had CRT turned on.

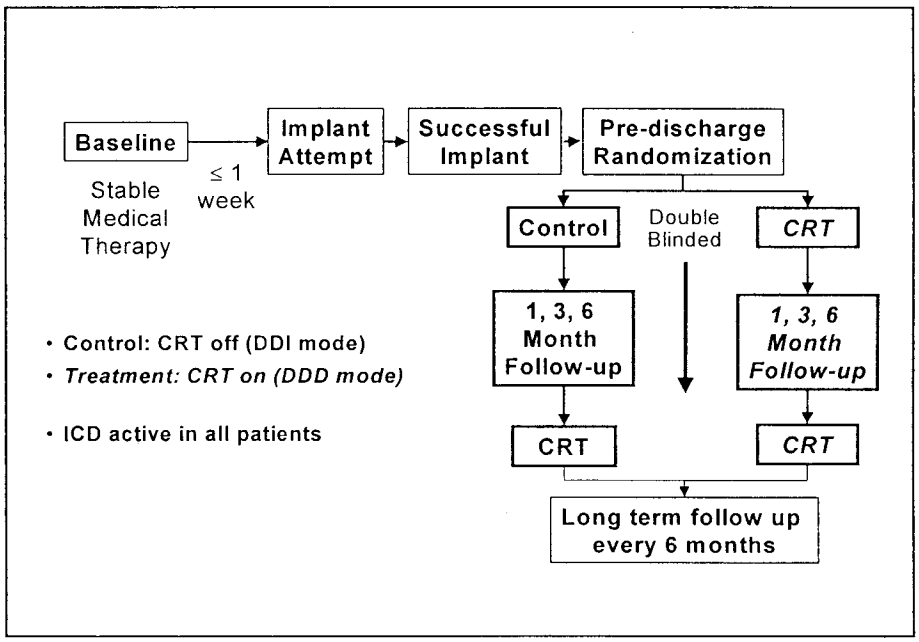


Figure 1. InSync® ICD Study Design

* These data are included for completeness in reporting the results of the clinical study. The 4189 lead is not currently market approved in the U.S.

Patient Selection Criteria

Inclusion Criteria

ICD Indication

- Patients who have had at least one episode of cardiac arrest (manifested by loss of consciousness) due to ventricular tachyarrhythmia;

or

- Patients having recurrent, poorly tolerated, sustained VT that occurs spontaneously or can be induced;

or

- ***Canada Only:*** Patients who have had a prior myocardial infarction, left ventricular ejection fraction less than or equal to 35%, a documented episode of non-sustained VT and inducible ventricular tachyarrhythmia.

And Heart Failure as defined by:

- Patients having symptomatic congestive heart failure (NYHA Class II, III, IV) with evidence of ventricular dysynchrony demonstrated by:
- QRS duration $\geq$ 130 ms,
- LV Ejection Fraction $\leq$ 35%,
- LV End Diastolic Diameter $\geq$ 55 mm.
- Stable medical regimen for at least 1 month prior to enrollment (to include at least ACE inhibitors, or ACE inhibitor substitute) patients currently on stable beta blockade regimes for at least 3 months prior to enrollment were allowed in the study. Patients may not be started on beta-blockers during the 6-month randomization period.
- 18 years of age or older.

Exclusion Criteria

- Baseline Six Minute Hall Walk distance greater than 450 meters (Class III and IV only).
- Unstable angina, or acute MI, CABG, or PTCA within the past 3 months.
- Recent CVA or TIA (within the previous 3 months).
- Intermittent positive inotropic drug therapy (intermittent is defined as more than two infusions per week).
- Patients having indications or contraindications for standard cardiac pacing.
- Systolic blood pressure of less than 80 mm or greater than 170 mm.
- Resting heart rate greater than 140 bpm.
- Serum Creatinine greater than 3 mg/dl.
- Hepatic function (serum) greater than 3 times the upper limit of normal.
- Primary valvular disease.
- Severe primary pulmonary disease.
- Chronic atrial arrhythmias (or cardioversion for afib within the past month) or paroxysmal atrial fib event within the previous month.
- Post heart transplant (patients who are waiting for a heart transplant are allowed entry into the study).
- Enrolled in any concurrent study that may confound the results of this study.
- Patients who are not expected to survive for 6 months of study participation.
- Women who are pregnant or with child bearing potential and who are not on a reliable form of birth control.
- Patients with mechanical right heart valves.
- Patients with VT associated with reversible causes.

Study Blind

The InSync® ICD trial was double-blinded to reduce the effect of bias. Implanting physicians and staff responsible for programming the InSync® ICD were required to be aware of the mode to which the device was programmed. The EP staff (electrophysiologist, EP nurses, etc.) performed all tests that required viewing of the programmed pacing mode or the patient's ECG. The heart failure staff (heart failure physician, nurses, etc.) and the patients remained blinded and did not view these materials. Neither the patient nor the heart failure physician had knowledge of the pacing mode assigned. Because of their blinded status, the evaluations of QOL, NYHA classification, and 6-minute hall walk were conducted by the heart failure staff. All non-electrophysiological patient management decisions were made by the blinded heart failure physicians and nurses.

B. Clinical Study Results

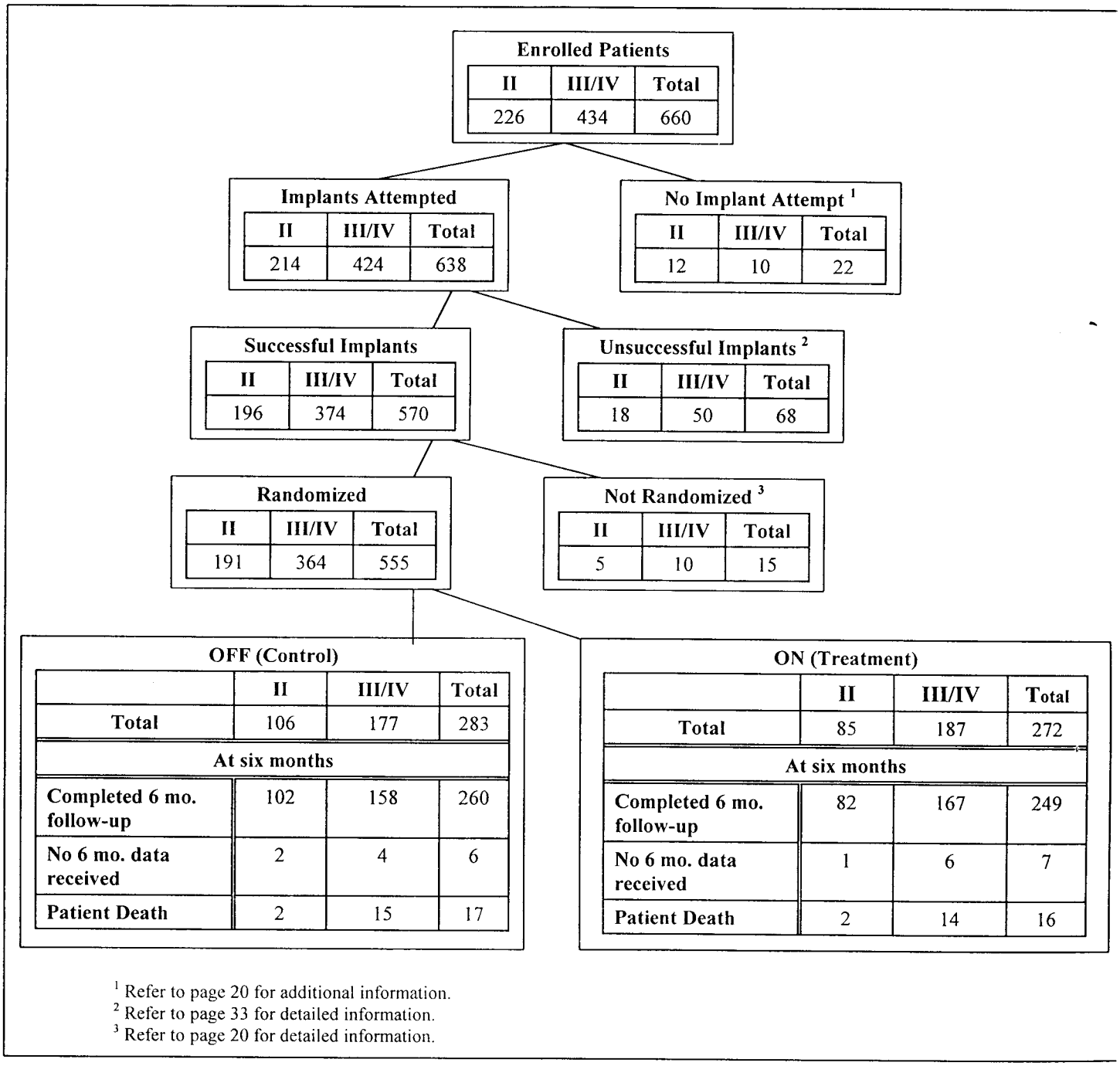
1. Patient Population

Study Enrollment

The first successful implant of the Model 7272 InSync® ICD cardiac resynchronization system was performed on October 4, 1999. Fifty-three centers provided data for this clinical report (48 in USA, 5 in Canada) and 638 patients (Class II, III and IV) had implant attempts. There were 570 patients with successful implants, of which 555 were randomized. The patients received the commercially available LV Lead Models 2187 or 2188 or the Model 4189* LV Lead which is not a subject of this PMA approval. In total, there were 283 patients randomized to the control arm (OFF), and 272 patients randomized to the treatment arm (ON). Of the 283 control patients, 106 were NYHA Class II and 177 were NYHA Class III and IV. Of the 272 treatment patients, 85 were NYHA Class II and 187 were NYHA Class III and IV treatment patients. For the purposes of FDA approval, results from NYHA Class III and IV patients only will be presented unless otherwise noted.

