SUMMARY OF SAFETY AND EFFECTIVENESS

General Information

Device Generic Name:	Implantable Pacemaker Pulse Generator and Permanent Pacemaker Electrode
Device Trade Name:	Medtronic® InSync® Biventricular Pacing System including the InSync® Model 8040 Pulse Generator, Attain™ LV Model 2187 and Attain™ CS Model 2188 Leads
Applicant's Name and Address:	Medtronic, Inc. 710 Medtronic Parkway Minneapolis, MN 55432-5604
PMA Number:	P010015
Date of Panel Recommendation:	July 10, 2001
Date of Notice of Approval to Applicant:	August 28, 2001

Indications for Use

InSync Model 8040 Pulse Generator

The InSync Model 8040 pulse generator 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.

Attain Leads

The Attain LV Model 2187 lead has application as part of a Medtronic biventricular pacing system.

The Attain CS Model 2188 lead has application where permanent atrial, or dual-chamber pacing systems are indicated, or as part of a Medtronic biventricular pacing system.

Contraindications

InSync Model 8040 Pulse Generator

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.

Attain Leads

The leads are contraindicated for patients with coronary venous vasculature that is inadequate for lead placement, as indicated by venogram.

System Description

Device Description

The implantable InSync Model 8040 Pulse Generator is an atrial synchronous, biventricular pacing, cardiac resynchronization device. In addition to an atrial channel for atrial pacing and sensing, the Model 8040 Pulse Generator has two ventricular channels to provide simultaneous biventricular pacing and sensing from two ventricular leads. The Model 8040 Pulse Generator 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. 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 Model 8040 Pulse Generator is programmed with a Medtronic Model 9790 series programmer loaded with Model 9980 software.

The Model 8040 Pulse Generator is used with the Model 9980 software, and the Model 2187 or Model 2188 lead. The InSync pulse generator utilizes the same electronics as in the approved Medtronic Thera-*i* family of pulse generators and the same mechanical

configuration and battery as in the Medtronic Kappa 400 pulse generator. The primary difference between the InSync Model 8040 pulse generator and the Kappa 400 is the addition of a three-port IS-1 connector to support the one atrial and two ventricular leads.

Description of Attain Leads

The Medtronic Attain LV Model 2187 transvenous, unipolar, left ventricular, cardiac vein pacing lead is designed for pacing and sensing via the cardiac vein, as part of a Medtronic biventricular pacing system. The lead features a platinum alloy electrode, nickel alloy conductors, polyurethane insulation, and an IS-1[1] unipolar (UNI) lead connector.

> **Note:** To implant the Model 2187 in a cardiac vein, a compatible delivery system is required. A compatible delivery system includes a guide catheter and hemostasis valve which allows passage through or removal from an IS-1 connector.

The Medtronic Attain CS Model 2188 transvenous, bipolar, coronary sinus/cardiac vein pacing lead is designed for atrial pacing and sensing in the coronary sinus **or** pacing and sensing via the cardiac vein, as part of a Medtronic biventricular pacing system. The lead features two platinum alloy electrodes, nickel alloy conductors, polyurethane insulation, and an IS-1[2] bipolar (BI) lead connector.

Warnings

InSync Model 8040 Pulse Generator

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.

[1] IS-1 UNI refers to an international Connector Standard (ISO 5841-3: (E)) whereby pulse generators and leads so designated are assured of a basic mechanical fit.
[2] IS-1 BI refers to an international Connector Standard (ISO 5841-3: (E)) whereby pulse generators and leads so designated are assured of a basic mechanical fit.

- **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.
- **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.
- **Full Electrical Reset** is indicated by VVI pacing at a rate of 65 ppm without 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 physician immediately.

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.**

  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.
- **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.

Medical Therapy

- An **implantable defibrillator** may be implanted concomitantly with an InSync system provided implant protocols are followed for device and defibrillator lead placement and device configuration.

- 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 system who are subjected to MRI should be closely monitored and the programmed parameter settings should be verified upon cessation of MRI.
- **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.

Attain Leads

Necessary hospital equipment – Keep external defibrillation equipment nearby for immediate use during the acute lead system testing, implantation procedure, or whenever arrhythmias are possible or intentionally induced during post-implant testing. Back-up pacing should be readily available during implant. Use of the delivery system and/or leads may cause heart block.

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.

Do not force the guide catheter and/or leads if significant resistance is encountered. Use of guide catheters or leads may cause trauma to the heart.

To minimize the likelihood of trauma to the vein and to maintain lead flexibility while advancing the lead through the vein keep the stylet withdrawn 1-2cm or select a more flexible stylet.

Precautions

InSync Model 8040 Pulse Generator

Storage and Resterilization

The InSync pulse generator 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).	Do not implant the device if it has been dropped on a hard surface from a height of 12 inches (30cm) 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 (103kPa) when sterilizing. **Do not** resterilize the device more than two times.

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.
- **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.

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 pulse generator'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.
- **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.
- **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.

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.
- **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 pulse generator if the pulse generator is at the focal point of the lithotripsy beam. If lithotripsy must be used, program the pulse generator to a single chamber non-rate responsive mode (VVI/AAI or VOO/AOO) prior to treatment; and keep the pulse generator at least 1 to 2 inches (2.5 to 5 cm) away from the focal point of the lithotripsy beam.
- **Caution: Radiofrequency ablation** procedure in a patient with an InSync pulse generator 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 pulse generator.
  3. Positioning the ground plate so that the current pathway does not pass through or near the pulse generator 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 pulse generators similar to the InSync pulse generator has shown that exposure to diagnostic X-ray or fluoroscopic radiation should not affect the pulse generator.

