Chapter 1 - Prescribing the InSync Device

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Device Description

The implantable InSync Model 8040 device is an atrial synchronous, biventricular pacing, cardiac resynchronization device. In addition to an atrial channel for atrial pacing and sensing, the InSync device has two ventricular channels to provide simultaneous biventricular pacing and sensing from two ventricular leads. The InSync device has activity-based rate responsive pacing capabilities.

Three ports in the lead connector accommodate one IS-1 atrial lead and two IS-1 ventricular leads.[1] The two ventricular channels are connected in parallel so that a single set of programmable ventricular pacing and sensing parameters controls both ventricular leads. Single chamber and dual chamber pacing modes such as DDDR are not affected by the biventricular pacing capability.

The hermetically sealed titanium shield contains:

- a lithium-iodine battery,
- a piezoelectric crystal sensor for detection of body activity, and
- integrated circuits to control device timing sequences and output characteristics, which are non-invasively programmable and permit transmission of data about their operation.

The InSync device is programmed with a Medtronic Model 9790 series programmer loaded with Model 9980 software.

1. IS-1 refers to an International Connector Standard (see Document No. ISO 5841-3; 1992) whereby pulse generators and leads so designated are assured of meeting the electrical and mechanical parameters specified in the IS-1 International Standard.

Indications and Usage

The InSync Model 8040 device is 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 ≤ 35% and a QRS duration ≥ 130 ms.

Contraindications

Asynchronous pacing is contraindicated in the presence (or likelihood) of competitive paced and intrinsic rhythms.

Unipolar pacing is contraindicated in patients with an implanted defibrillator or cardioverter-defibrillator (ICD) because it may cause unwanted delivery or inhibition of defibrillator or ICD therapy.

Warnings

Programming and Device Operation

- **Atrial tracking modes.** Do not use atrial tracking modes in those patients with chronic refractory atrial tachyarrhythmias. Tracking of atrial arrhythmias could result in VT or VF.
- **Atrial only modes.** Do not use atrial only modes in the following patients:
  - patients with heart failure because such modes do not provide cardiac resynchronization.
  - patients with impaired AV nodal conduction because ventricular capture cannot be assured.
- **Temporary high-rate stimulation.** Temporary high-rate stimulation of the ventricles could result in ventricular tachycardia or fibrillation. Application of temporary high-rate stimulation should be performed only under careful patient monitoring and control.
- **Single chamber hysteresis.** For heart failure patients, the use of single chamber hysteresis will not provide cardiac resynchronization.

Warnings (continued)

- **Ventricular Sensing.** Ventricular sensitivity should be programmed to the highest setting (lowest sensitivity) that will provide ventricular sensing with adequate sensing margin. Left ventricular lead dislodgement, to a position near the atria, can result in atrial oversensing and ventricular inhibition. (See "Sensitivity" on page 3-16 for more information.)
- **Lead Monitor.** Do not program Lead Monitor on prior to implanting the device in the patient. With no leads connected, lead impedance is infinitely high and determined by the device to be out-of-range. If the device has been programmed to switch polarity, the resulting unipolar condition will not support pacing until the device is placed in the pocket, thereby completing the circuit.
- **Elective Replacement Indicator (ERI).** ERI results in the device switching to VVI pacing at 65 ppm. In this mode, patients may experience loss of cardiac resynchronization therapy and/or loss of AV synchrony.

  For this reason, the device should be replaced prior to ERI being set. (See "Elective Replacement Indicator" on page 4-7 for more information.)
- **Full electrical reset** is indicated by VVI pacing at a rate of 65 ppm without the elective replacement indicator set. In this mode, patients may experience loss of cardiac resynchronization therapy and/or loss of AV synchrony.

  If there is concern that reset occurred, patients should be seen by their physicians immediately. (See "Electrical Reset" on page 4-7 for more information.)

Warnings (continued)

Pacemaker Dependent Patients

- **Diagnostic modes.** Never program diagnostic modes (ODO, OVO, and OAO) for pacemaker-dependent patients. For such patients, use the programmer's inhibit function for brief interruption of outputs.
- **Electrogram (EGM).** An EGM of the patient's intrinsic activity should be obtained with care since the patient is without pacing support when using the programmer's inhibit function.
- **Polarity override.** Overriding the bipolar verification prompt with Bipolar Polarity when a Unipolar lead is connected **results in no pacing output.** (See "Pacing and Sensing Operations" on page 3-14 for more information.)

  Do not override bipolar polarity confirmation for an implanted lead. The override is intended only as a means to program the device for bipolar polarity before lead connection.
- **Loss of capture during threshold margin test** (TMT) at a 25% reduction in pulse width indicates that the stimulation safety margin is inadequate. Immediately perform a pacing threshold test (Auto Threshold) and reprogram outputs to establish a 2:1 voltage safety margin. (See "Magnet Operation" on page 4-6 for more information.)
- **Ventricular safety pacing** should always be programmed On for pacemaker-dependent patients. Ventricular safety pacing prevents ventricular systole due to inappropriate inhibition of ventricular pacing caused by cross talk or ventricular asystole. (See "Ventricular Safety Pacing" on page 3-21 for more information.)

Warnings (continued)

Medical Therapy

- **An implantable defibrillator** may be implanted concomitantly with an InSync device provided implant protocols are followed for device and defibrillator lead placement and device configuration. See **"Implantable Defibrillators" on page 2-11** for more information.
  - Use only bipolar pacing with these patients. In some cases, pacing in the unipolar configuration may cause the defibrillator either to deliver inappropriate therapy or to withhold appropriate therapy.
  - Do not program Lead Monitor with the optional polarity Switch because the monitor automatically reprograms the selected lead(s) to unipolar polarity when an out-of-range lead impedance is detected.
  - Do not program Transtelephonic Monitor On because the pacing polarity is temporarily set to unipolar when the magnet is applied.

- **Diathermy.** People with metal implants such as pacemakers, implantable cardioverter defibrillators (ICDs), and accompanying leads should not receive diathermy treatment. The interaction between the implant and diathermy can cause tissue damage, fibrillation, or damage to the device components, which could result in serious injury, loss of therapy, and/or the need to reprogram or replace the device.
- **Magnetic resonance imaging (MRI).** Patients with an InSync device who are subjected to MRI should be closely monitored and the programmed parameter settings should be verified upon cessation of MRI. (See "Magnetic Resonance Imaging (MRI)" on page 2-15 for more information.)
- **Electrosurgical cautery** could induce ventricular arrhythmias and/or fibrillation, or may cause asynchronous or inhibited device operation. If the use of electrocautery is necessary, the current path and ground plate should be kept as far away from the device and leads as possible. (See "Electrosurgical Cautery" on page 2-13 for more information.)

Precautions

Storage and Resterilization

The InSync device is intended for **single use only**. Do not resterilize and reimplant explanted devices.

The chart below gives recommendations on handling and storing the package. Medtronic has sterilized the device with ethylene oxide prior to shipment. **Resterilizing** the device is necessary if the seal on the sterile package is broken. Resterilization does not affect the "Use Before" date.

Handling and Storage: Acceptable	Unacceptable
Store and transport within Environmental Temperature limits: 0°F (- 18°C) to + 131°F (55°C). Note: A full or partial electrical reset condition may occur at temperatures below 0°F (- 18°C). See "Electrical Reset Parameter Settings" on page S-6.	Do not implant the device if it has been dropped on a hard surface from a height of 12 inches (30 cm) or more.

Resterilization: Acceptable	Unacceptable
Resterilize if the sterile package seal is broken. Place the device in an ethylene oxide permeable package and resterilize with ethylene oxide. Allow the device to aerate ethylene oxide residues. Refer to sterilizer instructions for details. Use an acceptable method for determining sterility, such as biological indicators.	Do not resterilize the device or the torque wrench using: ■ an autoclave, ■ gamma radiation, ■ organic cleaning agents, e.g., alcohol, acetone, etc., or ■ ultrasonic cleaners. Do not exceed 140°F (60°C) or 17 psi (103 kPa) when sterilizing. Do not resterilize the device more than two times.