* These data are included for completeness in reporting the results of the clinical study. The 4189 lead is not currently market approved in the U.S.

Figure 2 provides summary information on the study patient population.



[1] Refer to page 20 for additional information.
[2] Refer to page 33 for detailed information.
[3] Refer to page 20 for detailed information.

Figure 2. InSync® ICD Study Patient Population

Patients Enrolled But Implant Not Attempted

Of the 434 NYHA Class III and IV patients enrolled in the InSync® ICD study, 10 NYHA Class III and IV patients were consented, entailing enrollment, but an implant was not attempted. **Table 9** summarizes the reasons that an implant was not attempted in these patients.

Table 9. Patients Enrolled But Implant Not Attempted – NYHA Class III and IV Patients

Reason implant was not attempted	Total
Did not satisfy VT inclusion criterion	2
Did not satisfy LVEF inclusion criterion	2
Unable to obtain venous access	2
Death prior to implant attempt	2
Developed indications for standard cardiac pacing	1
Cancer diagnosed; chemotherapy initiated	1

Patients Not Randomized

Reasons for ten NYHA Class III and IV patients who were implanted with an InSync® ICD system but not randomized are summarized below:

- Patient unstable/pacing required (4)
- LV lead dislodgement (3)
- Respiratory arrest (1)
- Heart transplant prior to randomization (1)
- Patient death prior to randomization (1)

Crossovers

Biventricular Pacing OFF to ON

Fifteen NYHA Class III and IV patients were randomized to biventricular pacing OFF and had an early crossover to biventricular pacing ON prior to the 6-month follow-up visit. The reasons for the programming changes are described below:

- Worsening heart failure requiring CRT (11)
- Inadvertent programming (2)
- Bradycardia (1)
- AV nodal ablation (1)

Biventricular Pacing ON to OFF

Ten NYHA Class III and IV patients were randomized to biventricular pacing ON and had an early crossover to biventricular pacing OFF prior to the 6-month follow-up visit. The reasons for the programming changes are described below:

- Inadvertent programming (6)
- LV lead dislodgment (2)
- Diaphragmatic stimulation (2)

2. Baseline Demographic Data

Baseline demographic data for randomized NYHA Class III and IV patients are summarized in **Table 10**. P-values < 0.05 are noted with an asterisk.

Table 10. Comparison of Control and Treatment Patients at Baseline – NYHA Class III and IV Patients

InSync® ICD Comparison of Demographics by Treatment Assignment All Randomized NYHA Class III/IV Patients			
	Control (OFF) **(n=177)**	**Treatment (ON)** **(n=187)**	**P-value**
Gender (n,%)			
Male	136 (76.8%)	142 (75.9%)	0.90
Female	41 (23.2%)	45 (24.1%)	
Age (years)			
Mean ± Standard deviation	67.4 ± 9.4	66.6 ± 11.3	0.88
n(%)	177 (100.0%)	187 (100.0%)	
New York Heart Classification (n,%)			
III	158 (89.3%)	165 (88.2%)	0.87
IV	19 (10.7%)	22 (11.8%)	
QRS Width (ms)			
Mean ± Standard deviation	162 ± 22	165 ± 22	0.15
n (%)	177 (100.0%)	187 (100.0%)	
Ejection Fraction (%)			
Mean ± Standard deviation	20.1 ± 6.1	20.5 ± 7.0	0.74
n (%)	176 (99.4%)	187 (100.0%)	
LVEDD (mm)			
Mean ± Standard deviation	70.9 ± 9.1	70.4 ± 9.0	0.51
n (%)	174 (98.3%)	186 (99.5%)	
MN Living with HF Score			
Mean ± Standard deviation	55.2 ± 22.9	56.5 ± 22.9	0.56
n (%)	174 (98.3%)	185 (98.9%)	
6 –Minute Hall Walk (meters)			
Mean ± Standard deviation	245 ± 118	243 ± 130	0.87
n (%)	175 (98.9%)	183 (97.9%)	
Peak VO_2/kg (ml/kg/min.)			
Mean ± Standard deviation	13.5 ± 3.9	13.4 ± 3.6	0.96
n (%)	135 (76.3%)	144 (77.0%)	
Exercise Time (seconds)			
Mean ± Standard deviation	511 ± 229	473 ± 213	0.27
n (%)	136 (76.8%)	143 (76.5%)	
Supine Heart Rate (bpm)			
Mean ± Standard deviation	71.5 ± 12.9	70.9 ± 12.4	0.82
n (%)	171 (96.6%)	186 (99.5%)	
Baseline CV Medical History (n, %) (non-exclusive)			
n recorded	177	186	
Coronary Artery Disease	135 (76.3%)	122 (65.6%)	0.03*
Congenital Heart Disease	0 (0%)	2 (1.1%)	0.50

InSync® ICD Comparison of Demographics by Treatment Assignment All Randomized NYHA Class III/IV Patients			
	Control (OFF) (n=177)	Treatment (ON) (n=187)	P-value
HF etiology: ischemic	133 (75.1%)	119 (64.0%)	0.02*
HF etiology: non-ischemic	49 (27.7%)	67 (36.0%)	0.09
Myocardial Infarction	112 (63.3%)	100 (53.8%)	0.07
Anterior	46 (26.0%)	48 (25.8%)	1.00
Lateral	13 (7.3%)	16 (8.6%)	0.70
Posterior	3 (1.7%)	5 (2.7%)	0.72
Inferior	32 (18.1%)	31 (16.7%)	0.78
Non Q-wave	15 (8.5%)	6 (3.2%)	0.04*
Cardiomyopathy	166 (93.8%)	176 (94.6%)	0.82
Primary electrical disease	5 (2.8%)	6 (3.2%)	1.00
Valvular Disease	0 (0%)	0 (0%)	1.00
Hypertension	90 (50.8%)	84 (45.2%)	0.29
Chronotropic incompetence	2 (1.1%)	0 (0%)	0.24
Syncope/presyncope	46 (26.0%)	49 (26.3%)	1.00
Other	28 (15.8%)	31 (16.7%)	0.89
Prior Cardiac Intervention (n, %) (non-exclusive)			
n recorded	173	182	
CABG	87 (50.3%)	82 (45.1%)	0.34
Valve replacement	9 (5.2%)	13 (7.1%)	0.51
Ablation	7 (4.0%)	6 (3.3%)	0.78
Coronary Artery Intervention	48 (27.7%)	44 (24.2%)	0.47
Repair/Correction of Cong. Abnormality	0 (0%)	2 (1.1%)	0.50
ICD currently implanted	51 (29.5%)	54 (29.7%)	1.00
None	48 (27.7%)	55 (30.2%)	0.64
Spontaneous Arrhythmia History (non-exclusive)			
n recorded	177	187	
Atrial Fibrillation	31 (17.5%)	49 (26.2%)	0.06
Atrial Flutter	7 (4.0%)	10 (5.3%)	0.62
AV Nodal Reentrant Tachycardia	0 (0%)	0 (0%)	0.62
Sustained Monomorphic VT	67 (37.9%)	64 (34.2%)	0.51
Sustained Polymorphic VT	10 (5.6%)	7 (3.7%)	0.46
Nonsustained VT	52 (29.4%)	73 (39.0%)	0.06
Ventricular Flutter/Fibrillation	28 (15.8%)	26 (13.9%)	0.66
Torsades de Pointes	1 (0.6%)	1 (0.5%)	1.00
Long QT Syndrome	0 (0%)	0 (0%)	1.00
Bradycardia[1]	101 (57.1%)	105 (56.2%)	0.92
Right Bundle Branch Block	24 (13.6%)	24 (12.8%)	0.88
Left Bundle Branch Block	126 (71.2%)	141 (75.4%)	0.41
Others	32 (18.1%)	39 (20.9%)	0.51
Other Medical History (n, %) (non-exclusive)			
n recorded	177	187	
Endocrine (includes diabetes)	32 (18.1%)	24 (12.8%)	0.19
Pulmonary (includes COPD)	37 (20.9%)	49 (26.2%)	0.27
Renal	33 (18.6%)	28 (15.0%)	0.40

InSync® ICD Comparison of Demographics by Treatment Assignment All Randomized NYHA Class III/IV Patients			
	Control (OFF) **(n=177)**	**Treatment (ON)** **(n=187)**	**P-value**
Medications (n, %) **(non-exclusive)** **n recorded**	177	187	
ACE Inhibitor	155 (87.6%)	172 (92.0%)	0.17
Anti-Arrhythmic	57 (32.2%)	79 (42.2%)	0.05
Anti-Depressant	35 (19.8%)	36 (19.3%)	1.00
Anti-Coagulant	143 (80.8%)	144 (77.0%)	0.44
Beta Blocker	103 (58.2%)	118 (63.1%)	0.39
Ca++ Blocker	10 (5.6%)	13 (7.0%)	0.67
Diuretic	167 (94.4%)	173 (92.5%)	0.53
Positive Inotrope	129 (72.9%)	142 (75.9%)	0.55
Nitrate	59 (33.3%)	68 (36.4%)	0.58
Other Medication	108 (61.0%)	108 (57.8%)	0.59

* $p < 0.50$

[1] Includes sinus bradycardia, sick sinus syndrome, 1°, 2° and 3° atrioventricular block and bradycardia-tachycardia syndrome.

3. Primary Effectiveness Endpoint Results

The primary endpoints of the study were improvement in NYHA Class, Quality of Life and 6-minute Hall Walk. The study results were analyzed using the Hochberg criteria in that there would be a statistical success for effectiveness if one of the three endpoints was statistically significant at alpha =0.0167, if any two were significant at alpha = 0.025, or if all three were significant at alpha = 0.05.

Quality of Life

Patient quality of life (QOL) was assessed with the Minnesota Living with Heart Failure (MLWHF) questionnaire. A lower score indicates an improvement in quality of life. Both the patient and study personnel administering the questionnaire were blinded to the randomization assignment. **Table 11** summarizes the paired baseline and 6 month QOL results for NYHA Class III and IV patients. P-values were based on the paired median difference.