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 pulse generator 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 pulse generator 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 pulse generator 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 pulse generator operation. There are reports of pacemaker disturbances caused by electric hand tools or electric razors used directly over the pulse generator implant site.

Commercial electrical equipment

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

Electronic Article Surveillance (EAS)

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

Cellular Phones

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

This InSync pulse generator contains a filter that allows usage, without interaction, of all cellular phones having one of the transmission technologies listed in Table 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. Cellular Phone Transmission Technologies

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

[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

Attain Leads

Inspecting the sterile package – Carefully inspect the package prior to opening:

- If the seal or package is damaged, contact your local Medtronic representative.
- Do not use the product after its expiration date.
- The lead has been sterilized with ethylene oxide prior to shipment. If the integrity has been compromised prior to the expiration date, resterilize using ethylene oxide.

Ethylene oxide Resterilization – If the sterile package seal is broken, resterilize the pulse generator using a validated ethylene oxide process. Avoid Resterilization techniques that could damage the lead:

- Refer to sterilizer instructions for operating instructions.
- Use an acceptable method for determining sterilizer effectiveness, such as biological indicators.
- Before Resterilization, place the pulse generator in an ethylene oxide permeable package.
- Do not exceed temperatures of 55°C (131°F).
- Do no resterilize more than one time.
- After Resterilization, allow the pulse generator to aerate ethylene oxide residues.

Handling the lead – Leads should be handled with great care at all times:

- If the lead is damaged, do not implant it. Return the lead to your local Medtronic representative.

- Protect the lead from materials shedding particles such as lint and dust. Lead insulators attract these particles.
- Handle the lead with sterile surgical gloves that have been rinsed in sterile water or a comparable substance.
- Do not severely bend, kink, or stretch the lead.
- Do not use surgical instruments to grasp the lead or connector pin.
- Do not immerse leads in mineral oil, silicone oil, or any other liquid, except blood at the time of implantation.
- Use an anchoring sleeve with all leads. Ensure that the anchoring sleeve is positioned close to the lead's connector pin, to prevent inadvertent passage of the sleeve into the vein. If wiping the lead is necessary prior to insertion, ensure that the anchoring sleeve remains in position.

Handling the stylets – Use care when handling stylets:

- Do not use excessive force or surgical instruments when inserting a lead.
- Avoid overbending, kinking, or blood contact.
- Use a new stylet when blood or other fluids accumulate on the stylet. Accumulated fluids may cause damage to the lead or difficulty in passing the stylet through the lead.
- Curving the stylet prior to insertion into the lead will achieve a curvature at the lead's distal end. Do not use a sharp object to impart a curve to the distal end of the stylet.

Line-powered equipment – An implanted lead forms a direct current path to the myocardium. During lead implantation and testing, use only battery-powered equipment or line-powered equipment specifically designed for this purpose, to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

Concurrent devices – Output pulses, especially from unipolar devices, may adversely affect pulse generator sensing capabilities. If a patient requires a separate stimulation device, either permanent or temporary, allow enough space between the leads of the separate systems to avoid interference in the sensing capabilities of the devices. Previously implanted pulse generators, implantable cardioverter defibrillators, and leads should generally be explanted.

Chronic repositioning or removal – Chronic repositioning or removal of leads may be difficult because of fibrotic tissue development. The clinical study was not designed to evaluate the removal of left ventricular leads from the coronary venous vasculature. If a lead must be removed or repositioned, proceed with extreme caution. Return all removed or unused leads to Medtronic:

- Lead removal may result in avulsion of the endocardium, valve, or vein.

- Lead junctions may separate, leaving the lead tip and bare wire in the heart or vein.
- Cap abandoned leads to avoid transmitting electrical signals.
- For leads that have been severed, seal the remaining lead end and suture the lead to adjacent tissue.

Adverse Events

Clinical study of the InSync system began on October 28, 1998. As of March 19, 2001 there were 536 patients implanted with an InSync system in the United States and Canada with an average follow-up of 9.0 months (range: 0 – 26 months).

There were a total of 74 deaths in the study. The cause of deaths and study period when the death occurred are indicated in Table 2 below.

Table 2. Deaths that occurred during the study

Study Period	Number of patient deaths	Cause of Death		
		Progressive Heart Failure	Sudden Cardiac Death	Other Causes
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**

Nine InSync systems and three InSync Model 8040 pulse generators were explanted for the reasons as indicated in Table 3 below. Seven systems were explanted due to infection (four of these patients were successfully implanted with another InSync system) and two systems were replaced with an InSync Model 7272 ICD system. The three Model 8040 pulse generators were replaced with another Model 8040 pulse generator. All of the events associated with these explants were resolved.

Table 3. Reasons for explants that occurred during the study

Explanted Due to:	Number of Patients	Status
Infection (InSync system explanted)	7	4 were reimplanted with an InSync system
ICD Indication (InSync system explanted)	2	Implanted with InSync ICD system
Model 8040 Generator Explant	3	InSync generator replaced with another InSync pulse generator due: to partial ERI setting (1), sensing issue (1) and muscle stimulation (1)
Total	**12**	**All resolved**

Observed Adverse Events

A prospective, randomized, controlled, multi-center trial 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 table below 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.