Precautions (continued)

Lead Evaluation and Lead Connection

- **Connector compatibility.** Do not use any lead with this device without first verifying connector compatibility. Using incompatible leads can damage the connector or result in a leaking or intermittent connection.
- **Pacing and sensing safety margins.** Consider lead maturation when choosing pacing amplitudes, pulse widths, and sensing levels. (See "Device Programming Recommendations" on page 3-24.)
- **Hex wrench.** Do not use a hex wrench with a blue handle or a right-angled hex wrench. These wrenches have torque capabilities greater than is designed for the lead connector. (See "Connecting Leads to the InSync Device" on page 2-4 for lead connection instructions.)

Programming and Device Operation

- **Shipping values.** Do not use shipping values for pacing amplitude and sensitivity without verifying that they provide adequate safety margins for the patient.
- **Constant current devices.** Do not use constant current devices (such as the Medtronic Model 5880A, 5375, 5348, or 5346 External Pacemaker) to test lead performance. They may damage the InSync device's constant voltage output circuits.
- **Crosstalk** occurs in dual chamber systems when atrial pacing output pulses are sensed by the ventricular lead. Crosstalk results in self-inhibition and is more likely to occur at high sensor-driven pacing rates, high atrial amplitudes, and wide atrial pulse widths. To prevent self-inhibition caused by crosstalk, program Ventricular Safety Pacing (VSP) On or lengthen the Ventricular Blanking period.

Precautions (continued)

- **AV intervals.** For consistent ventricular pacing, the programmed setting for PAV and SAV must be less than the patient's intrinsic AV delay.
- **Slow retrograde conduction,** especially with conduction time greater than 400 ms, may induce pacemaker-mediated tachycardia (PMT).
- **PMT intervention.** Even with the feature turned On, PMTs may still require clinical intervention such as device reprogramming, magnet application, drug therapy, or lead evaluation. (See ""PMT Intervention" on page 3-19 for more information.)
- **Lead Monitor.** If the Lead Monitor detects out-of-range lead impedance, investigate lead integrity more thoroughly.
- **Mode Switch** - Mode Switch should be programmed OFF unless the patient has a history of atrial fibrillation. Mode Switch automatically selects values for PVARP and Rate Adaptive AV that may not be optimal for providing cardiac resynchronization.

Precautions (continued)

Rate Increases

- **External pressure** on the device may cause an increase in the pacing rate up to the programmed Upper Activity Rate in rate responsive modes. This might occur when the patient is lying on the device while sleeping, or by pressing the programming head over the device. (See "Device Programming Recommendations" on page 3-24 for more information.)
- **Twiddler's syndrome**, i.e., patient manipulation of the device after implant, may cause the pacing rate to increase temporarily if the device is programmed to a rate responsive mode.
- **Muscle stimulation**, e.g., due to unipolar pacing, may result in pacing rates up to the Upper Activity Rate in rate responsive modes.

Unipolar Sensing

Continuous myopotentials cause reversion to asynchronous operation when sensed in the refractory period. Sensing of myopotentials is more likely when atrial sensitivity settings of 0.5 through 1.0 mV and ventricular sensitivity settings of 1.0 and 1.4 mV are programmed.

Environmental and Medical Therapy Hazards

Hospital and Medical Environments

- **Caution: External defibrillation** may damage the device or may result in temporary and/or permanent myocardial damage at the electrode-tissue interface as well as temporary or permanent elevated pacing thresholds. Attempt to minimize current flowing through the device and lead system by following these precautions when using external defibrillation:
  - Position defibrillation paddles as far from the device as possible (minimum of 5 inches [13 cm]). Attempt to minimize current flowing through the device and leads by positioning the defibrillation paddles perpendicular to the implanted device/lead system.
  - Use the lowest clinically appropriate energy output (watt seconds).
  - Confirm device function following any defibrillation.
- **Caution: High radiation sources** such as cobalt 60 or gamma radiation should not be directed at the implanted device. If a patient requires radiation therapy in the vicinity of the device, place lead shielding over the device to prevent radiation damage and confirm its function after treatment.
- **Caution: Lithotripsy** may permanently damage an InSync device if the device is at the focal point of the lithotripsy beam. If lithotripsy must be used, program the device to a single chamber non-rate responsive mode (VVI/AAI or VOO/AOO) prior to treatment; and keep the device at least 1 to 2 inches (2.5 to 5 cm) away from the focal point of the lithotripsy beam.

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- **Caution: Radiofrequency ablation** procedure in a patient with an InSync device may cause any of the following:
  - Asynchronous pacing above or below the programmed rate.
  - Reversion to an asynchronous operation.
  - Device electrical reset.
  - Premature triggering of the elective replacement indicator.

  RF ablation risks may be minimized by:

  1. Programming a non-rate responsive, asynchronous pacing mode prior to the RF ablation procedure.
  2. Avoiding direct contact between the ablation catheter and the implanted lead or the device.
  3. Positioning the ground plate so that the current pathway does not pass through or near the device system, i.e., place the ground plate under the patient's buttocks or legs.
  4. Having a Medtronic programmer available for temporary pacing.
  5. Having defibrillation equipment available.
- **X-Ray and Fluoroscopy.** Tests on devices similar to the InSync device has shown that exposure to diagnostic X-ray or fluoroscopic radiation should not affect the device.

Home and Occupational Environments

Patients should be directed to exercise reasonable caution in avoidance of devices which generate a strong electric or magnetic field. If the implanted device inhibits or reverts to asynchronous operation at the programmed pacing rate or at the magnet rate while in the presence of electromagnetic interference (EMI), moving away from the source or turning it off will allow the device to return to its normal mode of operation.

High voltage power transmission lines

Caution: High voltage power transmission lines may generate enough EMI to interfere with device operation if approached too closely.

Communication equipment

Caution: Communication equipment such as microwave transmitters, linear power amplifiers, or high-power amateur transmitters may generate enough EMI to interfere with device operation if approached too closely.

Home appliances

Caution: Home appliances which are in good working order and properly grounded do not usually produce enough EMI to interfere with device operation. There are reports of pacemaker disturbances caused by electric hand tools or electric razors used directly over the device implant site.

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Commercial electrical equipment

Caution: Commercial electrical equipment such as arc welders, induction furnaces, or resistance welders may generate enough EMI to interfere with device operation if approached too closely.

Electronic Article Surveillance (EAS)

Caution: Electronic Article Surveillance (EAS) equipment such as retail theft prevention systems may interact with devices. Patients should be advised to walk directly through and not to remain near an EAS system longer than is necessary.

Cellular Phones

The InSync device has been tested to the frequency ranges used by the cellular phones included in Table 1-1. Based on this testing, this device should not be affected by the normal operation of such cellular phones.

This InSync device contains a filter that allows usage, without interaction, of all cellular phones having one of the transmission technologies listed in Table 1-1. These transmission technologies represent most of the cellular phones in use worldwide. Patients can contact their local cellular phone service provider to confirm that the provider uses one of these technologies.

Table 1-1. Cellular Phone Transmission Technologies

Transmission Technology	Frequency Range
Analog	
FM (Frequency Modulation)	824 - 849 MHz
Digital TDMA[a] North American Standards	
TDMA - 11 Hz	806 - 821 MHz
NADC[b] (TDMA - 50 Hz)	824 - 849 MHz
PCS[c] 1900	1850 - 1910 MHz
Digital TDMA[a] International Standards	
GSM[d]	880 - 915 MHz
DCS[e] 1800	1710 - 1785 MHz
Digital CDMA	
CDMA - DS[f]	824 - 849 MHz

[a] Time Division Multiple Access
[b] North American Digital Cellular
[c] Personal Communication System
[d] Global System for Mobile Communications
[e] Digital Cellular System
[f] Code Division Multiple Access - Direct Sequence

Adverse Events

Observed Adverse Events

A prospective, randomized, controlled, multi-center trial (refer to Figure 1-1) conducted at 44 participating sites (39 in the United States and 5 in Canada) compared the effectiveness results for patients receiving InSync system cardiac resynchronization therapy (treatment group) to the control group (patients were implanted with the InSync system but did not receive cardiac resynchronization therapy).