Table 11. MLWHF QOL Paired Baseline and 6-Month Data NYHA III/IV Patients

	Control Group *(CRT OFF)*	Treatment Group *(CRT ON)*	P-value
6-month change in QOL score	153 patients with paired data **Baseline:** median 57.0 Mean 55.1 ± 22.5 **6-month:** median 43.0 mean 42.0 ± 22.9 **Median Paired Difference: – 11.0**	162 patients with paired data **Baseline:** median 55.0 mean 54.2 ± 23.1 **6-month:** median 34.0 mean 35.9 ± 23.4 **Median Paired Difference: – 17.5**	0.02

Figure 3 presents the median change in QOL for the control and treatment groups at baseline through 6 month follow up.

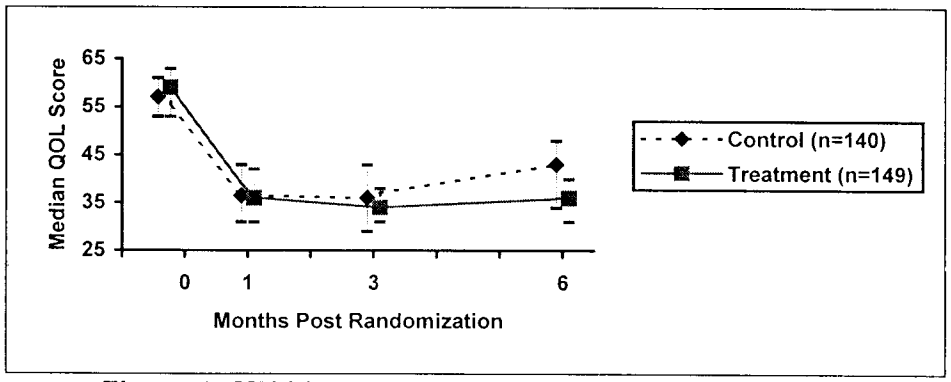


Figure 3. MN Living With Heart Failure Data Summary

NYHA Classification

NYHA functional classification was determined by a physician who was blinded to the patient's randomization assignment. **Table 12** summarizes the paired baseline and 6 month NYHA results for NYHA Class III and IV patients. The P-value was based on the median paired difference.

Table 12. NYHA Paired Baseline and 6-Month Data– NYHA III/IV Patients

	Control Group *(OFF)*	Treatment Group *(ON)*	P-value
6-month change in NYHA Classification	158 patients with paired data **Baseline:** median 3.0 Mean 3.09 ± 0.29 **6-month:** median 3.0 mean 2.51 ± 0.6 **Median Paired Difference: – 0.5**	165 patients with paired data **Baseline:** median 3.0 mean 3.10 ± 0.30 **6-month:** median 2.0 mean 2.31 ± 0.72 **Median Paired Difference: – 1**	0.01

Figure 4 presents the median change in NYHA class for the control and treatment groups at baseline through 6 month follow up.

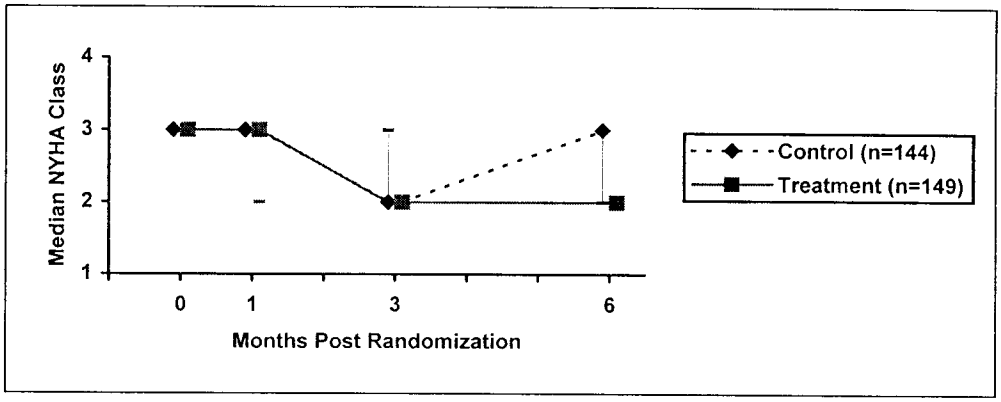


Figure 4. NYHA Classification Data Summary

6-Minute Hall Walk

Patients performed a 6-minute hall walk test in order to assess sub-maximal exercise capacity. Study personnel administering the test were blinded to the patient's randomization assignment. **Table 13** summarizes the paired baseline and 6 month 6 minute hall walk results for NYHA Class III and IV patients. The P-value was based on the median paired difference.

Table 13. 6-Minute Hall Walk Paired Baseline and 6 Month Data– NYHA III/IV Patients

	Control Group *(OFF)*	Treatment Group *(ON)*	P-value
6-month change in 6 minute hall walk (meters)	150 patients with paired data **Baseline:** median 275 Mean 254 ± 112 **6-month:** median 334 mean 324 ± 114 **Median Paired Difference: 53**	153 patients with paired data **Baseline:** median 254 mean 252 ± 128 **6-month:** median 340 mean 339 ± 106 **Median Paired Difference: 55**	0.43

Figure 5 presents the median change in 6-minute hall walk distance for the control and treatment groups at baseline through 6 month follow up.

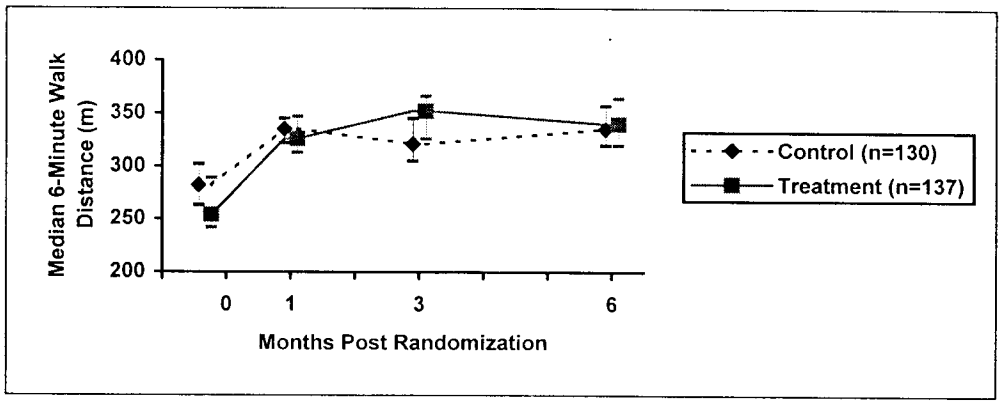


Figure 5. 6-Minute Hall Walk Data Summary

4. Primary Safety Endpoint Results

ICD-Related Complications

Table 14 summarizes the 5 NYHA Class III and IV patients who experienced 7 complications at 3 months post-implant related to the Model 7272 InSync® ICD.

Table 14. InSync® ICD-Related Complications – NYHA III/IV Patients

Event Type	Number of events	Events in the First 3 Months
Pain at pocket site	1	1
Pocket seroma/hematoma	2	2
Abnormal impedance measurement	1	1
Dizziness	1	1
Electrical reset of ICD	1	1
Pocket infection	1	1
Pacemaker-mediated tachycardia*	1	0
TOTAL	**8 events (in 6 patients)**	**7 events (in 5 patients)**

*after 3 months

Table 15 summarizes the freedom from ICD-related complications at three months post-implant.

Table 15. Freedom from InSync® ICD-Related Complications During First 3 Months – NYHA III/IV Patients

# Patients With ICD-Related Complications	# Implanted Patients	Estimated survival	Lower 95% confidence limit	95% lower bound criterion
5	371	98.6%	97.6%	89.0%

Attain Model 4189 LV Lead-Related Complications

Table 16 summarizes Model 4189* LV lead-related complications in NYHA Class III and IV patients at six months. The Model 4189* lead is not the subject of this approval decision.

Table 16. Model 4189-Related Complications – NYHA III/IV Patients

Event Type	Number Of Events In All Patients	Events In All Patients In The First 6 Months
Lead dislodgement	31	29
Extra cardiac stimulation	12	11
Elevated pacing thresholds	4	4
Failure to capture	3	3
Muscle stimulation – pectoral	1	1
Pericardial effusion	1	1
TOTAL	**52 events (in 46 patients)**	**49 events (in 44 patients)**

Table 17. Freedom from Model 4189 Complications During First 6 Months – NYHA III/IV Patients

Number of Patients With Events	Number of Implanted Patients	Estimated Survival	Lower 95% Confidence Bound	95% Lower Bound Criterion
44	315	85.1%	81.7%	75%

* These data are included for completeness in reporting the results of the clinical study. The 4189 lead is not currently market approved in the U.S.

5. Attain Models 2187 and 2188 LV Lead-Related Complications

The following table presents the summary of the market approved Model 2187 and 2188 complications in NYHA Class III and IV patients.

Table 18. Model 2187/2188 Related Complications NYHA III/IV Patients

Event Type	Number of Events	Events in the First 6 Months
Lead dislodgment	6	3
Failure to capture	1	1
Elevated pacing thresholds	1*	1*
TOTAL	**8 (in 8 patients)**	**5 events (in 5 patients)**

*Related to Model 2188

Table 19. Freedom from 2187/2188 Related Complications During First 6 Months – NYHA III/IV Patients

Number of patients with complications	Number of Implanted Patients	Estimated survival	Lower 95% confidence limit	95% Lower Bound Criterion
5	56	89.9%	82.9%	75%

System-Related Complications

Table 20 summarizes the system-related complications for NYHA Class III and IV patients.