Table 4. Adverse Events During the Randomization Period
879 events in 532 randomized patients, 4769 total device months
(3 month randomization period study patients N = 71,
6 month randomization period study patients N = 461)

	Total Number Of Events/ (Number of Patients)	% Comps (Patients)[a]	% Comps/ Device Month[b] (Events)	% Obs (Patients)[c]	% Obs/ Device Month[d] (Events)
Total	**879 (414)**	**39.3 (209)**	**5.7 (272)**	**72.0 (385)**	**12.7 (607)**
8040 Generator Events					
Migration (1) Sense Issue (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 Repositioning Events Due to:					
Dislodgment	14 (10)	1.9 (10)	0.3 (14)	0	0
High Thresholds	10 (10)	1.9 (10)	0.2 (10)	0	0
Extra Cardiac Stim (3) Unable to Capture (1) Hypotension (1)	6 (5)	0.9 (5)	0.1 (6)	0	0
LV Lead Replacement Events 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					
Repositionings/ Replacements (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)
Other Lead Events 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)	7 (7)	0.2 (1)	0.02 (1)	1.1 (6)	0.1 (6)
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)**
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 Possible Device/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
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)	8 (8)	1.5 (8)	0.2 (8)	0	0

VF (IV amiodarone) (1)					
Sub Total ArrhythmiaEvents	**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)
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)
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)**

[a] Percent of patients who experienced a complication

[b] Complication rate per device month of experience

[c] Percent of patients who experienced an observation

[d] Observation rate per device month of experience.

Note:

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.

Potential Adverse Events

Adverse events (in alphabetical order) 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)

Alternative Practices and Procedures

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

Marketing History

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

As of July 31, 2001, approximately 3,200 InSync generators, 5,100 Attain Model 2187 leads, and 1,180 Attain Model 2188 leads have been distributed outside the United States. Neither the pulse generator nor leads have been withdrawn from the market in any country for any reason related to safety and effectiveness.

Summary of Pre-clinical Studies

Non-clinical Laboratory Studies – Model 8040 InSync

IC / Hybrid

The integrated circuits that are used in the InSync pulse generator are the L88 microcontroller IC and the L132 RAM/ROM IC. The L88 and the L132 are the same ICs that were used in the approved Medtronic Thera-*i* pulse generator (ICs - approved in Thera-*i*, P890003/S31, approved January 10, 1995. Hybrid - approved in Thera-*i*, P890003/S37 approved, October 31, 1995). The hybrid electronic module used for the Model 8040 InSync system is the same as the hybrid module used in the Thera-*i* pulse generator. Since the qualification of the ICs and the hybrid electronic module was performed for the Thera-*i* pulse generator; it was not necessary to requalify these components with the InSync pulse generator.

Battery

The InSync pulse generator utilizes the Promeon Sigma 303 lithium-iodide cell which provides the energy to operate the timing, detection, telemetry and charging circuits. This cell is currently used in the Kappa 400 (P970012, approved January 30, 1998) and other approved pulse generators.

The Sigma 303 battery was subjected to accelerated and application discharge testing: 40 at 400μA, 10 at 200μA, and 12 at 100μA. Twelve samples were subjected to

application discharge testing at a 26μA rate, but switched to 20μA at 2.5 volts. All samples exceed the minimum three month time requirement between 2.5 and 1.8 volts at 20μA.

Sixteen Sigma 303 samples were also subjected to environmental stress testing to demonstrate that cells exposed to various environmental conditions will meet specified performance requirements. All samples showed normal and expected behavior.

Current Drain Characterization

Since the InSync pulse generator utilizes the same hybrid and integrated circuits as the Medtronic Thera-*i*, thus the current drain characterization for the InSync is the same as for the Thera-*i* pulse generator and this testing was not repeated.

Connector Testing

The Model 8040 InSync pulse generator uses a 3-bore connector built in accordance with IS-1 design specifications. Twenty-two connector assemblies were subjected to IS-1 Go-Gage testing, IS-1 insertion testing, Medtronic IS-1 lead insertion and extraction testing and connector electrical leakage testing.

All of the InSync pulse generators met the connector design test requirements.

Environmental and Mechanical Testing

To ensure that the InSync pulse generator performs acceptably in typical shipping, handling and operating environments, 22 samples were subjected to environmental stress tests including temperature storage (-25°C to 55°C), mechanical vibration (5 to 500 to 5 Hz at 2.5g acceleration), and mechanical shock (effective free fall drop of 18"). All of the InSync pulse generators met the environmental stress test requirements.

The uplink telemetry, downlink telemetry and reed switch closure patterns for the InSync pulse generator was assessed using two devices. The coincident telemetry area of the InSync pulse generator was found to be comparable to the approved Medtronic Thera-*i*.

Electromagnetic Compatibility (EMC) Testing

Twenty-two InSync pulse generators were exposed to modulated (pulsed) and continuous wave (CW) 450MHz radiated electric fields, 50, 60 and 400Hz conducted sinusoidal currents, electrosurgical currents *in vitro*, transthoracic (high-level) and implantable cardioverter-defibrillator defibrillation pulses *in vitro* and testing to evaluate the effect of the InSync pulse generator on ICD operation. Two of the devices exhibited safety pacing after cessation of the cautery exposure; this is addressed in device manual caution statements (see Section 2, page 2-13 and 2-14 of the *Product Information Manual*, as well as G-19 and G-20 of the *Device Reference Guide*). All other test results were within requirements.

Testing of the effects of cellular phone on the operation of the InSync pulse generator was performed using 6 InSync pulse generators; there were no observed effects on device operation.

