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Medtronic® InSync®
Implantable Cardioverter
Defibrillator Model 7272
System
PMA Application P010031
PDLB/DCCRD/ODE/FDA
March 5, 2002
Gaithersburg, MD

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PMA Review Team

Doris Terry, Lead Reviewer
Helen Barold, M.D., Clinical Review
Gerry Gray, Ph.D., Statistical Review
James Lee/Fred Lacy, Preclinical Testing
Kevin Hopson, Biosearch Monitoring
Walter Scott, Ph.D., Patient Labeling
Abraham Karkowsky, M.D., CDER

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Regulatory History

PMA Modular Shell - M000025

- M1 – Model 7272 preclinical testing, software validation and animal testing
- M2 – Preclinical tests on leads and sterilization

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Regulatory History

- PMA originally filed using pooled data from the MIRACLE trial (May 4, 2001)
 - data was found by FDA not to be poolable with the MIRACLE study
- PMA amended with current dataset (November 13, 2001)

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Medtronic InSync® ICD Model 7272 System Components

- InSync® Model 7272 ICD pulse generator
 - 5 port header
 - RV sensing, independent RV/LV leads
- Attain® Model 4189 Left Ventricular Lead
 - 4F, unipolar lead
- Model 9969 Software
- Other commercially available leads and accessories

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Model 7272 Preclinical Testing

- Component and Subassembly Qualification Testing
- Design Verification Testing
- Device Qualification Testing
- Animal Testing

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Software Validation

- Detailed Software Development
- Hazard Analysis
- Verification/Validation Testing

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Attain® Model 4189 LV Lead Preclinical Testing

- Environmental Testing
- Mechanical Testing
- Electrical Testing
- Biocompatibility (materials identical to other Medtronic commercially available leads)
- Sterilization Qualification

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Clinical and Statistical

Summary:

Medtronic InSync ICD
Cardiac Resynchronization System

Helen S. Barold, M.D.

Gerry Gray, Ph.D.

FDA, CDRH

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Indications for Use

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

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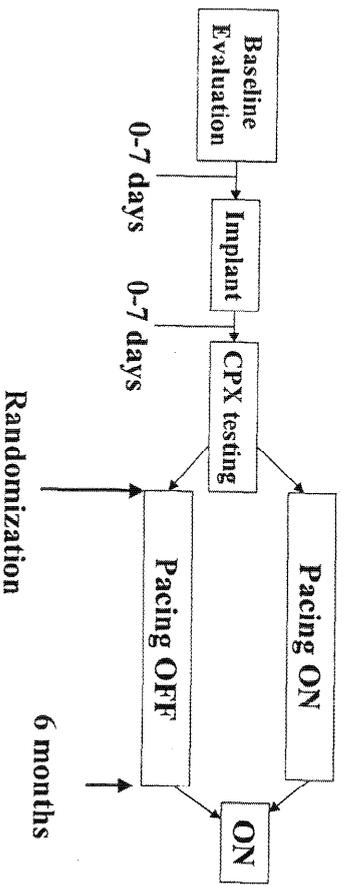
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It is important to keep in mind that the primary function of this device is that of an ICD. It is indicated for those patients who need an ICD. It will be necessary to distinguish between the Biventricular pacing features and the ICD features and to assure that the BIV pacing does not interfere in any way with the primary function of the ICD or the ability to adequately program the ICD functions.

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Study Design



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Timing of Testing

Prior to Implant/Part of Baseline Screening	After Implant/Randomization	Prior to 6 month visit
<ul style="list-style-type: none"> • QOL • NYHA • 6 MHW • Echo • Neurohormones 	<ul style="list-style-type: none"> • CPX testing 	<ul style="list-style-type: none"> • QOL • NYHA • 6 MHW • Echo • Neurohormones • CPX Testing

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Maintenance of the Blind

- EP physicians were unblinded
- CHF physicians/staff were blinded
- Patients were blinded

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Effectiveness

- **3 Co-Primary Effectiveness Endpoints**
 - NY Heart Association (NYHA) class
 - Quality of Life score
 - 6-minute hall walk distance
- **Hochberg adjustment for multiplicity:**
 - All three at $p < 0.05$, any two at $p < 0.025$, any one at $p < 0.0167$
 - This gives an experimentwise error rate < 0.05

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Primary Safety Objectives

- InSync ICD generator complications
- InSync system related complications
- Model 4189 complications

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Secondary Objectives

- Mortality
- CHF composite response
- Healthcare Utilization (hospitalizations)
- Cardiopulmonary Testing
- Echo Indices
- Plasma Neurohormones
- All adverse events
- LV lead sensing
- VT/VF episodes
- Implant ventricular defibrillation criterion