Table 20. System-Related Complications – NYHA III/IV Patients

Device Relatedness	Event Type	# Events	# Events at 6 mo.
InSync® ICD related	Pain at pocket site	1	1
	Abnormal impedance measurement	1	1
	Pocket seroma/hematoma	2	2
	Pocket infection	1	1
	Dizziness	1	1
	Electrical reset of ICD	1	1
	Pacemaker mediated tachycardia	1	1
	Subtotal:	**8**	**8**
LV lead related (2187/88)	Lead dislodgment	6	3
	Failure to capture	1	1
	Elevated pacing thresholds	1	1
	Subtotal:	**8**	**5**
LV lead related (4189)	Lead dislodgment	31	29
	Muscle stimulation – diaphragm	12	11
	Elevated pacing thresholds	4	4
	Failure to capture	3	3
	Muscle stimulation – pectoral	1	1
	Pericardial effusion	1	1
	Subtotal:	**52**	**49**
RA lead related	Lead dislodgment	6	6
	Elevated pacing thresholds	2	2
	Failure to capture	2	2
	Far-field R-wave sensing	1	1
	Subtotal:	**11**	**11**
RV lead related	Muscle stimulation – diaphragm	1	1
	Elevated pacing thresholds	1	1
	Failure to capture	1	1
	Chronic RV lead discovered implanted in cardiac vein	1	1
	Subtotal:	**4**	**4**
System related	Pocket infection	1	1
	Twiddler's syndrome	1	1
	Subtotal:	**2**	**2**
Total		**85 events (in 69 pts.)**	**79 events (in 65 pts.)**

Table 21 summarizes the freedom from system-related complications at six months post-implant.

Table 21. Freedom from System-Related Complications During First 6 Months – NYHA III/IV Patients

# Patients With System-Related Complications	# Implanted Patients	Estimated survival	Lower 95% confidence limit	95% lower bound criterion
65	371	81.1%	77.6%	67.0%

6. Primary LV Lead Effectiveness Endpoint Results

LV Lead Implant Success

Four hundred and twenty-four NYHA Class III and IV patients underwent implant attempts. 374 patients were successfully implanted with an InSync® ICD system (85% received a Model 4189*, 14% received a Model 2187 and 1% received a Model 2188). Three hundred and sixty-five patients were successfully implanted on their first attempt. Eleven of the unsuccessful patients underwent a second implant attempt. Nine of those patients were successfully implanted the second time.

Table 22. Implant Success Rate – NYHA III/IV Patients

Number of Patients With Implant Attempts	Number of Successful Implants	Successful Implant Rate	Two-sided 95% Confidence Interval	95% Lower Bound Criterion
424	374	88.2%	84.8%-91.1%	83%

Table 23 summarizes the reasons for the unsuccessful implants (patients may have more than one reason).

Table 23. Summary of Unsuccessful Implants (Model 2187, 2188 and 4189 LV Leads) – NYHA III/IV Patients

Reason For Unsuccessful Implant	Number (not mutually exclusive)
Dislodgement/unstable position	31
Unable to obtain adequate distal location	26
Unable to cannulate coronary sinus ostium	23
Unacceptable pacing thresholds	21
Dissection/perforation	17
Unable to access coronary vein	12
Coronary vein too small	4
Patient decompensation during implant	4
Delivery system/tool problems	4
Patient venous anatomy	3
Diaphragmatic stimulation	2
Complete heart block	1

* These data are included for completeness in reporting the results of the clinical study. The 4189 lead is not currently market approved in the U.S.

Model 4189 LV Lead Voltage Thresholds

For all patients receiving a Model 4189* LV lead, the mean 6-month voltage threshold measured at 0.5 ms was 1.5V; the two-sided 95% confidence interval was (1.4V, 1.7V). The following table summarizes the voltage thresholds measured at implant, 1-month, 3-month, and 6-month follow-up visits, with two-sided 95% confidence intervals.

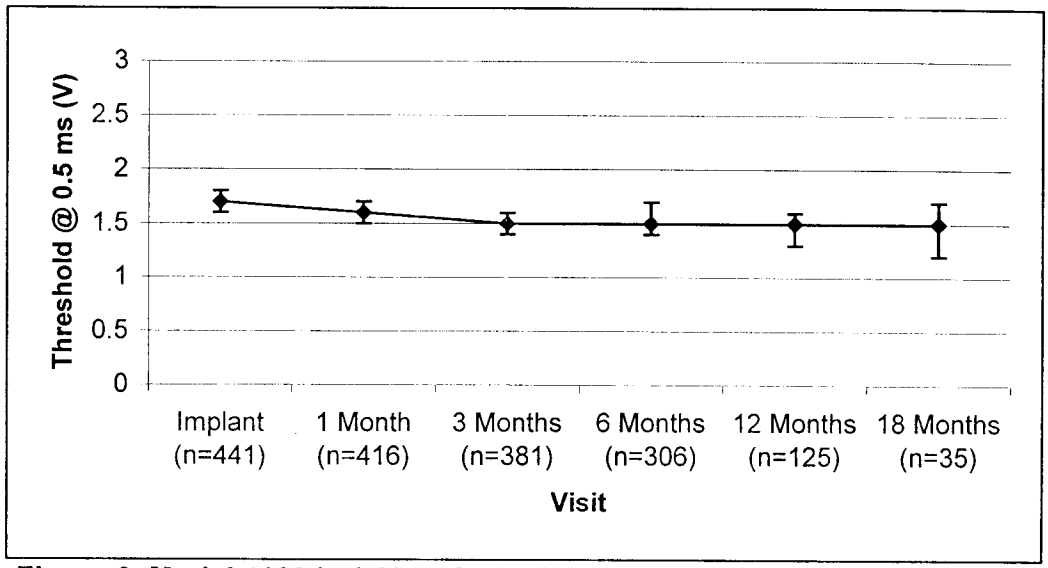


Figure 6. Model 4189 Left Ventricular Voltage Threshold Data (@ 0.5 ms)

* These data are included for completeness in reporting the results of the clinical study. The 4189 lead is not currently market approved in the U.S.

Models 2187 and 2188 LV Lead Voltage Thresholds

For all patients receiving a Model 2187 or 2188 lead, the mean 6-month voltage threshold measured at 0.5 ms was 1.9V; the two-sided 95% confidence interval was (1.7V, 2.2V). The following table summarizes the voltage thresholds measured at implant, 1-month, 3-month, and 6-month follow-up visits, with two-sided 95% confidence intervals.

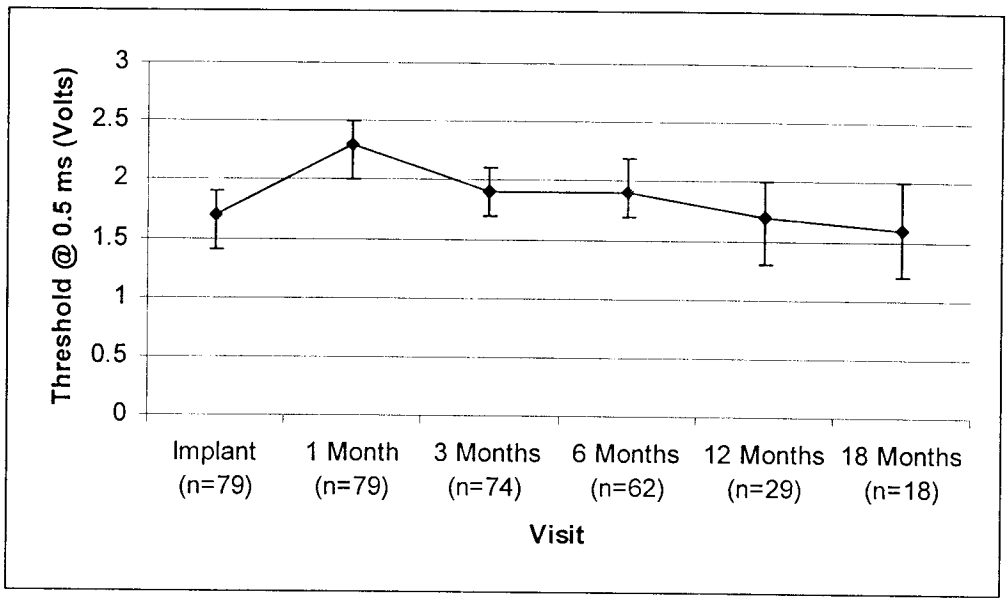


Figure 7. Model 2187/2188 Left Ventricular Voltage Threshold Data (@ 0.5 ms)

7. Secondary Endpoint Results

Patient Survival

Table 24 summarizes survival from all-cause mortality and the number of patient deaths at 3 and 6 months in randomized NYHA Class III and IV patients, comparing control and treatment groups. Survival from all-cause mortality at 6 months for the treatment group is 92.4%, and for the control group it is 92.0%. There is no difference in survival from all-cause mortality between treatment and control (p=0.72).

Table 24. Survival Estimates for Control vs. Treatment Groups – NYHA III/IV Patients

	Estimated Survival – 3 Months				Estimated Survival – 6 Months			
	# of Deaths	Patients At Risk	Estimated Survival	95% Confidence Interval	# of Deaths	Patients At Risk	Estimated Survival	95% Confidence Interval
Control Group (n=177)	6	171	96.6%	92.6%-98.5%	14*	87	92.0%	86.8%-95.2%
Treatment Group (n=187)	7	178	96.2%	92.3%-98.2%	14	99	92.4%	87.5%-95.4%

*One additional patient died after six months, but before their six-month follow-up

Figure 8 depicts all-cause survival for control and treatment groups.