Electronic Article Surveillance (EAS) testing was performed using two InSync pulse generators paired with both bipolar and unipolar leads. The behavior observed with EAS units was consistent with Medtronic labeling.

Biocompatibility Testing

The materials used in the InSync pulse generator are identical to those used in the Medtronic Kappa 400 (P970012, approved January 30, 1998) pulse generator. Therefore, no additional biocompatability testing was conducted.

Predicted Reliability

Because of the similarity in the mechanical and electrical aspects of the InSync pulse generator and the Thera-*i* pulse generator family, the predicted reliability is expected to be the same. Therefore, a reliability analysis was not repeated.

Non-clinical Laboratory Testing – Software Validation

The InSync Software (Model 9980E) was developed and tested in accordance with Medtronic's formal procedures for software development and testing. These procedures include development of the Software Application Specification, a detailed software development, a hazard analysis, a retest strategy, and a Verification Test Strategy. The software was tested per the Verification Test Strategy. Errors, anomalies, and inconsistencies were noted in Software Change Reports and all issues addressed. Following final retest of the software, an audit was performed by Software Quality Engineering to ensure that all documents and code were properly controlled and released. The testing is adequate to demonstrate the reliable operation of the software.

Performance Standards

Performance standards for implantable cardiac pulse generators have not been promulgated per Section 514 of the Federal Food, Drug and Cosmetic Act; therefore no action is required.

Non-clinical Laboratory Testing – Attain Leads

Environmental Conditioning

Thirty Attain Model 2187 and 30 Attain Model 2188 leads were subjected to four cycles of ethylene oxide (EtO) sterilization and five cycles of thermal shock (-45°C to +70°C) prior to undergoing mechanical and electrical testing. No damage or degradation to the test leads was noted following sterilization and thermal shock.

Mechanical Testing

Thirty Attain Model 2187 and 30 Attain Model 2188 leads were subjected to the following mechanical tests: connector mating insertion / withdrawal, leak testing, lead composite pull testing (minimum 1.0 lb tensile strength), conductor joint testing (minimum 3.0 lb distal, 2.5 lb proximal), anchoring sleeve suture test and stylet insertion / withdrawal testing. All leads met all test requirements.

Twenty-two Attain Model 2188 leads were subjected to the lead body flex test (B_{50} flex life > 2.0×10^5 cycles at bend radius of 0.236"); all leads exceeded the requirements. Eighteen samples of each model were subjected to the composite distal fatigue test (no failures of metallic joints up to 400,000,000 cycles); all of the samples passed.

Electrical Testing

Thirty Attain Model 2187 and 30 Attain Model 2188 leads were subjected to DC resistance, IS-1 connector impedance (>50K ohms) and Medtronic AC impedance of multipolar leads (>50k ohms). All test requirements were met.

Biocompatibility Testing

The blood-contacting materials used in the Attain Models 2187 and 2188 leads are identical to those used in currently-marketed Medtronic pacing leads, such as the Model 4524 (P830061/S12, approved August 19, 1991). Therefore, no additional biocompatability testing was conducted.

Sterilization Validation

The 100% ethylene oxide (EtO) sterilization process used to sterilize the InSync pulse generator and pacing leads is identical to that used on previously approved Medtronic pulse generators and leads. The validation process consists of determining a maximum allowable bioburden, microbial lethality characteristics, and minimum sterilization process specifications. All Medtronic products intended to contact tissue are specified to have a sterility assurance level (SAL) of at least 10^{-6} . In addition, determination of lethality (D-value testing), bioburden, and EtO residual levels were completed.

Sterilization validation was performed by comparison to "worst case" devices. The Model 7961 Thera-*i* was identified as the worst case for implantable pulse generators and the Model 4068 lead was identified as the worst case lead, based on geometric design and dimensional considerations.

Package qualification testing was performed on both the device and leads to ensure suitability for their intended purpose. These tests included temperature storage; mechanical shock, vibration and stacking; package leak test; and peel (seal) strength testing. All testing was successfully completed, and is adequate to demonstrate that the device can be sterilized, and that sterilization will be maintained under expected handling conditions.

Animal Studies

GLP studies were conducted in canines with the InSync pulse generator and with the Attain Model 2187 lead. The purpose of the InSync system study was to evaluate the acute and chronic safety and effectiveness (sensing and pacing performance with right atrial, right ventricular and coronary sinus leads, single and dual site capture and output pace/recharge) of the device. Six canines were in the InSync system study; four were terminated at 12 weeks and two were carried out to 12 months. In the Attain Model 2187 study, four canines were followed to 12 weeks and two to 115 weeks. Appropriate pacing, sensing and thresholds were documented in both studies.

Additional non-GLP research testing was conducted to evaluate longer-term device performance (to 12 months) and to evaluate the effects of external defibrillation on the pacing leads. The potential impact of external defibrillation on the pacing system and/or myocardial tissue is documented in the physician's manual (*Product Information Manual*) and guidelines for performing external defibrillation are provided.

Conclusion Regarding 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 testing was successfully completed.

Summary of Clinical Studies

Study Design

A prospective, randomized, controlled, multi-center trial (refer to Figure 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 $\geq$130 ms,
- left ventricular end diastolic diameter of $\geq$ 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.

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 2 for an overview of patient enrollment and follow-up.

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 6 below. These reasons are not mutually exclusive.