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Inclusion Criteria

- ICD indication
- NYHA class II/III or IV *
- QRS > 130 ms
- LVEF < 0.35
- LVEDD >55mm by echo
- Stable medical regimen for 1 mo, 3 for BB (cannot be put on BB during study)
- Stable dose of positive inotropic OP Rx for 1 mo

* Only Class III/IV results will be presented

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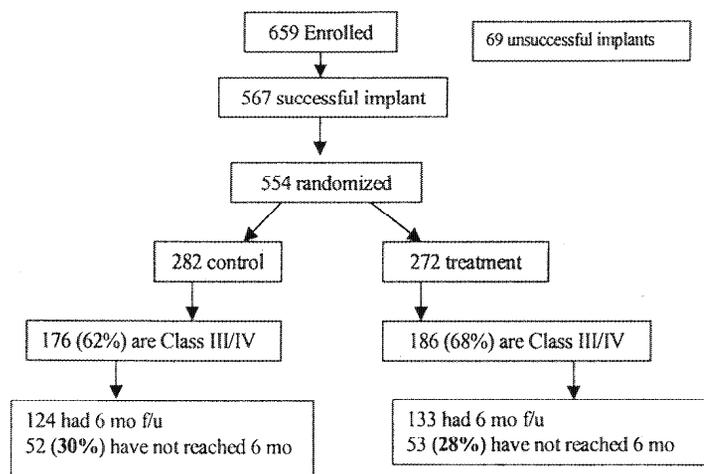
Exclusion Criteria

- Baseline 6MHW > 450 meters
- Unstable angina, AMI, CABG, PTCA, CVA/TIA w/in 3 mo
- Intermittent inotropic drug rx
- prior pacing system or indications/contraindications for standard cardiac pacing
- chronic or paroxysmal atrial arrhythmias
- enrollment in concurrent investigation
- primary valvular disease
- not expected to survive 6 mo
- women who are pregnant or not on BC
- severe primary pulmonary disease
- SBP <80 or >170mm Hg
- CVA/TIA w/in 3 mo
- s/p heart transplant
- supine resting HR >140 bpm
- serum creatinine > 3.0 mg/dL
- serum hepatic fxn 3x ULN
- VT with reversible causes

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Patient Accountability



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Patient Accountability

- 362 NYHA III/IV patients randomized
- At 6 months:
 - 27 died before 6-month visit (7%)
 - 257 with six-month visit (15 later died)
 - 247 with QOL responses
 - 254 with NYHA responses
 - 240 with 6-minute hall walk
 - 7 lost to follow-up (2%)
 - 71 “administratively censored” (20%)

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Blinding Issues and Crossovers

- 69 protocol deviations from blinding
 - 49 related to the collection of a primary endpoint
- 25 NYHA III/IV patients crossed over

REASON FOR CROSSOVER	RANDOMIZATION	
	CR OFF	CR ON
Worsening heart failure	10	0
Center oversight / error	2	6
Other	3	4

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Baseline Characteristics

Characteristic	OFF=176	ON=186
Age	68±9	67±11
Gender (%male)	77.3%	76.3%
NYHA (% Class III)	88.6%	88.2%
EF	20±6	21±7
%ACE-	88%	91%
%BB	57%	63%
Etiology % Ischemic	74%	63% ***
6 minute HW	247±118	245±127
Peak VO2	13.5±4.1	13.5±3.7
ICD currently impl	30%	30%
RBBB%	13%	13%

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Primary Safety Objectives

- ICD generator complications at 3 mo
 - 1 case of electrical reset
- Attain Model 4189 complications at 6 mo
 - 31 lead dislodgements
 - 85.1% (lower 95% CI 81.7%)
- ICD system complications at 6 mo
 - 81.1% (lower 95% CI 77.6%)

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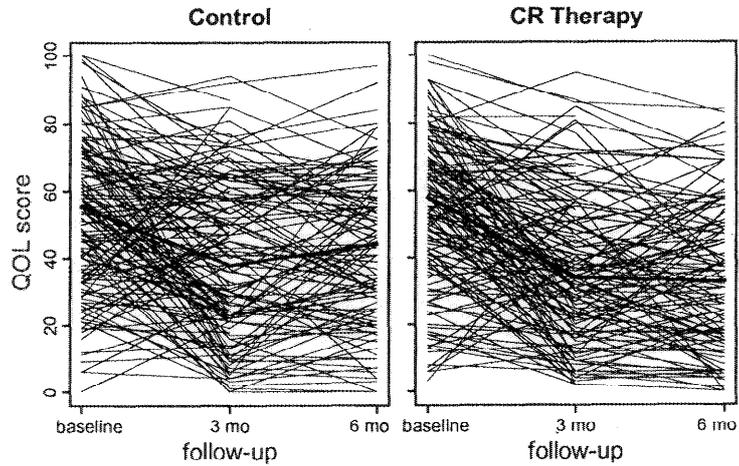
Quality of Life Results

	N	Median at Baseline	6 months	Paired difference	p-value
Pacing OFF	119	57	44	-10	
Pacing ON	128	55.5	33	-19	
Difference					0.01

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QOL Score



Individual patient responses and medians.