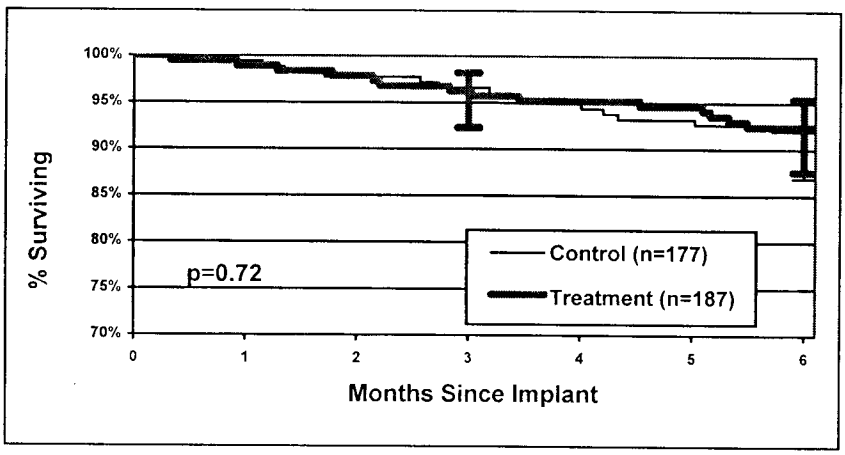


Figure 8. Survival From All-cause Mortality During Randomization Period – NYHA Class III and IV

Table 25 summarizes survival from all-cause mortality at 3, 6, 12, and 18 months and number of deaths for all NYHA Class III and IV patients receiving an InSync® ICD system (n=374). Note that at the conclusion of the 6-month follow-up visit, all patients had CRT turned on.

Table 25. Estimated Survival From All Causes of Death – NYHA III/IV Patients

Time Post-implant	Number of Deaths	Estimated Survival	95% Confidence Interval
3 Months	18	95.2%	92.4%-96.9%
6 Months	34	90.8%	87.3%-93.3%
12 Months	52	84.3%	79.8%-87.8%
18 Months	62	76.2%	69.5%-81.7%

Figure 9 depicts all-cause survival curve through 18 months for NYHA Class III and IV patients.

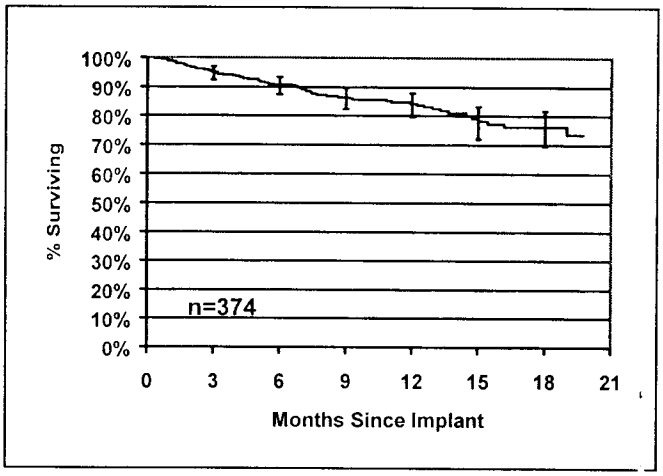


Figure 9. Survival From All-cause Mortality, NYHA Class III and IV

Cardiopulmonary Exercise

Peak VO_2, an indicator of a patient's exercise capacity, was the secondary effectiveness endpoint specifically identified for NYHA Class III and IV patients. **Table 26** and **Figure 10** summarize the peak VO2 data. P-values were based on the median paired difference.

Cardiopulmonary exercise testing was performed on a treadmill using a modified Naughton protocol.[1] Data were analyzed by an independent core lab. **Table 27** summarizes the paired baseline and 6-month cardiopulmonary exercise results for NYHA Class III and IV patients and additional cardiopulmonary exercise data collected in the study. P-values were based on the median paired difference.

Table 26. Peak VO_2 – NYHA III/IV Patients

	Cardiopulmonary Exercise Testing - Results for NYHA Class III and IV Patients		
	Control Group *(CRT OFF)*	**Treatment Group *(CRT ON)***	**P-value**
Peak VO_2 (ml/kg/min)	118 patients with paired data **Baseline:** median 13.4 Mean 13.7 ± 3.9 **6-month:** median 13.5 mean 14.0 ± 4.0 **Median Paired Difference: 0.0**	118 patients with paired data **Baseline:** median 13.4 mean 13.5 ± 3.5 **6-month:** median 14.3 mean 14.4 ± 3.7 **Median Paired Difference: 1.1**	0.03

Figure 10 presents the median change in Peak VO_2 for the control and treatment groups at baseline and 6 month follow up.

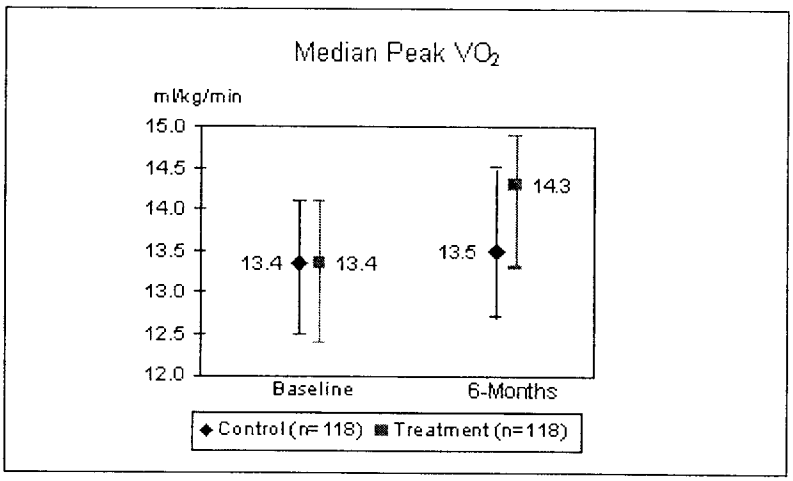


Figure 10. Peak VO_2 Data Summary

[1] Weber KT, Janicki JS. "Cardiopulmonary Exercise Testing: Physiologic Principles And Clinical Applications". WB Saunders Company, 1986.

Table 27. Cardiopulmonary Exercise Data – NYHA III/IV Patients

	Cardiopulmonary Exercise Testing - Results for NYHA Class III and IV Patients		
	Control Group *(CRT OFF)*	**Treatment Group *(CRT ON)***	**P-value**
Exercise Time (sec)	119 patients with paired data **Baseline:** median 494 Mean 518 ± 226 **6-month:** median 435 mean 483± 265 **Median Paired Difference: -9**	118 patients with paired data **Baseline:** median 479 mean 494 ± 479 **6-month:** median 526 mean 537± 219 **Median Paired Difference: 56**	0.0008
Respiratory Exchange Ratio (RER) Max	112 patients with paired data **Baseline:** median 1.14 Mean 1.13 ± 0.10 **6-month:** median 1.09 mean 1.07 ±0.12 **Median Paired Difference: -0.06**	116 patients with paired data **Baseline:** median 1.14 mean 1.13± 0.10 **6-month:** median 1.12 mean 1.11 ± 0.10 **Median Paired Difference: -0.02**	0.01
Ventilatory Exchange (VE)	112 patients with paired data **Baseline:** median 47.3 Mean 48.3 ± 15.2 **6-month:** median 44.7 mean 47.6 ± 16.4 **Median Paired Difference: -1.0**	115 patients with paired data **Baseline:** median 47.8 mean 49.6 ± 17.9 **6-month:** median 48.5 mean 51.0 ± 16.1 **Median Paired Difference: 0.9**	0.13
VE/VCO2	112 patients with paired data **Baseline:** median 41.0 Mean 42.6 ± 10.4 **6-month:** median 40.9 mean 42.2 ± 10.6 **Median Paired Difference: -0.6**	115 patients with paired data **Baseline:** median 39.8 mean 41.8 ± 10.4 **6-month:** median 38.0 mean 39.9 ± 8.9 **Median Paired Difference: -1.0**	0.19
Anaerobic Threshold (AT)	68 patients with paired data **Baseline:** median 8.90 Mean 9.11 ± 2.56 **6-month:** median 9.65 mean 10.30 ± 3.22 **Median Paired Difference: 0.90**	87 patients with paired data **Baseline:** median 9.80 mean 9.61 ± 2.20 **6-month:** median 10.30 mean 10.24 ± 2.02 **Median Paired Difference: 0.70**	0.41

QRS Duration

The change in patients' QRS duration from baseline to 6 months was analyzed to assess the effects of cardiac resynchronization therapy. **Table 28** summarizes the paired baseline and 6-month peak QRS results for NYHA Class III and IV patients. The P-values were based on the median paired difference.

Table 28. QRS Duration – NYHA III/IV Patients

	QRS Duration – Results for NYHA Class III and IV Patients		
	Control Group *(CRT OFF)*	**Treatment Group *(CRT ON)***	**P-value**
Change in QRS duration from baseline through 6-months (ms)	119 patients with paired data **Baseline:** median 160 Mean 162 ± 22 **6-month:** median 160 mean 157 ± 37 **Median Paired Difference: –6**	129 patients with paired data **Baseline:** median 160 mean 163 ± 20 **6-month:** median 150 mean 146 ± 28 **Median Paired Difference: –20**	0.01

Health Care Utilization (Hospitalization)

Emergency room, outpatient, clinic and hospital admission data ware collected in the study. An independent Adverse Events Review Committee reviewed the hospitalization data and adjudicated hospitalizations as either related or not related to heart failure. The analysis included all admissions of at least 24 hours. **Table 29** summarizes the hospitalization (all-cause and heart failure (CHF) related) results for NYHA Class III and IV patients. The P-values were based on the comparison of the number of patients hospitalized in the two groups. For the Length of Stay P-values were based on median number of days.