Table 1-2 provides information on all reported events during the randomization period. There were 532 patients randomized; 269 patient were randomized to the control group, and 263 patients were randomized to the treatment group. During the randomized period, there were a total of 879 reported adverse events. Of these, 239 were classified as complications, 607 as observations, and 33 deaths.

Potential Adverse Events

Adverse events (in alphabetical order), including those reported in Table 1-2, associated with the use of transvenous leads and pacing systems include:

- Cardiac dissection
- Cardiac perforation
- Cardiac tamponade
- Coronary sinus dissection
- Death
- Endocarditis
- Erosion through the skin
- Fibrillation or other arrhythmias
- Heart block

- Heart wall or vein wall rupture
- Hematoma/seroma
- Infection
- Muscle or nerve stimulation
- Myocardial irritability
- Myopotential sensing
- Nerve and muscle stimulation
- Pericardial effusion
- Pericardial rub
- Pneumothorax
- Rejection phenomena (local tissue reaction, fibrotic tissue formation, pulse generator migration)
- Threshold elevation
- Thrombolytic and air embolism
- Thrombosis
- Transvenous lead-related thrombosis
- Valve damage (particularly in fragile hearts)

There was a total of 74 deaths in the study. The cause of deaths and study periods when the deaths occurred are indicated in Table 1-2A.

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Table 1-2. Adverse Events During the Randomization Period
3 month randomization period study patients N = 71,
6 month randomization period study patients N = 461
(879 events in 532 randomized patients, 4769 total device months)

	Total Number Of Events/ (Number of Patients)	% Comps (Patient) N=532 Patients[a]	% Comps/ Device Month 4769 months[b]	% Obs/ Patient N=532 Patients[c]	% Obs/ Device Month 4769 months[d]
Total Adverse Events	879 (414)	39.3 (209)	5.7 (272)	72.0 (385)	12.7 (607)
8040 Generator Events					
Migration (1) Sense Iseue (1) PMT (1)	3 (3)	0.2 (1)	0.02 (1)	0.4 (2)	0.04 (2)
LV Lead Related Observation Events					
Elevated Thresholds	17 (17)	0	0	3.2 (17)	0.4 (17)
Extra cardiac stimulation (7) Dislodgement (1) Hypotension IV fluids (1)	9 (8)	0.2 (1)	0.02 (1)	1.3 (7)	0.2 (8)
LV Lead Reposition Events Due to:					
Dislodgment	14 (10)	1.9 (10)	0.3 (14)	0	0
Due to High Thresholds	10 (10)	1.9 (10)	0.2 (10)	0	0
Due to Extra Cardiac Stim (3) Unable to Capture (1) Hypotension (1)	6 (5)	0.9 (5)	0.1 (6)	0	0

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3 month randomization period study patients N = 71,
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(879 events in 532 randomized patients, 4769 total device months)

	Total Number Of Events/ (Number of Patients)	% Comps (Patient) N=532 Patients[a]	% Comps/ Device Month 4769 months[b]	% Obs/ Patient N=532 Patients[c]	% Obs/ Device Month 4769 months[d]
LV Lead Replacement Events Due to:					
Due to High Thresholds	6 (6)	1.1 (6)	0.1 (6)	0	0
Dislodgement (9) Extra Cardiac Stim(1) UTC(1)	11 (11)	2.1 (11)	0.2 (11)	0	0
RV Lead Related Events					
Repositions/ Replacement (4) Invasive Evaluation (1)	6 (6)	0.9 (5)	0.1 (5)	0.2 (1)	0.02 (1)
RA Lead Related Events					
Repositions/Replacement (9) Elevated Thresholds (1)	10 (10)	1.7 (9)	0.2 (9)	0.2 (1)	0.02 (1)

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3 month randomization period study patients N = 71,
6 month randomization period study patients N = 461
(879 events in 532 randomized patients, 4769 total device months)

	Total Number Of Events/ (Number of Patients)	% Comps (Patient) N=532 Patients[a]	% Comps/ Device Month 4769 months[b]	% Obs/ Patient N=532 Patients[c]	% Obs/ Device Month 4769 months[d]
Other Lead Events	7 (7)	0.2 (1)	0.02 (1)	1.1 (6)	0.1 (6)
LV/RV/RA Lead Related Extra Cardiac Stim (1) LV/RV Lead Related Extra Cardiac Stim (2) Inadequate P/R (1) Pain with pacing (1) Elevated threshold (1) RV/RA Lead Related wrong port connected to leads (1)					
System Related Events:					
Extra Cardiac Stimulation	17 (15)	0	0	2.8 (15)	0.4 (17)
Pocket Infections	6 (6)	1.6 (6)	0.1 (6)	0	0
Muscle Spasm, hiccupping	5 (5)	0	0	0.9 (5)	0.1 (5)
Sub Total Device/System Related Events	127 (91)	9.4 (50)	1.5 (70)	9.2 (49)	1.2 (57)

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3 month randomization period study patients N = 71,
6 month randomization period study patients N = 461
(879 events in 532 randomized patients, 4769 total device months)

	Total Number Of Events/ (Number of Patients)	% Comps (Patient) N=532 Patients[a]	% Comps/ Device Month 4769 months[b]	% Obs/ Patient N=532 Patients[c]	% Obs/ Device Month 4769 months[d]
Procedure Related Events:					
Pain/Discomfort/infection	37 (34)	0	0	6.4 (34)	0.8 (37)
Hemotoma/Seroma	14 (13)	0	0	2.4 (13)	0.3 (14)
Pericardial Effusion	7 (7)	0.4 (2)	0.04 (2)	0.9 (5)	0.1 (5)
Thrombosis	5 (5)	0.2 (1)	0.02 (1)	0.8 (4)	0.08 (4)
Other	17 (17)	0.9 (5)	0.1 (5)	2.3 (12)	0.3 (12)
Sub Total Procedure Related Events	**80 (77)**	**1.5 (8)**	**0.2 (8)**	**13.5 (72)**	**1.5 (72)**
Other PossibleDevice/Therapy Related					
Chest Pain Discomfort	33 (31)	0.9 (5)	0.1 (5)	4.9 (26)	0.6 (28)
Palpitations	13 (11)	0	0	2.1 (11)	0.3 (13)
Near Syncope/Syncope	8 (8)	0.2 (1)	0.02 (1)	1.3 (7)	0.1 (7)
MI/Cardiac Arrest	4 (4)	0.8 (4)	0.08 (4)	0	0
Anemia/ Thrombocytopenia	5 (5)	0.9 (5)	0.1 (5)	0	0

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3 month randomization period study patients N = 71,
6 month randomization period study patients N = 461
(879 events in 532 randomized patients, 4769 total device months)

	Total Number Of Events/ (Number of Patients)	% Comps (Patient) N=532 Patients[a]	% Comps/ Device Month 4769 months[b]	% Obs/ Patient N=532 Patients[c]	% Obs/ Device Month 4769 months[d]
Other	10 (10)	1.1 (6)	0.1 (6)	0.8 (4)	0.08 (4)
Sub Total Possible Device Therapy Related	73 (69)	3.6 (19)	0.4 (21)	9.4 (50)	1.1 (52)
Arrhythmias Events:					
A Fib/Flutter	34 (31)	0.8 (4)	0.08 (4)	5.1 (27)	0.6(30)
VT/VF/PVC	18 (16)	0	0	3.0 (16)	0.4 (18)
Bradycardia/Junction	6 (6)	0	0	1.1 (6)	0.1 (6)
Heart Block	5 (5)	0	0	0.9 (5)	0.1 (5)
VT/VF (ICD implanted) (5) VF (external CV, lidocaine, milrinone) (2) VF (IV amiodarone) (1)	8 (8)	1.5 (8)	0.2 (8)	0	0
Sub Total Arrhythmia Events	71 (53)	1.5 (8)	0.3 (12)	8.5 (45)	1.2 (59)
Worsening Heart Failure Events					
Increased diuretics	47 (42)	0	0	7.9 (42)	1.0 (47)