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Quality of Life Overall Assessment

	Pacing OFF	Pacing ON
Total Improvement	68.1%	82.8%
Worsening or No Change	31.9%	17.2%

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NYHA Class Results

	N	Baseline	6 mo	Paired difference	p-value
Pacing OFF	123	3	3	0	
Pacing ON	131	3	2	-1	
Difference					0.03

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Change in NYHA Classification from Baseline to 6 months

Change in NYHA at 6 mo	Pacing OFF (N=123)	Pacing ON (N=131)
IV-> I	0	0
IV-> II	8	8
III-> I	7	11
IV-> III	4	3
III->II	39	60
Total Improved	47.2%	62.6%
IV->IV	0	2
III->III	59	43
No Change	48%	34.4%
III->IV	6	4
Worsened	4.9%	3.1%

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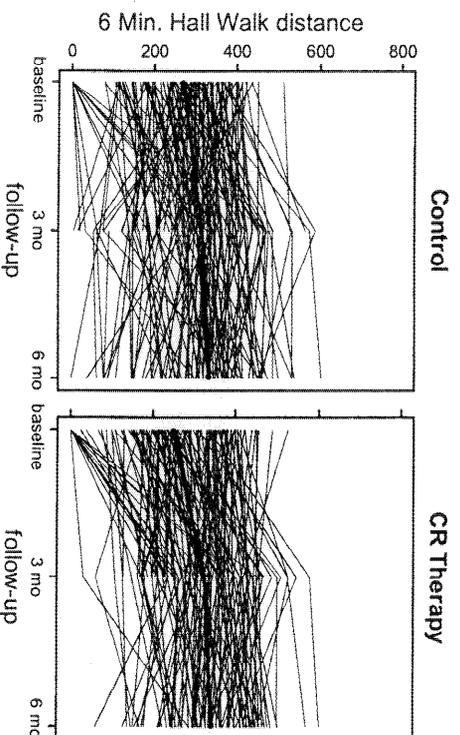
6 minute Hall Walk Results (meters)

	N	Baseline	6 months	Paired difference	p-value
Pacing OFF	118	275	333	53	
Pacing ON	122	260	342	56	
Difference					0.41

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Hall Walk Distance



Individual patient responses and medians.

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6 minute Hall Walk Results 6 months

	Pacing OFF	Pacing ON
Total Improvement	70.3%	75.4%
Worsening or no Change	29.7%	24.6%

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Effectiveness

- 3 Co-Primary Effectiveness Endpoints
 - NY Heart Association (NYHA) class
 - Quality of Life score
 - 6-minute hall walk distance
- Hochberg adjustment for multiplicity:
 - All three at $p < 0.05$, any two at $p < 0.025$, any one at $p < 0.0167$
 - This gives an experimentwise error rate < 0.05
- Device meets the third criteria
 - QOL $p = 0.01$, NYHA $p = 0.03$, WALK $p = 0.41$
- How to interpret this significant result?

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Primary Endpoint: LV Lead Effectiveness

- Implant success (all patients):
 - 636 attempts; 69 failures (10.85%)
- Electrical Performance (all patients)
 - thresholds stable
 - sensing stable
 - no information on impedance stability
- Breakdown of III/IV requested by FDA

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Secondary Objectives: Peak VO₂ (ml/kg/min)

	N	Baseline	6 mo	Diff	p-value
Pacing OFF	93	13.8+4.0	14.0+4.1	0.2+3.3	
Pacing ON	96	13.7+3.5	14.5+3.7	0.8+3.4	
Difference					0.05

- RER- significant difference between groups at 6 months
- VENC02- no difference
- AT- small number of patients

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Secondary Objectives

- CHF Composite
 - improvement of treatment group over control group (55% vs 40%, $p=0.038$)
 - no difference in Patient Global Assessment Score
- Hospitalizations
 - No difference between groups

