FDA Executive Summary

Circulatory System Devices Panel Meeting

December 7, 2011

P010031 / S232

Expanded Indications for

Medtronic Cardiac Resynchronization Therapy Defibrillators

Based on REVERSE & RAFT Studies

Table of Contents

Table of Tables

Table of Figures

FDA Executive Summary

P010031/S232

Expanded Indications for Medtronic Cardiac Resynchronization Therapy Defibrillators Based on REVERSE & RAFT Studies

1. Introduction & Background

This is an Executive Summary for P0100131/S232. The application has been reviewed by the Division of Cardiovascular Devices within the Center for Devices and Radiological Health of the Food and Drug Administration.

Medtronic is requesting an expansion of the indications for Medtronic CRT-D devices, which were originally approved by FDA in June 2002 (P010031), based on the results of the MIRACLE ICD study[1], for New York Heart Association (NYHA) class III-IV patients with left ventricular ejection fraction (LVEF) ≤ 35% and QRS duration of ≥ 130ms. The indications were subsequently revised to state "prolonged QRS duration" instead of providing a specific QRS duration. The sponsor now seeks to expand the indications for their CRT-D devices to include NYHA Functional Class II patients who remain symptomatic despite stable, optimal medical therapy, and who have left bundle branch block (LBBB) with a QRS duration ≥ 120 ms, and left ventricular ejection fraction ≤ 30%.

This request to broaden the indications for use is based upon the results of the Medtronic-sponsored REVERSE study (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction), which was conducted under IDE G040004, with supporting information from the University of Ottawa Heart Institute-sponsored RAFT study (Resynchronization/defibrillation for Ambulatory heart Failure Trial)[2]. The RAFT study was funded by the Canadian Institutes of Health Research and Medtronic of Canada.

Note that the REVERSE and RAFT trials had different enrollment criteria and that the broadened indications being proposed by the sponsor are a subset of the patients enrolled in either trial.

[1] Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, Canby RC, Schroeder JS, Liem LB, Hall S, Wheelan K for The Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioverter defibrillation in advanced chronic heart failure. The MIRACLE ICD Trial. JAMA 2003; 289:2685-2694.
[2] Tang, A. S., G. A. Wells, et al. (2010). "Cardiac-resynchronization therapy for mild-to-moderate heart failure." N Engl J Med 363(25): 2385-2395.

1.1 Pivotal REVERSE Study

The pivotal REVERSE study (IDE G040004) was a prospective, double-blind, randomized controlled trial which utilized Medtronic CRT devices. Both CRT-P (CRT pacemaker) and CRT-D (CRT defibrillator) devices were used in the study. The study enrolled a total of 684 subjects and randomized 610 subjects in 37 centers from the U.S., 35 centers in Europe, and one center in Canada. CRT devices were implanted in all patients and CRT was either turned "on" or turned "off". The study was designed to determine whether biventricular pacing (CRT ON) in addition to optimal medical therapy (OMT) limited the progression of heart failure in patients' clinical status compared to OMT alone (CRT OFF) in patients with asymptomatic or mildly symptomatic heart failure (NYHA Class I or II, ACC/AHA Stage C), ventricular conduction delay (QRS ≥120 ms), and reduced systolic left ventricular ejection fraction (LVEF ≤40%). The primary endpoint in the study was the heart failure Clinical Composite Response[3] that is based on mortality, hospitalizations for heart failure, crossover due to lack of sufficient therapeutic response secondary to worsening heart failure, NYHA Functional Class, and the Patient Global Assessment. Patients were classified as improved, unchanged, or worsened. The REVERSE study compared the proportion worsened at 12 months between the control and treatment groups. The predefined primary endpoint, a statistically significant difference in the proportion worsened at 12 months, was not met.

1.2 Supporting RAFT Study

The supporting RAFT study was submitted to FDA in 2006 as an IDE study (G060248) after the trial had been initiated and a substantial number of patients had been enrolled. FDA conditionally approved the study but had a number of remaining concerns regarding the endpoints, analysis plan, and sample size calculations that needed to be addressed. The IDE for the RAFT study was subsequently withdrawn after FDA provided feedback, and no patients were enrolled in the US. Because RAFT was conducted entirely outside of the United States, an IDE was not required.