Table 1-2. Adverse Events During the Randomization Period
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6 month randomization period study patients N = 461
(879 events in 532 randomized patients, 4769 total device months)

	Total Number Of Events/ (Number of Patients)	% Comps (Patient) N=532 Patients[a]	% Comps/ Device Month 4769 months[b]	% Obs/ Patient N=532 Patients[c]	% Obs/ Device Month 4769 months[d]
IV diuretics	40 (36)	6.8 (36)	0.8 (40)	0	0
No Treatment	29 (26)	0	0	4.9 (26)	0.6 (29)
IV inotropes	20 (16)	3.0 (16)	0.4 (20)	0	0
Increased ACE-I/diuretics	20 (18)	0	0	3.4 (18)	0.4 (20)
Hyperkalemia/ Hypokalemia	9 (9)	0	0	1.7 (9)	0.2 (9)
Reduce ACE-I/diuretic	10 (10)	0	0	1.9 (10)	0.2 (10)
Other Treatment	11 (11)	0	0	2.7 (11)	0.2 (11)
IV fluids	5 (5)	0.9 (5)	0.1 (5)	0	0
Reprogram device	5 (5)	0	0	0.9 (5)	0.1 (5)
Unknown treatment	18 (15)	2.4 (13)	0.3 (16)	0.4 (2)	0.04 (2)
Reduce diuretics	4 (4)	0	0	0.8 (4)	0.08 (4)

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Table 1-2. Adverse Events During the Randomization Period
3 month randomization period study patients N = 71,
6 month randomization period study patients N = 461
(879 events in 532 randomized patients, 4769 total device months)

	Total Number Of Events/ (Number of Patients)	% Comps (Patient) N=532 Patients[a]	% Comps/ Device Month 4769 months[b]	% Obs/ Patient N=532 Patients[c]	% Obs/ Device Month 4769 months[d]
Other: Heart Transplant (3) Monitor/Holter (3) Reduce BB/diuretics (3) Intubated (2) IV/PO (2) Vit K shot (1) Central Line (2) Increase ACE-I/ (2)	18 (17)	1.9 (10)	0.2 (10)	1.3 (7)	0.2 (8)
Sub Total Worsening Heart Failure	**236 (145)**	**1.3 (70)**	**5.8 (91)**	**1.9 (100)**	**3.0 (145)**
Deaths	**33 (33)**	**6.2 (33)**	**0.7 (33)**	**0**	**0**
Total of Not Device Therapy Related Events.	**259 (189)**	**6.0 (32)**	**0.8 (36)**	**29.5 (157)**	**4.7 (223)**

The following other procedure related adverse events were reported, but occurred in three or fewer patients; left shoulder pain (3), hypotension (2), general shoulder swelling, discolored skin, pocket swelling, left subclavian obstruction, hand molting, pericarditis, dermatitis due to tape, fever, left hemiparalysis, reaction to use of dye at implant, mouth ulcers, hypertension. Possibly device or therapy related: renal failure(2), stroke (2), cardiogenic shock, rule out sepsis, coronary disease, feels like magnet over pocket site, rule out myocardial infarction, abdominal pain.

[a] % of patients that experienced a complication.

[b] Complication rate per device month of experience.

[c] % of patients that experienced an observation.

[d] observation rate per device month of experience.

Table 1-2A. Deaths that occurred during the study

Study Period	Number of Patient Deaths	Cause of Death		
		Progressive Heart Failure	Sudden Cardiac Death	Other Cause
Screened but no implant procedure	5	2	3	0
After Unsuccessful Implant Procedure	6	2	1	3
After implant, Not Randomized	2	1	0	1
During Randomization period: Control group	19	10	5	4
During Randomization period: Treatment group	14	4	7	3
After Randomization period	28	9	12	7
Total	**74**	**28**	**28**	**18**

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Clinical Studies

Summary

A prospective, randomized, controlled, multi-center trial (refer to Figure 1-1) conducted at 44 participating sites (39 in the United States and 5 in Canada) compared the effectiveness results for patients receiving InSync system cardiac resynchronization therapy (treatment group) to the control group (patients were implanted with the InSync system but did not receive cardiac resynchronization therapy).

The investigational protocol pre-specified the cardiac resynchronization performance criteria for both safety and effectiveness. These criteria were generated based on results from a prior study conducted outside the United States (OUS) using the InSync cardiac resynchronization system. In the prior nonrandomized, prospective, multi-center OUS study, 103 patients were implanted with the InSync system.

For this study, patients who satisfied the inclusion and exclusion criteria underwent a baseline evaluation to determine study eligibility and then underwent an implant procedure of the InSync cardiac resynchronization system. Key study inclusion criteria included:

- patients diagnosed within the previous month with stable heart failure (NYHA classification III or IV),
- QRS duration of ≥130 ms,
- left ventricular end diastolic diameter of ≥ 55 mm,
- left ventricular ejection fraction ≤ 35% (via any method of measure within 6 months of study enrollment),
- patients on a stable pharmacological medical regimen prior to implant of the cardiac resynchronization system. This included ACE-I or substitute for at least one month and a beta blocker for at least three months if tolerated.

Key study exclusion criteria included patients with the following:

- Prior pacing systems or indications or contraindications for pacing,
- Chronic atrial arrhythmias,
- Unstable angina, or myocardial infarction (MI) or received coronary artery revascularization (CABG) or coronary angioplasty (PTCA) within the past 3 months,
- Existing implantable cardioverter defibrillator (ICD) or indications for an ICD.

1-30

Successfully implanted patients were then randomized to either the control arm (cardiac resynchronization therapy OFF pacing mode VDI lower rate 30) or to the treatment arm (cardiac resynchronization therapy ON – pacing mode VDD lower rate 30). The initial study protocol required a 3 month period of randomization. There were 84 patients enrolled into this initial phase. The protocol was later amended to extend the period of randomization to 6 months. There were 448 patients enrolled into the 6 month study, plus 13 patients who agreed to go from the 3 month study into the 6 month study. Refer to Figure 1-2 for an overview of patient enrollment and follow-up.

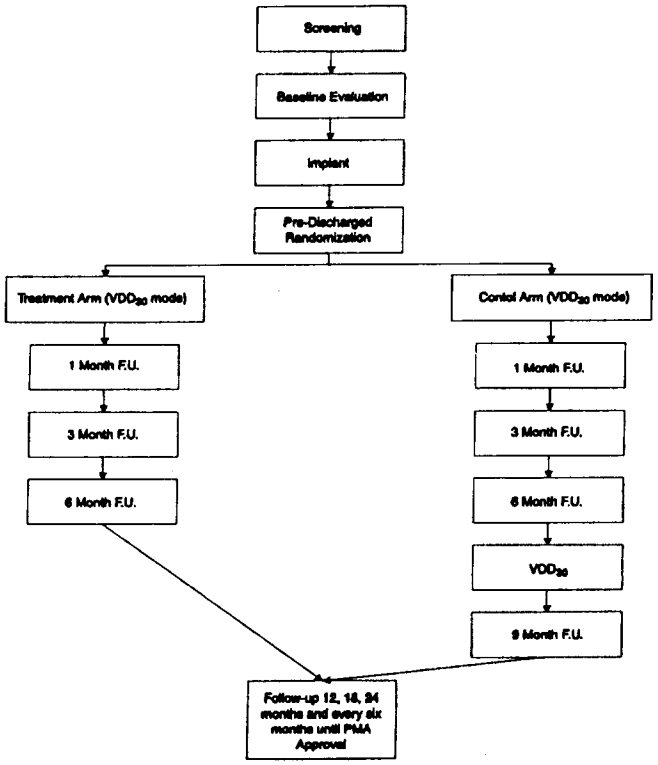

Figure 1-1. Study Design

1-32

All patients who underwent an InSync system implant procedure were included in the overall safety results. There were 579 implant procedures with 536 successful implants for a 93 % cardiac resynchronization system implant success rate. All of the unsuccessful implants were due to an inability to place the LV lead. Additional detail regarding the reasons for unsuccessful implants are summarized in Table 1-3 below. These reasons are not mutually exclusive.