Table 5. ***Reasons for Unsuccessful Cardiac Resynchronization 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

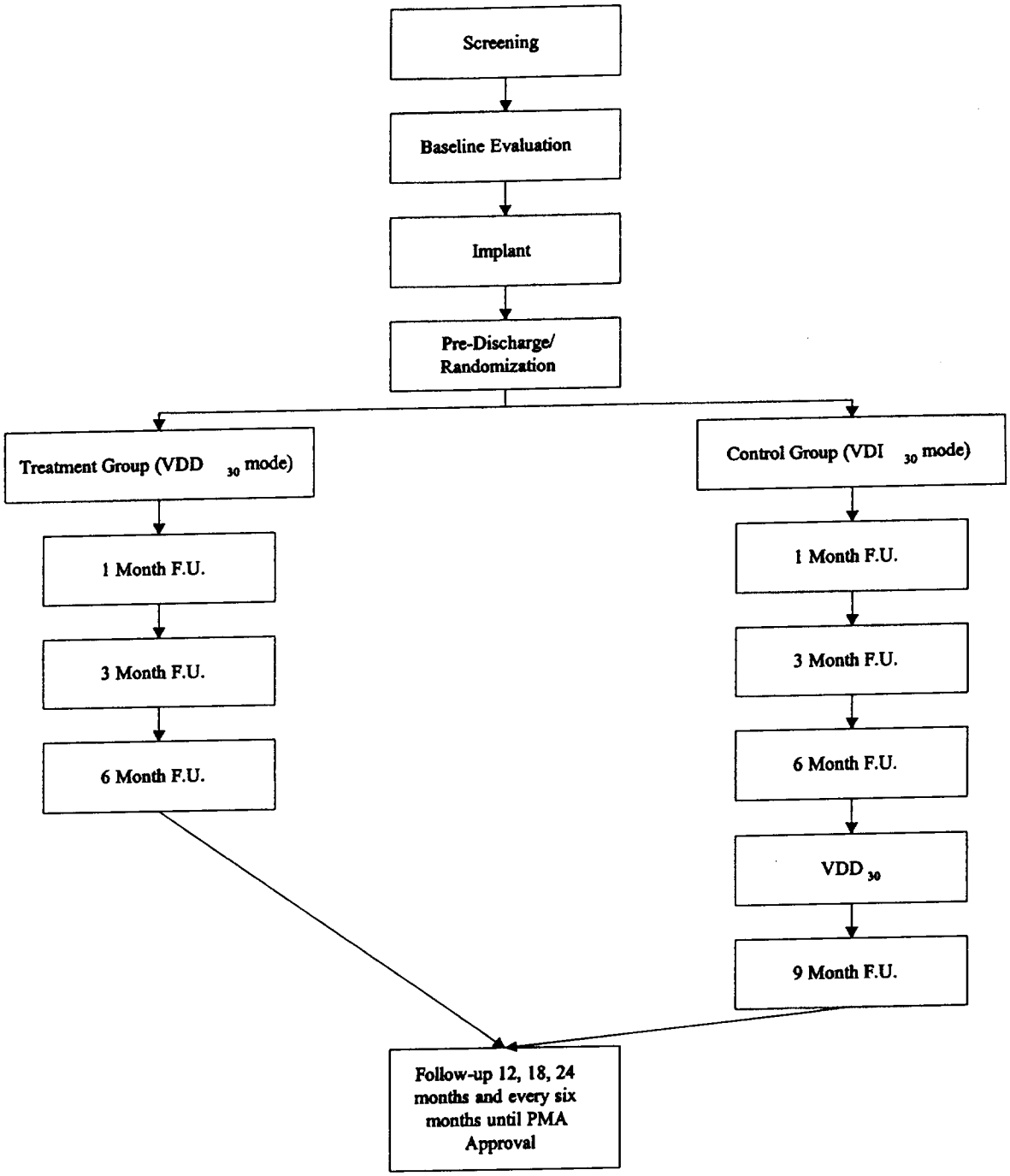

Figure 1. Overview of Study Design

There were a total of 532 patients randomized into the study: 269 patients were randomized to the control group and 263 were randomized to the treatment group. All patients who were randomized and completed 6 months of follow up were included in the comparative primary effectiveness results. Refer to Figure 2 below for an overview of patient accountability and disposition.

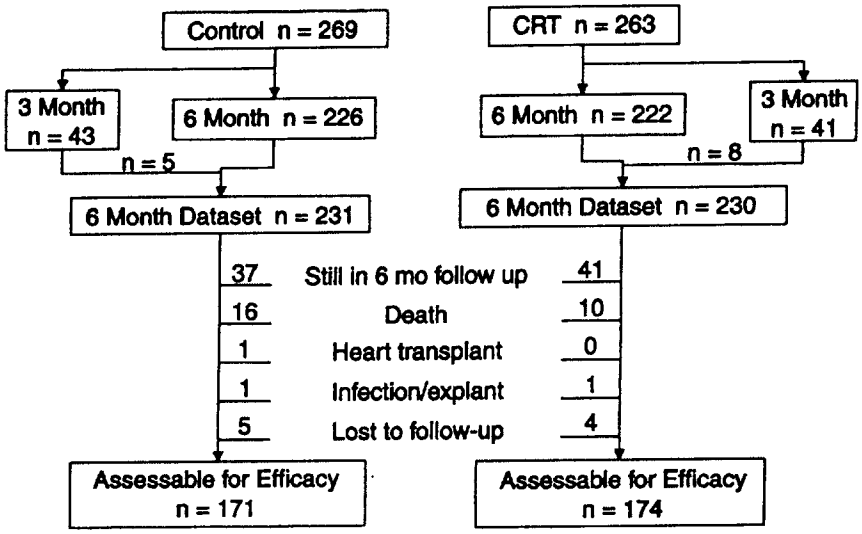

Figure 2. Enrollment and Follow-Up 532 Randomized Patients

Primary Safety and Effectiveness Results:

Safety

The primary safety endpoints were survival without complications related to the Model 8040 generator and survival without system-related complications. There was one Model 8040 generator related complication observed for a rate of 99.8% (lower 95% CI of 98%). This met the criteria that the lower 95% confidence interval be greater than 90%.