Table 29. Health Care Utilization – NYHA III/IV Patients

	Health Care Utilization - Results for NYHA Class III and IV Patients		
	Control Group *(CRT OFF)*	**Treatment Group *(CRT ON)***	**P-value**
Number of patients hospitalized	**All-cause:** n=176 79 (44.9%) **CHF related:** n=176 47 (26.7%)	**All-cause:** n=186 75 (40.3%) **CHF related:** n=186 39 (21.0%)	0.40 0.22
Length of Stay (days)	**All-cause:** 134 hospitalizations median; 7 days mean: 8.9 ± 7.8 **CHF related:** 70 hospitalizations median; 6 days mean: 8.0 ± 7.0	**All-cause:** 127 hospitalizations median; 5 days mean: 7.6 ± 8.2 **CHF related:** 54 hospitalizations median; 3 days mean: 6.6 ± 7.4	0.09 0.04

Echocardiographic Parameters

An echocardiographic study was performed to assess the effects of cardiac resynchronization therapy on left ventricular structure and function. Echo data were analyzed by an independent core lab. **Table 30** summarizes the echocardiographic results from baseline and 6 months for NYHA Class III and IV patients. P-values were based on the median paired difference.

Table 30. Echocardiographic Parameters – NYHA III/IV Patients

	Echocardiographic Indices – Results for NYHA Class III and IV Patients		
	Control Group *(CRT OFF)*	**Treatment Group *(CRT ON)***	**P-value**
LV Ejection Fraction (%)	98 patients with paired data **Baseline:** median 21.7 mean 23.3 ± 6.3 **6-month:** median 23.7 mean 24.4 ± 7.9 **Median Paired Difference 1.6**	97 patients with paired data **Baseline:** median 23.5 Mean 24.1 ± 6.7 **6-month:** median 25.5 mean 27.6 ± 8.9 **Median Paired Difference 3.0**	0.06
Mitral Regurgitation (cm^2, jet area)	68 patients with paired data **Baseline:** median 7.1 mean 8.5 ± 7.6 **6-month:** median 5.9 mean 7.2 ± 6.8 **Median Paired Difference –0.5**	68 patients with paired data **Baseline:** median 7.0 mean 7.8 ± 5.9 **6-month:** median 4.9 mean 6.7 ± 5.6 **Median Paired Difference -0.4**	0.98
Cardiac Index (four chamber view)	64 patients with paired data **Baseline:** median 2.45 mean 2.54 ± 0.90 **6-month:** median 2.34 mean 2.48 ± 0.88 **Median Paired Difference -0.02**	65 patients with paired data **Baseline:** 2.38 median mean 2.50 ± 0.78 **6-month:** 2.47 median mean 2.54 ± 0.79 **Median Paired Difference 0.03**	0.89
LV Systolic Volume (cm^3)	94 patients with paired data **Baseline:** median 230 mean 249 ± 88 **6-month:** median 225 mean 241 ± 80 **Median Paired Difference –8**	96 patients with paired data **Baseline:** median 232 mean 242 ± 84 **6-month:** median 212 mean 222 ± 94 **Median Paired Difference –26**	0.04
LV Diastolic Volume (cm^3)	94 patients with paired data **Baseline:** median 302 mean 320 ± 96 **6-month:** median 296 mean 315 ± 86 **Median Paired Difference -5**	96 patients with paired data **Baseline:** median 305 mean 315 ± 90 **6-month:** median 283 mean 298 ± 101 **Median Paired Difference –25**	0.046

	Echocardiographic Indices – Results for NYHA Class III and IV Patients		
	Control Group *(CRT OFF)*	**Treatment Group *(CRT ON)***	**P-value**
LV mass (g)	58 patients with paired data **Baseline:** median 358 mean 367 ± 80 **6-month:** median 348 mean 365 ± 85 **Median Paired Difference – 6**	63 patients with paired data **Baseline:** median 353 mean 359 ± 83 **6-month:** median 339 mean 354 ± 87 **Median Paired Difference – 3**	0.97
Interventricular mechanical delay (IVMD) (ms)	63 patients with paired data **Baseline**: median 31 mean 25.4 ± 44.2 **6-month:** median 25 mean 19.1 ± 34.4 **Median Paired Difference –2**	79 patients with paired data **Baseline:** median 35 mean 29.4 ± 40.8 **6-month:** median 20 mean 15.4 ± 30.1 **Median Paired Difference –18**	0.12
E Wave /A Wave ratio	70 patients with paired data **Baseline:** median 1.22 mean 1.54 ± 1.08 **6-month:** median 1.04 mean 1.45 ± 1.03 **Median Paired Difference -0.03**	90 patients with paired data **Baseline:** median 1.12 mean 1.50 ± 1.08 **6-month:** median 0.99 mean 1.43 ± 1.05 **Median Paired Difference -0.06**	0.82
LV Diameter in Systole	45 patients with paired data **Baseline:** median 6.8 mean 7.0 ± 1.0 **6-month:** median 6.9 mean 6.7 ± 1.0 **Median Paired Difference -0.3**	56 patients with paired data **Baseline:** median 6.4 mean 6.4 ± 1.0 **6-month:** median 6.3 mean 6.1 ± 1.2 **Median Paired Difference -0.2**	0.98
LV Diameter in Diastole	48 patients with paired data **Baseline:** median 7.8 mean 10.0 ± 10.9 **6-month:** median 7.6 mean 7.6 ± 0.9 **Median Paired Difference -0.1**	58 patients with paired data **Baseline:** median 7.5 mean 9.6 ± 11.6 **6-month:** median 7.3 mean 7.3 ± 1.0 **Median Paired Difference -0.3**	0.35

Composite Response

The Heart Failure Clinical Composite Response2 provides an overall assessment of a patient's condition. A patient is defined as "improved" if they decrease NYHA functional class by one or more or if there is a moderate or marked improvement in their global self-assessment score. A patient is defined as "worsened" if they died, were hospitalized for worsening heart failure. A patient is defined as "not changed" if the "improved" or "worsened" conditions are not met.

Table 31 summarizes the composite response results for NYHA Class III and IV patients. The P-value of 0.038 is an overall comparison of the two distributions.

Table 31. Composite Response – NYHA III/IV Patients

	Composite Response – Results for NYHA Class III and IV Patients		
	Control Group *(CRT OFF)*	Treatment Group *(CRT ON)*	P-value
Composite Response	n = 141	n = 150	0.038
Improved	40%	55%	
Unchanged	26%	19%	
Worsened	33%	26%	

At their six-month follow-up patients were asked to rate their global self assessment by answering the following question, "Specifically in reference to your heart failure symptoms, how do you feel today as compared to how you felt before having your InSync® ICD system implanted?"

69% of the treatment patients (n=131) reported at least mild improvement vs. 60% of the control patients (n=121). The overall p-value comparing the two distributions was 0.68. Note: Patients with global assessment scores are a subset of the patients used in the clinical composite response analysis.

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

Spontaneous VT/VF Therapy Efficacy

Table 32 summarizes spontaneous VT/VF therapy efficacy of the InSync® ICD in all patients.

Table 32. Spontaneous VT/VF Therapy Efficacy

Episode Detection Zone	# Patients	Percent Successfully Terminated
FVT	14	98.5%
VF	41	99.2%
VT	50	99.2%
OVERALL	78	99.1%*

*Of the episodes that did not satisfy the device's episode termination criteria, all episodes were eventually terminated.

Comparison of VT/VF Event Rates

Table 33 compares the VT/VF event rate during the randomization period between NYHA Class III and IV control and treatment groups. The P-value of 0.38 compares the number of episodes between the control and treatment group.

Table 33. Comparison of VT/VF Event Rates – NYHA III/IV Patients

	Control Group *(CRT OFF)*	Treatment Group *(CRT ON)*	P-value
Comparison of VT/VF Event Rates	n=177 # patients: 38 (21.6%) Total episodes: 321 Episodes per month: 0.39	n=187 # patients: 35 (18.8%) Total episodes: 356 Episodes per month: 0.41	0.38

ATP Therapy Efficacy With Biventricular Pacing

Table 34 summarizes the efficacy of biventricular and RV-only anti-tachycardia pacing (ATP) therapy efficacy for induced and spontaneous ventricular tachycardia (VT) episodes.

Table 34. ATP Therapy Efficacy With Biventricular Pacing

ATP Site	Rhythm	ATP Success rate	P-value
RV	Induced VT	11/20 (55%)	1.00
RV+LV	Induced VT	12/20 (60%)	
RV	Spontaneous VT	247/294 (84%)	<0.0001
RV+LV	Spontaneous VT	493/523 (94%)	
RV	Spontaneous FVT	67/74 (91%)	0.05
RV+LV	Spontaneous FVT	17/24 (71%)	

Plasma Neurohormone Levels

To characterize the effect of cardiac resynchronization, the following plasma neurohormone levels were assessed: brain natriuretic peptide (BNP), big endothelin (Big ET), epinephrine, norepinephrine and dopamine. Neurohormone data were analyzed by an independent core lab. **Table 35** summarizes the neurohormone results from baseline and 6 months for NYHA Class III and IV patients. P-Values were based on the median paired difference.