Table 1-3. Reasons for Unsuccessful Cardiac Resychronization Implant Procedure

Reason	N
Unable to access coronary vein	16
Unable to obtain distal location	15
Dislodgement/unstable LV lead	11
Elevated pacing thresholds	5
Cardiac vessel too small	3
Phrenic nerve stimulation	2
Other	6

There were a total of 532 patients randomized into the study, 269 patients were randomized to the control arm and 263 were randomized to the treatment arm. All patients who were randomized were included in the comparative effectiveness results. Refer to Figure 1-2 below for an overview of patient accountability and disposition.

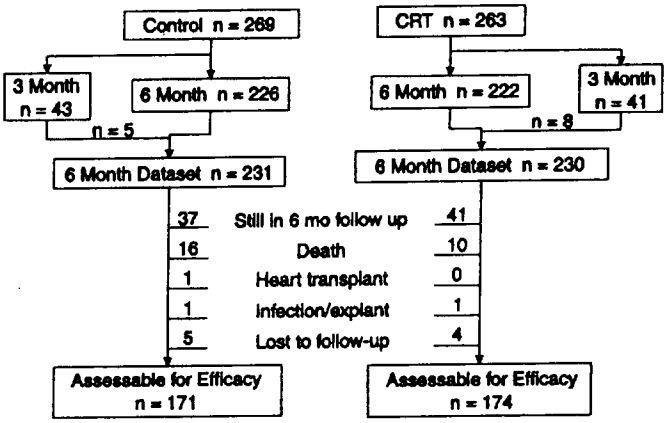

Figure 1-2. Enrollment and Follow-Up 532 Randomized Patients

1-34

Primary Safety and Effectiveness Objective Results:

1. **Objective: Estimate rate of survival without complications related to the Model 8040 generator**
   - Performance criterion: lower 95% confidence limit ≥ 90% (based on historical data for generator related complications)

   Results: there was one Model 8040 generator related complication during the 6 month randomization period (device explanted due to sensing issue)
   - Estimated survival: 99.8 %
   - Lower limit of 2 sided 95% confidence interval at 6-months: 98%
   - Objective met
2. **Objective: Estimate the rate of survival without complications related to the InSync system**
   - Performance criterion: Lower 95% confidence limit = 70% (based on initial OUS InSync trial results)

   Results: Fifty-five patients experienced at least one complication within 6 months of follow-up (74 total complication events).

Table 1-4. InSync System-Related Events Summary During 6-Month Follow-Up Period

(579 implant attempts, 536 successful implants)

Device	# of Complications	# of Patients[a]
Model 8040 generator related	1	1
Model 2187/2188 lead related	48	38
Right atrial (RA) lead related	10	10
Right ventricular (RV) lead related	5	5
Complete InSync system related (system explant due to infection)	9	9
RA and RV lead related	1	1
TOTAL	74	55

[a] Patients may experience more than one complication, hence the categories of complications are not mutually exclusive with respect to the number of patients.

- Estimated survival: 89.0%
- Lower limit of 2 sided 95% confidence interval: 85.9%
- Objective met

3. **Objective: To evaluate the clinical effectiveness of cardiac resynchronization in patients with heart failure.**
   - Performance criterion: The InSync cardiac resynchronization system will be considered clinically effective if patients in the treatment arm show statistically significant improvement at 6 months over Baseline when compared to the control arm in one of the following endpoints:
     - NYHA classification,
     - Six Minute Hall Walk Distance,
     - Minnesota Living with Heart Failure Quality Of Life scores.

   Results:

1-36

New York Heart Association Classification Results

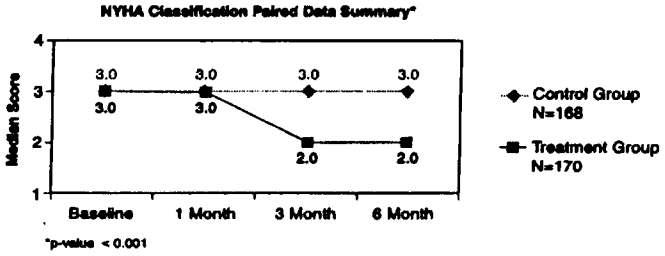

Figure 1-3. NYHA Classification Paired Median Data Summary

Figure 1-3 provides changes in NYHA class for those patients with data at each of the time points shown.

Table 1-5 shows the distribution of the changes in NYHA classification for patients with both baseline and six month data.

Table 1-5. Changes in Heart Failure Classification from Baseline to 6 Months

	Control Group N = 169	Treatment Group N =173	P-Value
			<0.001
Improved			
IV → III, II, I	10	15	
III → II, I	54	102	
Total Improved	**64 (38%)**	**117 (68%)**	
No change			
III → III	96	51	
IV → IV	3	1	
Total No Change	**99 (59%)**	**52 (30%)**	
Worsened			
III → IV	6 (4%)	4 (2%)	

1-38

MN Living with Heart Failure Quality of Life Questionnaire Results

Median
Note: 95% confidence intervals

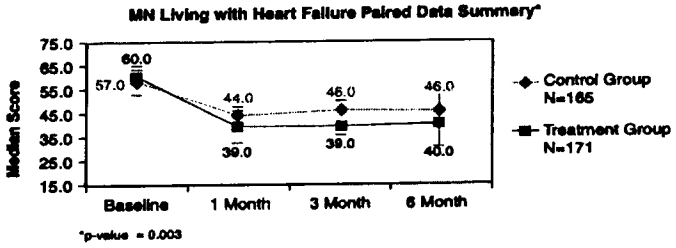

Figure 1-4. MN Living with Heart Failure Median Paired Data Summary

Figure 1-4 provides changes in Quality of Life scores for those patients with data at each of the time points shown.

Table 1-6 shows the distribution of changes in QOL scores for those patients with both baseline and 6-month follow-up data.

Table 1-6. MN Living with Heart Failure Score Distribution of Change from Baseline to 6 Months

Change in MN Living with Heart Failure Score from Baseline to 6 Months	Control Group (N=166)	Treatment Group (N=172)	P-Value
			0.016[a]
Improved ≥ 39 points	23 (13.9%)	40 (23.3%)	
Improved 26 - 38 points	23 (13.9%)	25 (14.5%)	
Improved 13 - 25 points	27 (16.3%)	34 (19.8%)	
Improved 1 - 12 points	38 (22.9%)	37 (21.5%)	
Total improved	**111 (66.9%)**	**136 (79.1%)**	
No change	**3 (1.8%)**	**2 (1.2%)**	
Worsened 0 - 12 points	28 (16.9%)	22 (12.8%)	
Worsened 13 - 25 points	16 (9.6%)	10 (5.8%)	
Worsened 26 - 38 points	6 (3.6%)	1 (0.6%)	
Worsened ≥ 39 points	2 (1.2%)	1 (0.6%)	
Total worsened or no change	**55 (33.1%)**	**36 (20.9%)**	

[a] P-value corresponds to distribution for cardiac resynchronization therapy versus control.

1-40

Six-Minute Hall Walk Results

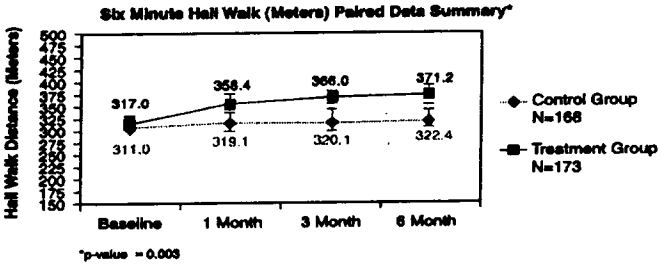

Figure 1-5. 6-Minute Hall Walk (Meters) Median Paired Data Summary

Figure 1-5 provides changes in six minute hall walk distances for those patients with data at each of the time points shown.

Table 1-7 shows the distribution of changes in 6 Minute Hall Walk distance for those patients with both baseline and 6- month follow-up data.