Fifty-five patients (89%, lower 95% CI of 85.9%) experienced at least one system-related complication within 6 months of follow-up (74 total complication events). This met the criteria that the lower 95% confidence interval for survival without system-related complications be greater than 70%. See Table 6 for details.

Table 6. ***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.

Effectiveness

The primary effectiveness hypothesis was that cardiac resynchronization therapy would show a statistically significant improvement over control therapy (when compared to baseline) at 6 months in at least one of the following endpoints:

- NYHA classification,
- Six Minute Hall Walk Distance,
- Minnesota Living with Heart Failure Quality Of Life scores.

(Note: the trial design defined success as occuring if any 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).

As shown in the following sections, Medtronic was able to demonstrate a statistically significant improvement in each of the three primary effectiveness endpoints.

A. NYHA Classification

The median NYHA Classification Data are presented below in Figure 3. Note that at baseline, the median NYHA score was 3 for control and treatment groups. The median value for the treatment group decreased to 2 at three and six months. The median value for the control group remained unchanged at 6 months. Only those patients with data at each of the time points were included in this analysis.

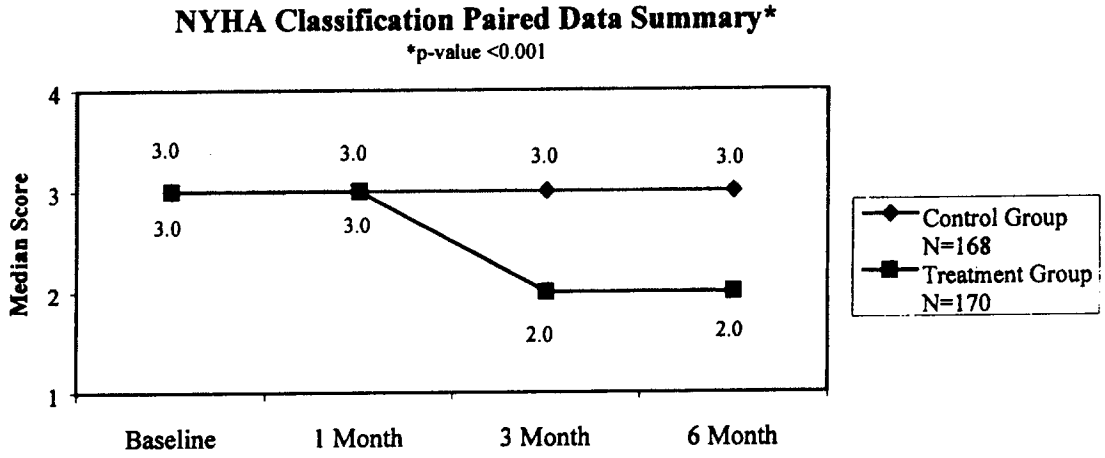

Figure 3. Median NYHA Classification Results

The distribution of the changes in NYHA classification is provided in the following table. The number of patients who showed improvement was greater in the treatment group (68%) as compared to the control group (38%), while the number of patients who worsened were about the same (4% in the control group and 2 % in the treatment group). Those patients with data at both the baseline and at six months were included in this analysis.

Table 7. Changes in Heart Failure Classification from Baseline to 6 Months*
* p –value < 0.001

	Control Group N = 169	Treatment Group N =173
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%)

B. MN Living with Heart Failure Quality of Life Questionnaire

An improvement in quality of life (reduction in score), as measured by the Minnesota Living with Heart Failure Questionaire, was observed in both the control and treatment groups. However, there was a statistically significant difference in the improvement in favor of the treatment group. Only those patients with data at each of the time points were included in this analysis.

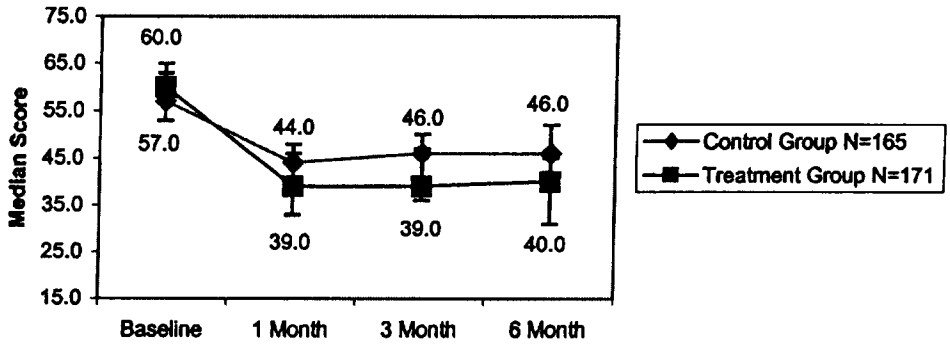

Figure 4. MN Living with Heart Failure Median Paired Data Summary

The distribution in MN Living with Heart Failure scores is shown in the following table. Although both groups showed improvement, the number of patients who improved was greater in the treatment group (79.1%) than in the control group (66.9%). In addition, the number of patients whho worsened was lower in the treatment group (20.9%) than in the control group (33.1%). Those patients with data at both the baseline and at six months were included in this analysis.