Table 35. Plasma Neurohormones – NYHA III/IV Patients

	Results for NYHA Class III and IV Patients		
	Control Group *(CRT OFF)*	**Treatment Group *(CRT ON)***	**P-value**
Brain Natriuretic Peptide (BNP)	70 patients with paired data **Baseline:** median 478.5 Mean 889.8 ± 1190.0 **6-month:** median 357.0 mean 799.9 ± 1249.6 **Median Paired Difference: -2.8**	83 patients with paired data **Baseline:** median 450.0 mean 813.0 ± 1063.6 **6-month:** median 320.0 mean 568.9 ± 708.2 **Median Paired Difference: -38.0**	0.41
Dopamine	73 patients with paired data **Baseline:** median 9.0 Mean 17.2 ± 20.9 **6-month:** median 9.0 mean 19.03 ± 26.3 **Median Paired Difference: 0.0**	79 patients with paired data **Baseline:** median 9.0 mean 13.9 ± 8.8 **6-month:** median 9.0 mean 14.0 ± 10.7 **Median Paired Difference: 0.0**	0.56
Norepinephrine	74 patients with paired data **Baseline:** median 454.5 Mean 516.9 ± 382.3 **6-month:** median 442.5 mean 478.0 ± 289.1 **Median Paired Difference: -38.0**	80 patients with paired data **Baseline:** median 331.0 mean 376.5 ± 263.1 **6-month:** median 339.5 mean 410.2 ± 273.0 **Median Paired Difference: 10.5**	0.24
Epinephrine	73 patients with paired data **Baseline:** median 25.0 Mean 53.2 ± 109.9 **6-month:** median 17.0 mean 23.6 ± 21.9 **Median Paired Difference: -4.0**	79 patients with paired data **Baseline:** median 16.0 mean 31.7 ± 43.6 **6-month:** median 17.0 mean 23.2 ± 18.5 **Median Paired Difference: 0.0**	0.03
Big Endothelin	77 patients with paired data **Baseline:** median 14.3 Mean 26.6 ± 34.9 **6-month:** median 16.4 mean 21.3 ± 23.0 **Median Paired Difference: –0.5**	88 patients with paired data **Baseline:** median 12.3 mean 19.5 ± 21.6 **6-month:** median 11.0 mean 18.1 ± 20.0 **Median Paired Difference: -0.5**	0.88

Attain LV Lead R-Wave Amplitude Sensing

The sensing performance of the LV leads was assessed by evaluating the R-wave amplitudes from the Model 4189*, 2187 and 2188 leads. **Table 36** summarizes the Model 4189* LV lead mean R-wave amplitude data and the two-sided 95 percent confidence intervals on all patients receiving a Model 4189* lead.

Table 36. Model 4189 R-wave Amplitude Data

Visit	N	Mean (mV)	Two-sided 95% CI
Implant	444	12.5 ± 4.6	12.1-13.0
Pre-hospital Discharge	454	12.6 ± 4.6	12.2-13.0
1 Month	435	13.6 ± 4.5	13.1-14.0
3 Months	412	13.8 ± 5.3	13.3-14.3
6 Months	317	13.7 ± 5.4	13.1-14.3
12 Months	130	14.2 ± 5.7	13.2-15.2
18 Months	37	14.0 ± 5.4	12.2-15.8

Table 37 summarizes the Model 2187 and 2188 LV lead R-wave amplitude data from all patients receiving a Model 2187 or 2188 lead.

Table 37. Model 2187/2188 R-wave Amplitude Data

Visit	N	Mean (mV)	Two-sided 95% CI
Implant	88	12.7 ± 4.9	11.7-13.8
Pre-hospital Discharge	90	12.4 ± 4.7	11.4-13.3
1 Month	85	13.3 ± 5.2	12.1-14.4
3 Months	81	13.8 ± 4.8	12.7-14.8
6 Months	63	13.5 ± 5.7	12.1-15.0
12 Months	30	13.9 ± 5.1	12.0-15.8
18 Months	18	12.0 ± 4.2	10.0-14.1

* These data are included for completeness in reporting the results of the clinical study. The 4189 lead is not currently market approved in the U.S.

8. CS Dissections and Perforations

Table 38 summarizes the adverse events (complications and observations) related to coronary sinus dissections and perforations in all patients. Of the 33 patients with CS dissection/perforation, there were six deaths (82, 263, 384, 415, 436 and 509 days post-implant). None of the deaths was reported as related to the dissection or perforation. Two of the patients that died received the InSync® ICD system, and four of the patients did not receive the InSync® ICD system (two received the GEM DR and two received the GEM III DR).

Table 38. CS Dissections and Perforations

Event	Complications (# pts.)	Observations (# pts.)	Total (# pts.)
CS dissection	15	9	24
Cardiac vein/ CS Perforation	9	0	9
Total	**24**	**9**	**33**

9. LV Lead Placement

Table 39 summarizes information related to LV lead placement and positioning. The majority of LV leads (72%) were positioned in lateral or posterior-lateral cardiac veins.

Table 39. Final LV Lead Placement and Position

Vessel/Location	Basal	Mid	Apical	Not indicated	Total
Lateral (marginal) cardiac	6%	31%	2%	< 1%	**39%**
Posterior-lateral cardiac	4%	25%	4%	< 1%	**33%**
Anterior cardiac	5%	10%	1%	< 1%	**17%**
Posterior cardiac	< 1%	3%	1%	< 1%	**5%**
Middle cardiac	< 1%	2%	1%	< 1%	**4%**
Great cardiac	< 1%	< 1%	< 1%	< 1%	**1%**
Not indicated	< 1%	< 1%	< 1%	1%	**1%**
Total	**16%**	**72%**	**10%**	**2%**	

C. Confirmation of Biventricular Pacing and ICD Function

To confirm proper biventricular pacing and ICD function, percent ventricular pacing, biventricular capture during cardiopulmonary exercise (CPX), VT/VF detection efficacy and VF detection time were assessed. To assess percent ventricular pacing, the percentage of time that patients were paced was determined from the pace/sense counters of the device at the 6- month follow-up. Electrocardiograms (ECGs) with biventricular pacing ON from the 6-month follow-up visit were compared to 12-lead ECGs at peak heart rate during the 6-month CPX test to confirm that biventricular pacing and capture were maintained. The incidence of inappropriate VT/VF episodes was analyzed to confirm that there is nothing unique to a CHF ICD population that would increase the risk of inappropriate detection. Analysis of VF detection times in InSync® ICD treatment vs. control patients was done to demonstrate that VF detection is not compromised by the presence of the LV lead and biventricular pacing.

1. Percent Ventricular Pacing

The percentage of time patients were paced during their randomized period was determined from each patient's six-month visit, using the pace/sense counters over the lifetime of the device. All NYHA Class III and IV randomized patients who did not cross over into the other group (OFF to ON or ON to OFF) are included (116 control and 125 treatment patients). Save-to-disk files were not available for 6 control and 7 treatment patients.

In **Figure 11**, the left-hand graph indicates that greater than 90% of the treatment patients received ventricular pacing more than 90% of the time, and conversely, greater than 90% of the control patients received no ventricular pacing more than 90% of the time. The right-hand graph indicates that more than 85% of the treatment patients had capture margins greater than or equal to 100%.

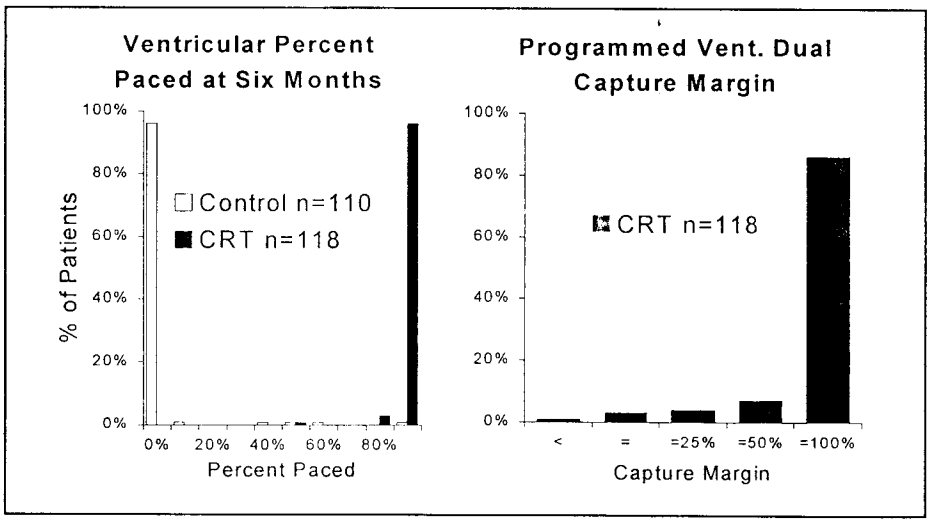
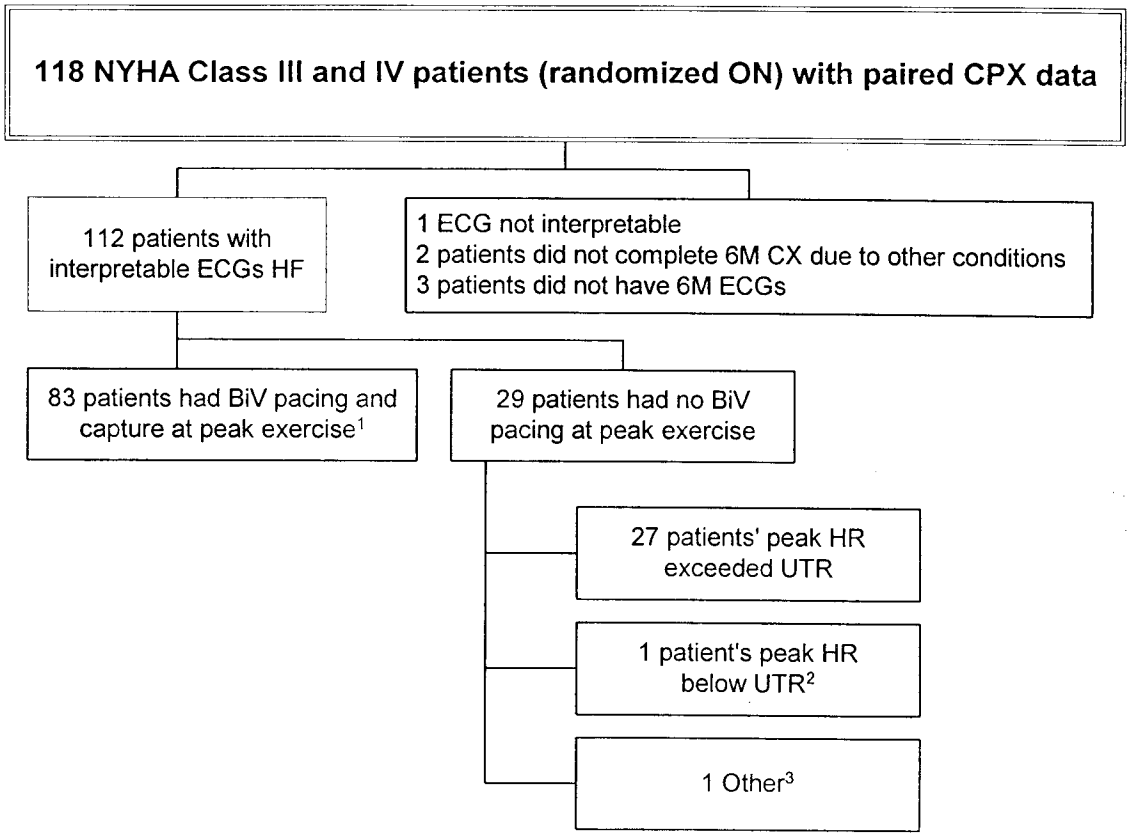


Figure 11. Biventricular Pacing and Capture Margin

2. Biventricular Capture During Exercise

NYHA Class III and IV patients with biventricular pacing randomized ON and with paired baseline and 6-month cardiopulmonary exercise (CPX) data (n=118) were included in the analysis. Of these 118 patients, 112 had interpretable 12-lead electrocardiograms (ECGs). ECGs with biventricular pacing ON from the 6-month follow-up visit (just prior to CPX testing) were compared to 12-lead ECGs at peak heart rate during the 6-month CPX test to confirm that biventricular pacing and capture was maintained.