Table 1-7. Six-Minute Hall Walk Score Distribution of Change from Baseline to 6 Months

Change in Six Minute Hall Walk Distance from Baseline to 6 Months	Control Group (N=170)	Treatment Group (N=174)	P-Value
			0.017
Increased ≥ 100 meters	20 (11.8%)	34 (19.5%)	
Increased 75 - 99 meters	12 (7.1%)	17 (9.8%)	
Increased 50 - 74 meters	14 (8.2%)	28 (16.1%)	
Increased 25 - 49 meters	25 (14.7%)	23 (13.2%)	
Increased 1 - 24 meters	24 (14.1%)	18 (10.3%)	
Total increased	**95 (55.9%)**	**120 (69.0%)**	
No change	**3 (1.8%)**	**1 (0.6%)**	
Worsened 0 - 24 meters	18 (10.6%)	16 (9.2%)	
Worsened 25 - 49 meters	19 (11.2%)	12 (6.9%)	
Worsened 50 - 74 meters	11 (6.5%)	4 (2.3%)	
Worsened 75 - 99 meters	6 (3.5%)	5 (2.9%)	
Worsened ≥ 100 meters	18 (10.6%)	16 (9.2%)	
Total no change or worsened	**75 (44.1%)**	**54 (31.0%)**	

1-42

Table 1-8. Summary of Effectiveness Results

Endpoints	Results		
	Control Group (Off)	Treatment Group (On)	P-Value
6-month change in NYHA Classification	169 patients with paired data Baseline median 3.0 mean 3.1 ±0.3 6-month median 3.0, mean 2.7 ±0.6 Median Paired Difference 0	173 patients with paired data Baseline median 3.0 mean 3.1 ±0.3 6-month median 2.0 mean 2.3 ±0.7 Median Paired Difference (-1.0)	<0.001
6-month change in QOL score	166 patients with paired data (95% confidence interval) Baseline median 57.0, (53, 62) mean 56.8 ±21.4 (95% C.I.) 6-month median 46.0, (40, 51) mean 44.8 ±23.9 (95% C.I.) Median Paired Difference (-9), (-13, -5) (95% C.I.)	172 patients with paired data (95% confidence interval) Baseline median 60.0, (58, 64) mean 59.2 ±19.9 (95% C.I.) 6-month median 40.5, (31, 45) mean 39.6 ±24.3 (95% C.I.) Median Paired Difference (-18.5) (-23, -12) (95% C.I.)	0.003
6-month change in 6-minute hall walk (meters)	170 patients with paired data (95% confidence interval) Baseline median 310, (290, 317) mean 297.0 ±94.9 (95% C.I.) 6-month median 321, (305, 340) mean 303.0 ±127.8 (95% C.I.) Median Paired Difference (9.8), (0, 24) (95% C.I.)	174 patients with paired data (95% confidence interval) Baseline median 317, (309, 329) mean 314.7 ±84.1 (95% C.I.) 6-month median 371, (351, 386) mean 339.5 ±127.3 (95% C.I.) Median Paired Difference 40.1, (28, 56) (95% C.I.)	0.003

Proportion of patients meeting one or more primary effectiveness endpoints

An estimate was made to determine the proportion of patients in the control and treatment groups that experienced an improvement in each of the primary effectiveness endpoints both separately and in combinations of 2 or more. Data for all patients in the control and treatment groups that completed a baseline and 6-month assessment for each of the 3 primary effectiveness endpoints is included. The following improvements were considered clinically meaningful improvements to conduct this analysis: NYHA reduction of 1, QOL score reduction of ≥ 13 points, 6-Minute hall walk distance ≥ 50 meters.

Table 1-9. Proportion of Patients Who Met One or More Primary Effectiveness Endpoints

	Control	Treatment	P-Value
Primary Endpoint Met			
NYHA Class	64 of 169=37.9%	117 of 173=67.6%	<0.001
QOL Score	73 of 166=44.0%	99 of 172=57.6%	0.017
6-Minute Hall Walk	46 of 170=27.1%	79 of 174=45.4%	<0.001
More than One Endpoint Met			
Hall Walk +QOL	30 of 166=18.1%	56 of 172=32.6%	0.003
Hall Walk +NYHA Class	25 of169=14.8%	65 of 173=37.6%	<0.001
QOL score +NYHA Class	43 of 166=25.9%	81 of 172=47.1%	<0.001
Hall Walk +QOL +NYHA	20/166=12.0%	51/172=29.7%	<0.001

– **Objective met**

1-44

Secondary Safety and Effectiveness Objective Results:

Secondary objectives were intended to provide additional information on patient status and the InSync system performance. There were no established performance requirements related to the secondary objectives as they were intended to support additional characterization of patient's response to therapy and performance of the InSync system.

4. **Objective: To characterize survival in patients receiving cardiac resynchronization therapy for up to 6 months.**

   Results:

   - A total of 74 deaths occurred during the study period. Of these, 43 deaths occurred during the first six months following an attempt of an implant procedure. Of these 43 deaths, 5 occurred after an unsuccessful implant procedure, 2 deaths occurred in patients who were implanted with an InSync system but were not randomized, and 36 deaths occurred in patients who were implanted with an InSync system and randomized to either the control or treatment groups. Table 1-10 shows the survival estimates through 12 months.

Table 1-10. InSync patient survival – All successful implants through 12 months

	0	1 month	3 months	6 months	9 months	12 months
All implants						
# at risk	536	518	468	329	219	139
# events	1	10	12	15	5	11
# censored	0	7	38	124	105	69
% survived	99.8%	97.9%	95.6%	92.3%	90.5%	85.5%
Standard error	0.2%	0.6%	0.9%	1.2%	1.4%	2.0%

Survival references:

Packer, M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE study research group. N Eng J Med. 1991;325:1468-1475.

Effects of enalpril on mortality in severe congestive heart failure. Results of the Cooperative North Scandanavian Enalapril Survival N Eng J Med 1987;316:1429-1435.

Farquharson CAJ, Struthers AD. Angiotensen II receptor blockers in chronic heart failure. J Renin-Angiotensin-Aldosterone Sys. 2000;1:21-222

Pitt B, Segal R, Martinez FA, et al. Randomized trial of losartan versus captopril in patients over 65 with heart failure Lancet. 1997;349:747-752

Gheorghiade P, No effect of amlopidine on mortality or cardiovascular morbidity in patients with severe chronic heart failure. Evidence-based cardiovascular Med. June, 1997:45

Hjalmarson A, Goldstein S, Fagerberg BI, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the metoprolol CR/XL Randomized Intervention trial in congestive heart failure. JAMA. 2000;283:1295-1302

1-46

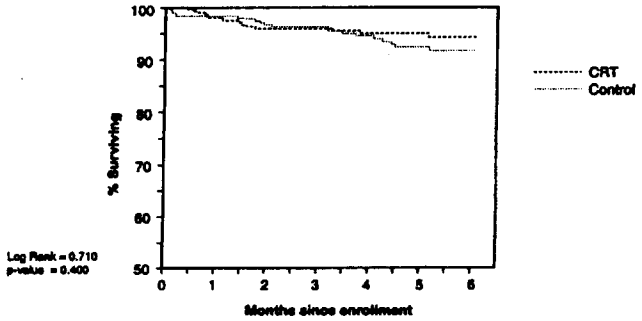

Figure 1-6. Kaplan-Meier Survival Curve Between 6 Month Patient Survival Control and Treatment Groups

Table 1-11. InSync patient survival – Control versus Treatment through 6 months

	0	1 month	2 months	3 months	4 months	5 months	6 months
Control							
# at risk	269	259	253	225	184	173	74
# events	0	4	5	1	4	4	1
# censored	0	4	1	27	37	7	98
% survived	100.0%	98.5%	96.6%	96.2%	94.4%	92.3%	91.8%
Standard error	-	0.7%	1.1%	1.2%	1.5%	1.8%	1.8%
Treatment							
# at risk	263	257	248	223	184	174	84
# events	0	5	6	0	2	0	1
# censored	0	1	3	25	37	10	89
% survived	100.0%	98.1%	95.8%	95.8%	94.8%	94.8%	94.3%
Standard error	-	0.8%	1.2%	1.2%	1.4%	1.4%	1.5%