Table 8. ***MN Living with Heart Failure Score Distribution of Change from Baseline to 6 Months (p-value = 0.016)***

Change in MN Living with Heart Failure Score from Baseline to 6 Months	Control Group (N=166)	Treatment Group (N=172)
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%)**

C. Six-Minute Hall Walk Results

The six-minute hall walk results are shown in Figure 5. There is a slight increase in the hall walk distance for the control group, and a larger increase for the treatment group. The increase in the treatment group is statistically significnantly greater than that in the control group. Only those patients with data at each of the time points were included in this analysis.

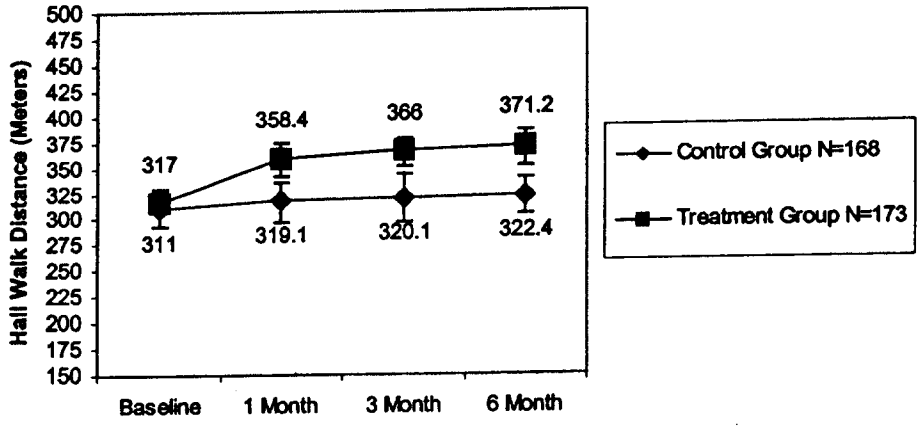

Figure 5. 6-Minute Hall Walk (Meters) Median Paired Data Summary*

* p-value = < 0.001

The following table shows the distribution of changes in 6 Minute Hall Walk distance from baseline to the 6- month follow-up visit. Once again, although both groups showed improvement, a greater number of patients in the treatment group (69%) were improved as compared to the control group (55.9%). In addition, fewer of the patients in the treatment group worsened (31%) as compared to the treatment group (44.1%). Those patients with data at both the baseline and at six months were included in this analysis.

Table 9. ***Six-Minute Hall Walk Score Distribution of Change from Baseline to 6 Months**** *p-value = 0.017*

Change in Six Minute Hall Walk Distance from Baseline to 6 Months	**Control Group (N=170)**	**Treatment Group (N=174)**
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%)**

Table 10 presentes a summary of the primary effectivness results. The improvement in each of the primary endpoints was statistically significantly greater for the treatment group when compared to the control group.

Table 10. Summary of Primary 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

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 11. Proportion of Patients Who Met One or More Primary Effectiveness Endpoints

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

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.

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 (see Table 5 in "Adverse Events" for additional information about cause of death). 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 the 532 patients who were implanted with an InSync system and randomized to either the control or treatment groups. Table 12 shows the survival estimates through 12 months for all patients implanted with a device. Table 13 shows the survival data for the control versus treatment group at 6 months.

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

	0 mo	1 mo	3 mo	6 mo	9 mo	12 mo
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%

Table 13. 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

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 14. ***Overall Complications Comparison During Randomized Period (532 Randomized Patients)***

	Randomized Mode		Total Events (patients)
Event Type (treatments)	**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)**
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,	0	4 (4)	4 (4)
PTCA, heparin gtt)	0	1 (1)	1 (1)
Cardiogenic shock (LVAD)	2 (2)	3 (3)	5 (5)
Chest pain (stent, IV meds, prednisone)	3 (3)	2 (2)	5 (5)
Anemia/Thrombocytopenia (transfused)	0	1 (1)	1 (1)
Near syncope/Syncope (sutures)	1 (1)	0 (0)	1 (1)
Pulmonary embolism (IV Heparin)	1 (1)	0 (0)	1 (1)
Hypotension (pericardio-centesis)	1 (1)	0 (0)	1 (1)
Hyponatremia, Sepsis (unknown)	**8 (7)**	**11 (11)**	**19 (18)**
Sub Total Other Cardiovascular Events			
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)**
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:	0	2 (2)	2 (2)
Dislodgement			
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)**

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

Results:

Table 15. ***ECG changes****
** p-value < 0.001*

	Control Group (Off)	**Treatment Group (On)**
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)

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

Results:

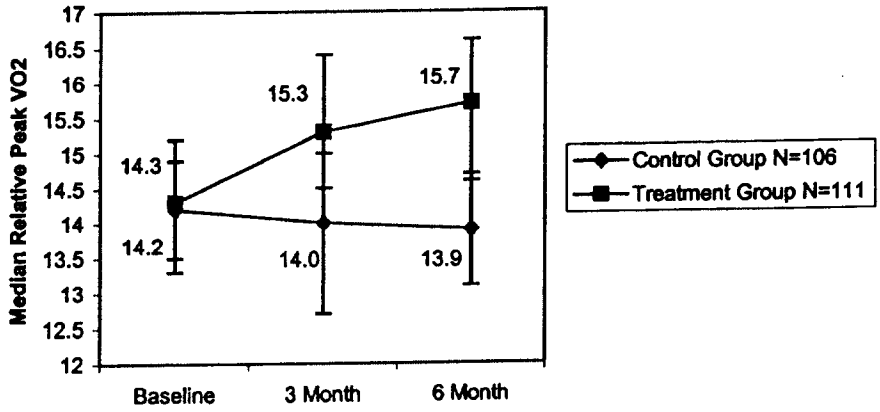

Figure 6. Cardiopulmonary Exercise Relative Peak VO_2 (ml/kg/min) (* p-value = 0.04)