Of the 112 NYHA Class III and IV patients with paired baseline and 6-month CPX data and interpretable 6-month pre- and peak exercise 12-lead ECGs, 83 patients had biventricular pacing at peak exercise. All of these patients maintained biventricular capture at peak exercise. Twenty-seven (27) patients lost biventricular pacing at maximum exercise due to the intrinsic rate exceeding the programmed Upper Tracking Rate (UTR). Two patients did not maintain pacing due to other unique rhythm/programming conditions described in **Figure 12**. There were no cases of LV-only or RV-only capture during biventricular pacing at any pacing rate.



[1]UTR programmed to a higher rate than their "normal" UTR setting during the CPX test for 2 patients.
[2]No biventricular pacing due to PVC initiated Vs-Ar-Vs-Ar... pattern.
[3]No biventricular pacing due to an intrinsic PR interval less than the programmed SAV interval at peak exercise (Rate Adaptive AV programmed OFF).

Figure 12. Biventricular Capture During Exercise Testing

3. VT/VF Detection Efficacy

The incidence of inappropriate VT/VF episodes was similar in the InSync® ICD study population as compared to the Gem DR study population (21.3% vs. 21.9%[3]). The reasons for the inappropriate detections were similar, and resulted from a similar proportion of atrial fibrillation or flutter as compared to 1:1 SVTs. None of the inappropriate detections in the InSync® ICD study were related to biventricular pacing or the LV lead, confirming that there is nothing unique to a CHF ICD population that would increase the risk of inappropriate detection. There were no VT/VF episodes for which therapy was inappropriately withheld. The InSync® ICD with its left ventricular lead and possibility of biventricular pacing did not adversely affect the device's ability to detect VT/VF or appropriately withhold VT/VF therapy or delay detection time. 47% of the 135 episodes were treated with at least one shock. No deaths, hospitalizations or worsening of heart failure were attributed to inappropriate shocks.

Table 40. Classification of VT/VF Episodes, Gem DR vs. InSync® ICD

	GEM DR[4]	InSync® ICD
Total episodes in VT/VF log	3945 (278 pts)	950 (100 pts)
Appropriate VT/VF episodes	3488 (232 pts)	815 (85 pts)
Inappropriate VT/VF episodes: **GEE adjusted rate:**	457 (86 pts) (12%) 21.9%	135 (31 pts) (14%) 21.3%
- Atrial or RV sensing related	93 (20%)	28 (21%)
- Ventricular rate during AF in VF zone	44 (10%)	5 (4%)
- SVT Criteria programming (PR Logic)	68 (15%)	53 (39%)
- Detection algorithm characteristics	252 (55%)	49 (36%)
Total patients	933	371
Average follow-up time (months)	3.9	7.9

[3] Lee, EW and Dubin, N. Estimation and Sample Size Considerations for Clustered Binary Responses. *Statistics in Medicine*, Vol 13, 1241-52 (1994).

[4] Wilkoff, BL, et al. Critical Analysis of Dual-Chamber Implantable Cardioverter-Defibrillator Arrhythmia Detection: Results and Technical Considerations. *Circulation*, Vol 103, 381-386 (2001).

4. VF Detection Time

Analysis of VF detection times in InSync® ICD treatment vs. control patients demonstrate that VF detection is not compromised by the presence of the LV lead and biventricular pacing.

When the number of intervals to detect VF (VF NID) was programmed to 12/16 intervals, the mean VF detection time for the treatment group was 3.8 seconds, and the mean detection time for the control group was 3.4 seconds. These data demonstrate that there was no delay in detection time compared to the theoretical time to detect (P=0.07) described below:

- VF at a rate of 280 ms *x* 12 intervals to detect = 3360 ms = 3.4 seconds

When the number of intervals to detect VF (VF NID) was programmed to 18/24 intervals, the mean VF detection time for the treatment group was 4.9 seconds, and the mean detection time for the control group was 5.3 seconds. These data demonstrate that there was no delay in detection time compared to the theoretical time to detect described below:

- VF at a rate of 280 ms *x* 18 intervals to detect = 5040 ms = 5.0 seconds

Table 41. VF Detection Times in Treatment and Control Patients During the Randomization Period

Randomization Assignment	VF NID = 12/16			VF NID = 18/24		
	N	Mean Vent. Cycle Length (ms)	Mean Detection Time (sec)	N	Mean Vent. Cycle Length (ms)	Mean Detection Time (sec)
Control	51	272	3.4	14	278	5.3
Treatment	42	283	3.8	28	256	4.9
p-value			0.07			0.84

D. Programmed Parameters

Table 42 shows how Upper Tracking Rate was programmed in NYHA Class III and IV treatment patients at the end of the randomization period (6 months).

Table 42. Programmed Upper Tracking Rate (UTR)

Programmed Value (ppm)	% of Patients
<120	5%
120	49%
125-130	11%
136-140	33%
>140	2%

Table 43 demonstrates that the majority of NYHA Class III and IV treatment patients were able to maintain over 90% ventricular pacing regardless of their programmed Upper Tracking Rate.

Table 43. Percent of Ventricular Pacing in Treatment Group By Programmed UTR

% Paced	UTR < 120 (% of patients)	UTR = 120 (% of patients)	UTR > 120 (% of patients)
<90%		6%	2%
90-94%		21%	16%
95-99%	100%	70%	71%
100%		4%	11%

E. Gender Bias Analysis

A sub-group analysis was performed to evaluate the association of gender with the primary effectiveness endpoints (NYHA functional class, quality of life and 6-minute hall walk distance). Based on this analysis, gender appears to be associated with an improvement in QOL scores, while gender was not associated with NYHA class or 6-minute hall walk distance. The InSync® ICD study enrolled 75 percent males and 25 percent females. There was no selection bias based on gender.

F. Conclusions Drawn from the Clinical Study

1. Safety

The InSync® ICD pulse generator met the primary and secondary safety endpoints. Results were within protocol specified performance criteria for the rate of severe device related adverse events and operative mortality. The study additionally demonstrated that the ICD portion of the InSync® ICD was not adversely affected by the addition of cardiac resynchronization as shown by adequate ventricular fibrillation detection times, antitachycardia pacing (ATP) conversion efficacy, and no increase in the amount of inappropriate ICD therapies.

There was no difference in the mortality, number of hospitalizations, or incidence of malignant ventricular arrhythmias between the control and the treatment group.

2. Effectiveness

The InSync® ICD cardiac resynchronization system demonstrated a six- month improvement in quality of life and a reduction in NYHA functional class which were two of the three primary endpoints of the study. The third endpoint, six-minute hall walk, showed no difference between the treatment and the control group. Given this, results from the secondary endpoint of cardiopulmonary exercise testing were used to show a significant improvement in peak VO_2 in the treatment group. Additional supporting evidence included an improvement in heart failure status as measured by a composite response assessment.

XI. Panel Recommendation

FDA's advisory panel met on March 5, 2002 and voted 6 to 5 for approvable with conditions. The conditions that were recommended by the Panel included a post-approval study to obtain longer-term information on mortality and performance of the device. They also requested information regarding the administrative censoring of patients, including documentation of the explicit original intent of the agreed upon sample size of the study. Additional concerns were raised regarding device programming and interaction issues between the ICD and CRT portions of the device. The Panel requested that questions that were raised on this issue be resolved by submitting

additional information to the Agency. There were significant concerns raised about the safety profile of the Attain Model 4189*.

CDRH Decision

FDA found Medtronic's facilities in compliance with the Quality System Requirements (21 CFR part 820).

FDA requested the additional information that was discussed at the panel meeting. The approval decision was based on reviewing the entire cohort of class III/IV patients that were enrolled in the study. Because of the subjective nature of the successful primary endpoints of the study, FDA specifically used data from the supporting secondary endpoints to determine a reasonable level of effectiveness of the device. Specifically, data from the cardiopulmonary exercise testing was used to demonstrate a functional improvement in the treatment group. Subgroup analysis did not delineate a specific group of patients that benefits more from this device.

Data were provided to the agency regarding device performance that included ICD/CRT interaction, percentage of time paced as well as other programming issues that were used to further define the limitations of the device. Lead performance data in the clinical trial did not support reasonable assurance of the safety and effectiveness of the 4189 lead.

The conditions of approval include a 3-year evaluation of mortality and chronic system performance, including adverse clinical events, on 1000 patients to assess the long-term safety of the device. Physicians will be required to undergo training by the sponsor prior to implanting the system.

FDA issued an approval order for P010031 on June 26, 2002. This decision was based on a complete dataset as well as additional supporting evidence regarding device functionality.

XII. Approval Specifications

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

* These data are included for completeness in reporting the results of the clinical study. The 4189 lead is not currently market approved in the U.S.