Tests between groups	Chi-square	Degrees of Freedom	p-value
Log-rank	0.710	1	0.400
Wilcoxon	0.385	1	0.535

1-48

Causes of death are reported in Table 1-12 below:

Table 1-12. Causes of death during 6 month randomization period

	Control Group	Cardiac Resynchronization Group
Sudden cardiac death	5	7
Heart failure death	10	4
Other death	4	3
Total	19	14

5. **Objective: To characterize adverse events (complications and observations) for up to 6 months in patients who underwent implantation of a cardiac resynchronization system. A complication is an adverse event that resolved invasively. An observation is an adverse event that resolved with non invasive means.**

   Results:

Table 1-13. Overall Complications Comparison During Randomized Period (532 Randomized Patient)

Event Type (treatments)	Randomized Mode		Total Events (patients)
	Control (patients)	Treatment (patients)	
Worsening Heart Failure Symptoms (N=91)			
Treated by:			
IV diuretics	27 (23)	13 (13)	40 (36)
IV inotropes	19 (15)	1 (1)	20 (16)
IV fluids	1 (1)	4 (4)	5 (5)
Heart transplant	2 (2)	1 (1)	3 (3)
IV/PO potassium	1 (1)	1 (1)	2 (2)
Vitamin K injection	0	1 (1)	1 (1)
Pharmacological treatment unknown	13 (10)	3 (3)	16 (13)
Central line placement	0	2 (1)	2 (1)
Intubation/Ventilatory support	2 (2)	0 (0)	2 (2)
Sub Total Worsening Heart Failure Symptoms	**65 (51)**	**26 (25)**	**91 (76)**

Table 1-13. Overall Complications Comparison During Randomized Period (532 Randomized Patient) (Continued)

Event Type (treatments)	Randomized Mode		Total Events (patients)
	Control (patients)	Treatment (patients)	
Arrhythmias (N=12) (treatment):			
A Fib/Flutter (IV amiodarone, burst pacing)	2 (2)	2 (2)	4 (4)
VT/VF (ICD implanted)	1 (1)	4 (4)	5 (5)
VF (IV amiodarone)	1 (1)	0	1 (1)
VF (external CV, lidocaine dobutamine, milrinone)	0	2 (2)	2 (2)
Sub Total Arrhythmias	**4 (4)**	**8 (6)**	**12 (10)**
Other Cardiovascular Events (N=19) (treatment):			
Myocardial infarction (dobutamine, nitrates, PTCA, heparin gtt)	0	4 (4)	4 (4)
Cardiogenic shock (LVAD)	0	1 (1)	1 (1)
Chest pain (stent, IV meds, prednisone)	2 (2)	3 (3)	5 (5)
Anemia/Thrombocytopenia (transfused)	3 (3)	2 (2)	5 (5)
Near syncope/Syncope (sutures)	0	1 (1)	1 (1)
Pulmonary embolism (IV Heparin)	1 (1)	0 (0)	1 (1)
Hypotension (pericardio-centesis)	1 (1)	0 (0)	1 (1)
Hyponatremia, Sepsis (unknown)	1 (1)	0 (0)	1 (1)
Sub Total Other Cardiovascular Events	**8 (7)**	**11 (11)**	**19 (18)**
Other Events (N=3): (Respiratory infection – renal failure IV antibiotics; CVA – heparin; abdominal pain phenergan IV)	0	3 (3)	3 (3)
Procedure Related Events (N=8): (hypertension – thrombosis – pleural effusion – shoulder pain – pocket swelling - pneumonia-hypotension)	5 (5)	3 (3)	8 (8)
8040 Generator Related (N=1): Sensing issue	0	1 (1)	1 (1)
LV Lead Replacements (N=16) Due To:			
Elevated thresholds	0	6 (6)	6 (6)
Dislodgement	4 (4)	5 (5)	9 (9)
Extra cardiac stimulation	0	1 (1)	1 (1)
Sub Total LV lead Replacements	**4 (4)**	**12 (12)**	**16 (16)**

1-50

Table 1-13. Overall Complications Comparison During Randomized Period (532 Randomized Patient) (Continued)

Event Type (treatments)	Randomized Mode		Total Events (patients)
	Control (patients)	Treatment (patients)	
LV lead Repositioning (N=30) Due To:			
Elevated thresholds	4 (4)	6 (6)	10 (10)
Dislodgement	5 (5)	9 (5)	14 (10)
Extra cardiac stimulation	1 (1)	3 (3)	4 (4)
Unable to capture	1 (1)	0	1 (1)
Hypotension (IV fluids)	1 (1)	0	1 (1)
Sub Total LV Lead Repositionings	**12 (11)**	**18 (14)**	**30 (25)**
LV Lead Explanted Due To Elevated Thresholds (N=1)	1 (1)	0	1 (1)
LV Lead Invasive Lead Evaluation (N=1)	1 (1)	0	1 (1)
RV Lead Repositioned (N=5) Due To:			
Dislodgement	2 (2)	1 (1)	3 (3)
Invasive lead evaluation	0	1 (1)	1 (1)
Pain with pacing	1 (1)	0	1 (1)
Sub Total RV Lead Repositionings	**3 (3)**	**2 (2)**	**5 (5)**
RA Lead Replaced (N=2) due to:			
Dislodgement	0	2 (2)	2 (2)
RA Lead Repositioned (N=7) Due To:			
Elevated thresholds	3 (3)	0	3 (3)
Dislodgement	3 (3)	1 (1)	4 (4)
Sub Total RA Lead Repositionings	**6 (6)**	**1 (1)**	**7 (7)**
RV/RA Lead Related (N=1):			
Wrong connector parts	1 (1)	0	1 (1)
System Related Explants (N=6) Due To Infection	3 (3)	3 (3)	6 (6)
Not Device/therapy Related Events (N=36)	21 (17)	15 (15)	36 (32)
TOTAL	**134 (119)**	**105 (100)**	**239 (219)**

6. **Objective: To compare the QRS duration via ECG change from Baseline to 6 months between the control versus the treatment group.**

   Results:

Table 1-14. Results Addressing Secondary Effectiveness Objectives

Secondary Effectiveness Objective	Results		
	Control Group (Off)	Treatment Group (ON)	P-Value
Change in QRS duration (ms) at 6-months as compared to Baseline for control (*OFF*) versus treatment (*ON*) groups	163 patients with paired data Baseline median 160 mean 164.5 ±20.9 6-month median 160 mean 159.2 ±30.1 Median Paired Difference 0	168 patients with paired data Baseline median 160 mean 167.1 ±20.6 6-month median 150 mean 149.9 ±31.1 Median Paired Difference (-20)	<0.001

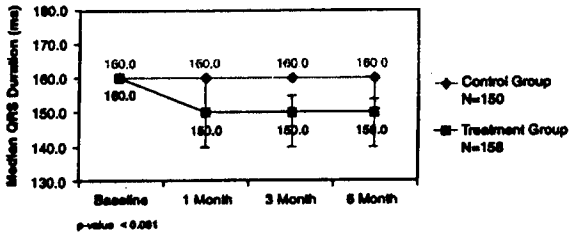

Figure 1-7. QRS Width Data Comparison (ms)

1-52

7. **Objective: To characterize the effect of cardiac resynchronization on peak VO_2 during cardiopulmonary exercise testing.**

Results:

Table 1-15. Results Addressing Secondary Effectiveness Objectives

Change in cardiopulmonary exercise test results at 6-months as compared to baseline for control *(OFF)* versus treatment *(ON)* groups:			
Peak VO_2 (ml/kg/min)	118 patients with paired data Baseline median 14.2 mean 14.1 ±3.4 6-month median 13.9 mean 14.3 ±3.9 Median Paired Difference 0.1	119 patients with paired data Baseline median 14.1 mean 14.6 ±3.4 6-month median 16.0 mean 15.7 ±3.8 Median Paired Difference 1.0	0.038
Exercise Duration (sec)	118 patients with paired data Baseline median 477 mean 490 ±221 6-month median 519 mean 528 ±247 Median Paired Difference 12	120 patients with paired data Baseline median 485 mean 507 ±185 6-month median 620 mean 606 ±212 Median Paired Difference 85	<0.001