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Secondary Objectives

- Echocardiographic Results
 - no improvement in EF, CI, E/A ratio
 - decrease in LVED and LVES
- Plasma Neurohormones
 - dataset incomplete
 - no difference between groups
 - NE level goes wrong way in Pacing ON group

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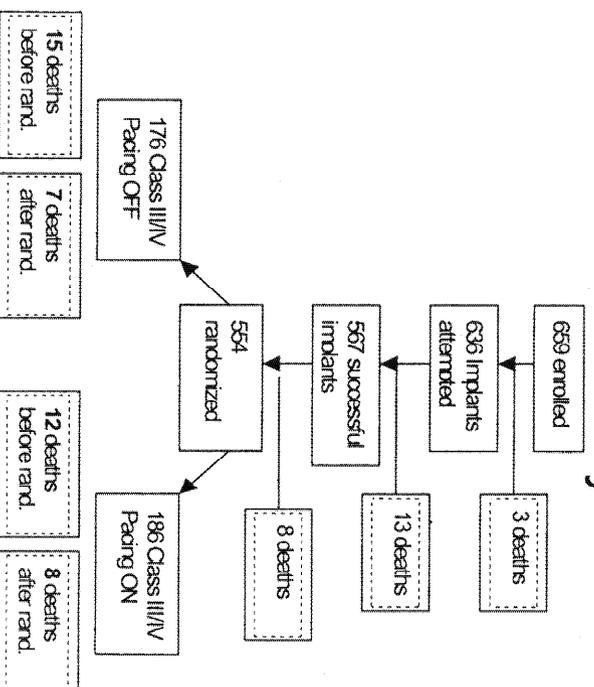
Secondary Objectives

- Sensing of LV lead
 - R wave adequate and does not change
- Change in QRS duration
 - shorter with biV pacing
- VT/VF Therapy
 - no difference between groups in incidence of VT/VF

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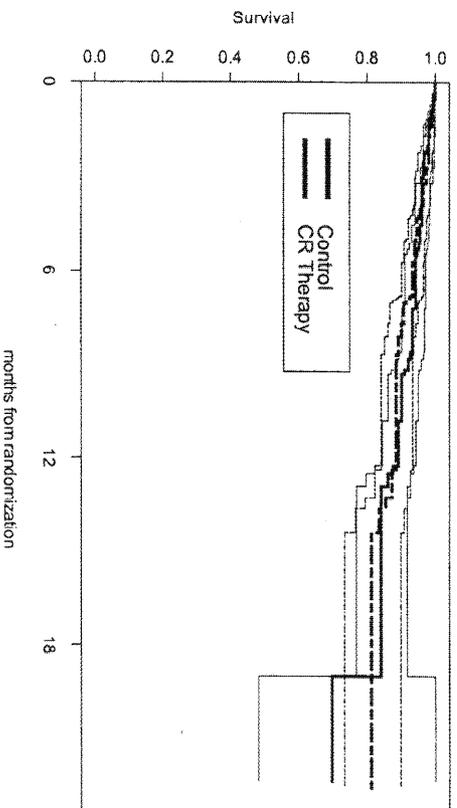
Mortality



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Mortality



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Coronary Sinus Trauma

Event	Complication	Observation	Total
CS dissection	15	9	24
Perforation	9	0	9
Total	24	9	33 (5%)

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Adverse Events: Observations

Event	Pacing OFF (N=176)	Pacing ON (N=186)
Atrial arrhythmias	27	31
Dizziness	24	17
Dyspnea	17	22
Fatigue	14	12
Heart Failure Decompensations	28	23
Hypotension	5	13
“Other”	178	240
Palpitations	1	7
Pericardial Effusion	2	1
Pleural Effusion	3	3
Stroke/CVA	2	4
Syncope	7	4

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Additional Issues Associated with ICD function

- VF detection time
 - assure that the addition of biV pacing does not interfere with the ability to sense VF
 - Information has been requested by FDA
- Inappropriate Shocks
 - assure that LV lead/ BiV pacing is not responsible for inappropriate shocks
 - Information presented not adequate

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Percentage of Time BiV Paced

- Continuous Biventricular capture
- does ICD programming interfere with ability to do this?
- FDA has requested this information

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Programming Issues: Device-Device Interaction and Limitations

- Goal is continuous BiV pacing
- VT zone programming-
 - 44% had VT detection turned off
 - 81% were programmed to VT zone of 400 msec or faster
 - ? Patient with slow VT
 - ? How flexible is BiV programming with VT zones on

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Programming Issues: Device-Device Interaction and Limitations

- Upper Tracking rate
 - 48% programmed to 120 bpm
 - ? How should this be programmed to optimize amount of pacing and limit upper rate phenomena which may cause detrimental hemodynamics
- Mode switching
 - 86% had feature turned off
 - ? how to deal with afib

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Panel Questions

Medtronic[®] InSync[®]
Implantable Cardioverter Defibrillator
Model 7272 System

Doris Terry
FDA, CDRH
ODE/DCRD/PDLB

Study Design and Analysis Method

1. Please comment on the sponsor's study design. Specifically, please address the following issues in your discussion:
 - a. Please comment on the adequacy of the sample size that contributed data in support of the primary endpoints. In particular, are there any concerns related to the "administrative censoring" of 20 percent of the enrolled patients who had not passed the 6-month point at the time of the submission?