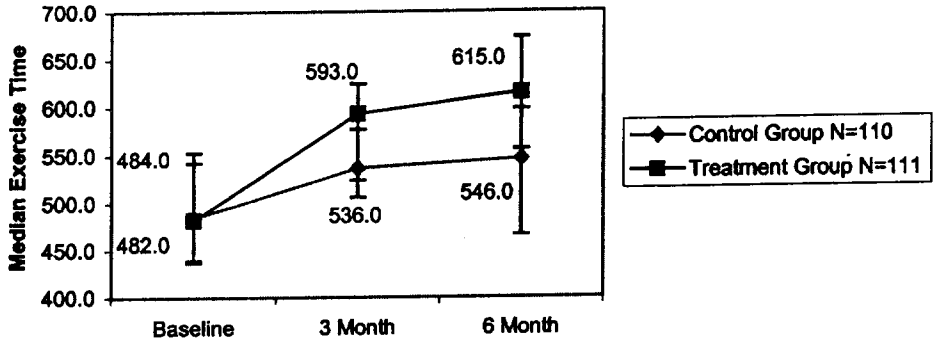

Figure 7. Exercise time (sec) (p-value < 0.001)

Table 16. Change in cardiopulmonary exercise test results at 6-months

	Control (off)	**Treatment (on)**	**p-value**
Peak VO_2 (ml/kg/min)	118 patients with paired data **Baseline** median 14.2 mean 14.1 ±3.4 **6-month**	119 patients with paired data **Baseline** median 14.1 mean 14.6 ±3.4 **6-month**	0.038

	median 13.9 mean 14.3 ±3.9 Median Paired Difference 0.1	median 16.0 mean 15.7 ±3.8 Median Paired Difference 1.0	
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

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

Table 18. Change in Echo indices at 6-months as compared to Baseline

	Control (off)	**Treatment (on)**	p-value
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	90 patients with paired data **Baseline** median 5.9 mean 7.3 ±6.2	<0.001

	6-month median 5.8 mean 7.3 ±5.9 Median Paired Difference (-0.5)	**6-month** median 2.9 mean 3.8 ±4.4 Median Paired Difference. (-2.7)	
Cardiac Index (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
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

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

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.

Conclusions Drawn from the Studies

Safety

The InSync cardiac resynchronization system met the primary safety objectives. Results were within protocol specified performance criteria for the following: the InSync system implant success rate, the 6 month freedom from InSync device related complications, Attain Models 2187/2188 lead complications, InSync system related complications and the Attain Models 2187/2188 lead voltage threshold.

The secondary safety objectives provide additional data to further support the safety of the InSync cardiac resynchronization system. Electrical performance (biventricular pacing impedance and R wave amplitude) of the Attain Models 2187/2188 leads is within anticipated limits, suggesting acceptable performance of the Attain lead systems for the 6 month period. Overall patient survival for those who underwent the implant procedure is within the rates reported for similar patient populations. There was no difference in the mortality or the total number of hospitalizations between the treatment and control groups.

Effectiveness

The effectiveness of the InSync cardiac resynchronization system has been demonstrated by a clinically and statistically significant improvement in New York Heart Association Classification, 6 minute hall walk distance and quality of life questionnaire score as compared to the control group. Although there was also an improvement seen in the control patients, the improvement in the InSync patients was statistically significantly greater than that seen in the control patients.

Supporting evidence shows improvement in certain echocardiographic measurements including a small improvement in ejection fraction, a reduction in mitral regurgitation, a reduction in both diastolic and systolic left ventricular volumes and mass in the treatment group as compared to the control group. The cardiopulmonary exercise results demonstrated statistically significant improvement in the peak VO_2 and exercise duration.

Panel Recommendation

The Circulatory Systems Devices Panel met on July 10, 2001 and voted unanimously (7-0) to recommend approval with conditions. The four specific conditions identified by the panel were 1) to acquire the remainder of the primary efficacy 6 month data; 2) to complete the echocardiographic data to the 6 month point; 3) to make modifications of the patient and physician labeling; and 4) to perform a 12 month mortality assessment with an intention-to-treat analysis.

Medtronic has agreed to provide the remainder of the six month efficacy data as part of the final report for the InSync clinical trial and has updated the patient and physician

labeling to address the Panel's concerns. The 12 month mortality data will be provided when available as a condition of approval. FDA has determined that the 6 month echocardiographic data is not necessary to demonstrate the safety and effectiveness of the InSync system.

CDRH Decision

FDA issued an approval order for P010015 on August 28, 2001. Conditions of approval included the 12 month mortality data on the IDE cohort, and a 3-year evaluation of mortality, particularly sudden cardiac death, and chronic lead performance, including electrical performance and adverse clinical events, on 1,000 patients. FDA expects that 1,500 patients will need to be enrolled in the 3 year study to allow for patient drop out and insure 1,000 patients are followed for the full 3 years.

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.
Post-approval Requirements, Restrictions:	See approval order.