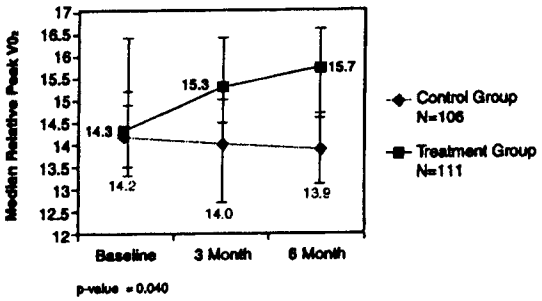

Figure 1-8. Cardiopulmonary Exercise Relative Peak VO_2 (ml/kg/min)

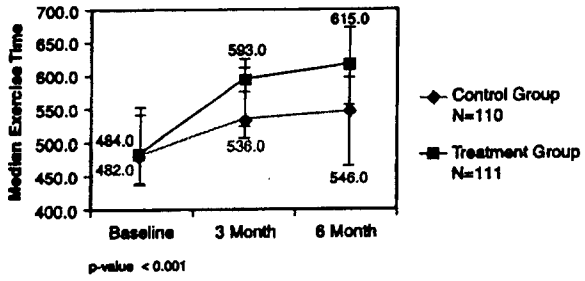

Figure 1-9. Exercise Time (seconds)

1-54

8. **Objective: To characterize the effect of cardiac resynchronization on echocardiographic parameters.**

Results:

Table 1-16. Results Addressing Secondary Effectiveness Objectives

Change in Echo indices at 6-months as compared to Baseline for control (*OFF*) versus treatment (*ON*) groups:			
LV ejection fraction (%)	95 patients with paired data Baseline median 23.6 mean 23.5 ±6.7 6-month median 24.6 mean 24.7 ±8.3 Median Paired Difference 0.9	116 patients with paired data Baseline median 24.1 mean 24.5 ±6.7 6-month median 29.5 mean 30.4 ±9.4 Median Paired Difference 5.1	<0.001
Mitral regurgitation (cm^2, jet area)	80 patients with paired data Baseline median 7.4 mean 7.4 ±4.9 6-month median 5.8 mean 7.3 ±5.9 Median Paired Difference (-0.5)	90 patients with paired data Baseline median 5.9 mean 7.3 ±6.2 6-month median 2.9 mean 3.8 ±4.4 Median Paired Difference. (-2.7)	<0.001
CardiacIndex (four chamber view)	72 patients with paired data Baseline median 2.29 mean 2.43 ±0.79 6-month median 2.22 mean 2.47 ±0.73 Median Paired Difference 0.14	102 patients with paired data Baseline median 2.19 mean 2.34 ±0.70 6-month median 2.30 mean 2.35 ±0.52 Median Paired Difference 0.09	0.897
LV Systolic volume (cm^3)	93 patients with paired data Baseline median 212.3 mean 236.3 ±106.5 6-month median 211.9 mean 239.9 ±122.7 Median Paired Difference 0.6	116 patients with paired data Baseline median 206.7 mean 219.2 ±93.6 6-month median 162.2 mean 180.7 ±91.8 Median Paired Difference (-36.5)	<0.001

Table 1-16. Results Addressing Secondary Effectiveness Objectives (Continued)

LV Diastolic volume (cm^3)	93 patients with paired data Baseline median 273.4 mean 300.9 ±113.9 6-month median 280.0 mean 309.4 ±131.1 Median Paired Difference 5.9	116 patients with paired data Baseline median 269.8 mean 284.1 ±100.7 6-month median 227.7 mean 249.0 ±99.2 Median Paired Difference (-29.9)	<0.001
LV mass (g)	70 patients with paired data Baseline median 340.7 mean 338.9 ±88.7 6-month median 335.8 mean 354.5 ±97.0 Median Paired Difference 19.7	91 patients with paired data Baseline median 330.1 mean 349.0 ±83.9 6-month median 324.3 mean 337.7 ±106.6 Median Paired Difference (-18.0)	0.006
Interventricular mechanical delay (ms)	86 patients with paired data Baseline median 35.0 mean 34.6 ±35.1 6-month median 44.0 mean 36.1 ±34.7 Median Paired Difference 3.0	93 patients with paired data Baseline median 49.0 mean 45.8 ±36.5 6-month median 29.0 mean 29.3 ±28.6 Median Paired Difference (-19.0)	<0.001
E Wave /A Wave ratio	71 patients with paired data Baseline median 0.99 mean 1.54 ±1.23 6-month median 1.04 mean 1.53 ±1.15 Median Paired Difference 0.02	93 patients with paired data Baseline median 1.02 mean 1.70 ±1.67 6-month median 0.84 mean 1.33 ±1.22 Median Paired Difference (-0.02)	0.113

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9. **Objective: To characterize the health care utilization of this patient population during the study.**

Results:

Table 1-17. Health Care Utilization for the First 6 Months of Follow-Up

	Control Group	Treatment Group	P-Value
Number of patients hospitalized	60 (26.0%)	57 (24.8%)	0.852
Number of hospitalizations	Median 1 (Range 1 to 6) Mean 1.65 ± 0.95	Median 1 (Range 1 to 4) Mean 1.40 ± 0.70	0.107
Number of days hospitalized	Median 6.5 days (Range 1 to 71 days) Mean 11.1 ± 13.2	Median 3.0 days (Range 1 to 24 days) Mean 4.8 ± 4.9	0.002

Table 1-18. Health Care Utilization for CHF During the First 6 Months of Follow-Up

	Control Group	Treatment Group	P-Value
Number of patients hospitalized	27 (11.7%)	14 (6.1%)	0.051
Number of hospitalizations	Median 1 (Range 1 to 3) Mean 1.44 ± 0.70	Median 1 (Range 1 to 3) Mean 1.43 ± 0.76	0.855
Number of days hospitalized	Median 5.0 days (Range 1 to 47 days) Mean 11.2 ± 12.8	Median 2.0 days (Range 1 to 13 days) Mean 4.0 ± 3.5	0.083

10. **Objective: Characterize the effect of cardiac resynchronization on plasma neurohormone levels.**

    Results:

    - There were no statistically significant difference in the changes from baseline to 6 months between the control and cardiac resynchronization treatment groups in the neurohormones.

11. **Objective: To summarize and compare the composite response endpoint for patients in the control and treatment groups.**

    Randomized patients were classified into one of the following "heart failure status" categories:

    Worsened: Patient dies; is hospitalized due to or associated with worsening heart failure; permanently discontinues double-blinded treatment due to or associated with worsening heart failure, treatment failure or lack of insufficient therapeutic response; permanently discontinues double-blinded treatment due to withdrawal of consent or other administrative reason and has worsening heart failure at the time of study discontinuation; demonstrates worsening in NYHA class at last observation carried forward (LOCF) or moderate-marked worsening of patient global assessment score at LOCF.

    Improved: Patient has not worsened (as defined above), and demonstrates improvement in NYHA class at LOCF and/or moderate-marked improvement in patient global assessment score at LOCF.

    Unchanged: Patient is neither improved nor worsened.

    For patients enrolled in the original protocol, heart failure status was determined through the 3-month follow-up visit. For patients enrolled after approval of protocol Amendment 1.0, heart failure status was determined through the 6-month follow-up visit. For all patients, it was first determined if the patient's heart failure status had worsened. If the patient's heart failure status

had not worsened, then an assessment was made to determine if the patient's heart failure status had improved at the most recent observation up to either the 3-month or 6-month follow-up visit, depending on whether the patient was enrolled under the original protocol or after protocol Amendment 1.0. If the patient had neither worsened nor improved, then the patient's heart failure status was classified as unchanged.

Results:

Table 1-19. Results Addressing Secondary Effectiveness Objectives

Secondary Effectiveness Objective	Results		
	Control Group (Off)	Treatment Group (ON)	P-Value
Composite Response:	N = 194	N = 189	<0.001
Improved	76 (39.2%)	123 (65.1%)	
Unchanged	68 (35.1%)	34 (18.0%)	
Worsened	50 (25.8%)	32 (16.9%)	