Study Design and Analysis Method

- b. Please discuss the benefits and limitations associated with the 6-month follow-up duration for the primary endpoints.
- c. Please discuss any concerns about the propensity for crossovers and any additional issues related to blinding.

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Study Design and Analysis Method

- d. The intent-to-treat analysis on NYHA Class, Quality of Life and 6-minute Hall Walk produced nominal p-values of 0.027, 0.009 and 0.407, respectively. Thus the study results meet the pre-specified Hochberg criteria for statistical significance in that one of the endpoints (Quality of Life) produced a p-value less than 0.0167. In light of this, please comment on the possible interpretation of the results for each of the co-primary endpoints individually.

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Effectiveness of the System in Treating CHF

2. The primary endpoints of the study were improvement in NYHA Class, Quality of Life, and 6-Minute hall Walk. Please discuss the clinical relevance of these endpoints for evaluating a therapy for congestive heart failure (CHF)
3. Please discuss the clinical relevance of the sponsor's choice of secondary endpoints for evaluating a therapy for CHF. Are there specific secondary endpoints, such as peak VO2, that should be more heavily weighted in the assessment of the device?

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Effectiveness of the System in Treating CHF

4. Please comment on whether the results of the clinical study support the effectiveness of the device for the treatment of patients with medically stable Class III/IV CHF.

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Safety of the System in Treating CHF

5. When evaluating the safety of the device, one concern is whether the treatment contributes to the worsening of CHF. The sponsor has identified several measures designed to capture this including the CHF Composite response, hospitalizations, medication changes and mortality. Please comment on whether the results support the safety of the system for treating CHF in the population studied.

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Effectiveness of the System as an ICD

6. Please comment on whether the sponsor has provided adequate information to assure that there is no interference of proper ICD functionality with the addition of biventricular pacing, and that both biventricular pacing and ICD therapy can be delivered simultaneously.
7. Please discuss whether you have any comments or recommendations regarding programming considerations for the device.

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Safety of the System

8. For the Model 7272 ICD pulse generator, the sponsor has provided analyses of the ICD system-related complications at 3 months. Please comment on whether the results provide a reasonable assurance of the safety of the Model 7272 ICD pulse generator.
9. For the Model 4189 Lead, the sponsor has provided analyses of lead-related complications at 6 months. Please comment on whether the results provide a reasonable assurance of the safety of the Model 4189 Lead.

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Safety of the System

10. The sponsor has provided analyses of the system-related complications at 6 months and the adverse events (complications and observations) reported in the clinical study. Please comment on whether the results provide a reasonable assurance of the safety of the InSync ICD System.

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Risk-Benefit of the System for Treatment of CHF

11. FDA defines safety as reasonable assurance that the probable benefits to health outweigh any probable risks. Effectiveness is defined as reasonable assurance that, in a significant portion of the population, the use of the device for its intended uses will provide clinically significant results. Please discuss the overall risk-benefit of the system.

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Labeling

12. One aspect of the premarket evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize benefits and minimize adverse effects. If you recommend approval of the device, please address the following questions regarding product labeling.

- a. Do the Indications for Use adequately define the patient population studied?

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Labeling

- b. Based on the clinical experience, should there be additional Contraindications, Warnings and Precautions for the use of the InSync Model 7272 ICD System? Do the Indications for Use adequately define the patient population studied?
- c. Please comment on the operator instructions as to whether they adequately describe how the device should be used to maximize the benefits and minimize the adverse events.

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Labeling

- d. Please provide any other recommendations or comments regarding the labeling of this device.

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Post-market Study

13. With approval of the Medtronic InSync biventricular pacing system, FDA and the sponsor agreed on the following post-approval conditions: a) obtaining 12 -month mortality data on the IDE cohort, and b) performing a 3-year evaluation of mortality and chronic lead performance, including electrical performance and adverse events, on 1,000 patients. If you recommend approval, please comment on whether additional clinical follow-up or post-market studies are necessary for this device.

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