RAFT was a prospective, double-blind, randomized, controlled study using Medtronic CRT-D devices. A total of 1798 patients were randomized in 24 centers in Canada, 8 centers in Western Europe and Turkey, and 2 centers in Australia. The RAFT study was designed to determine whether biventricular pacing with an ICD (CRT-D) plus optimal medical therapy (OMT) reduces total mortality and heart failure (HF) hospitalizations as compared to ICD plus OMT, in patients with mild to moderate HF (NYHA Functional Class II or III patients, subsequently changed to only NYHA Class II patients), ventricular dyssynchrony (intrinsic QRS ≥130 ms, subsequently changed to ≥120 ms), and reduced systolic left ventricular ejection fraction (LVEF ≤30%). The primary endpoint for the study was the combined endpoint of time to first HF hospitalization or all-cause death[4]. All hospitalizations greater than 24 hours were adjudicated by a blinded Event (Adjudication) Committee to be either heart failure related or not heart failure related. The primary outcome occurred in 364 of 904

[3] Packer, M. Proposal for a new clinical endpoint to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. Journal of Cardiac Failure. 2001; 7:176-182

[4] DeMets DL, Califf RM. Lessons learned from recent Cardiovascular trials: Part I. Circulation 2002; 106(6):746-51

subjects (40.3%) in the ICD group and 297 of 894 subjects (33.2%) in the CRT-D group. There was a difference in the two groups in the primary endpoint favoring the CRT-D group.

1.3 Recent Panel Meeting

In March 2010, the Circulatory System Devices Panel discussed an application from Boston Scientific to expand the indications for their CRT-D devices. This modification to the indications for use was subsequently approved by the FDA based on an extensive review of clinical data from the MADIT-CRT study (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). The overall results of the study were published in a peer-reviewed journal article.[5] Another journal article was subsequently published supporting the use of QRS morphology as a predictor of patients that benefit from CRT-D devices, which was consistent with the final indications approved by FDA.[6]

However, the source data from the MADIT-CRT study are proprietary and not available to Medtronic for this PMA request. The indications for CRT-D devices from a specific sponsor must be supported by clinical data in the submission from that sponsor. In general, published literature does not provide verifiable data source and therefore does not constitute valid scientific data that is necessary to support an application. The focus of this application and panel meeting is the REVERSE and RAFT trials.

1.4 FDA's Review of the Application

FDA's comments to the panel are identified throughout the document starting with the text "FDA Comment" and encompassed by a border (see example below). The text in these sections is intended to highlight relevant findings, potential discussion topics, and questions for the panel. In addition, a summary of these comments is provided in Section 11: Summary of FDA's Comments.

FDA Comment

Example Text

2. Proposed Indications for Use

The portion of the sponsor's approved Indications for Use statement that is relevant to heart failure currently reads as follows:

> *"The system is also indicated for the reduction of the symptoms of moderate to severe heart failure (NYHA Functional Class III or IV) in those patients who*

[5] Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. New England Journal of Medicine 2009:361.

[6] Zareba, W. Klein, H. et al. Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011;123:1061-1072

remain symptomatic despite stable, optimal medical therapy and have a left ventricular ejection fraction ≤35% and a prolonged QRS duration."

The sponsor has proposed the following revised Indications for Use statement based on the results of the REVERSE and RAFT studies:

"The [name of device family] CRT-D system is indicated for heart failure patients who meet any of the following classifications:

- *New York Heart Association (NYHA) Functional Class III or IV who remain symptomatic despite stable, optimal medical therapy, and who have a left ventricular ejection fraction ≤ 35% and a prolonged QRS duration.*

- *NYHA Functional Class II who remain symptomatic despite stable, optimal medical therapy, and who have left bundle branch block (LBBB) with a QRS duration ≥ 120 ms, and left ventricular ejection fraction ≤ 30%."*

The contraindications, warnings, and precautions remain unchanged as compared to the sponsor's current labeling.

The sponsor also proposes to make the following specific claims:

- *Medtronic CRT-D devices reduce all-cause mortality in NYHA Class II patients who remain symptomatic despite stable, optimal medical therapy and who have left bundle branch block, a QRS ≥ 120 ms, and a left ventricular ejection fraction ≤ 30%*

- *Medtronic CRT-D devices reduce heart-failure hospitalizations in NYHA Class II patients who remain symptomatic despite stable, optimal medical therapy and who have left bundle branch block, a QRS ≥ 120 ms, and a left ventricular ejection fraction ≤ 30%*

- *Medtronic CRT-D devices reduce heart-failure hospitalizations or all-cause mortality in NYHA Class II patients who remain symptomatic despite stable, optimal medical therapy and who have left bundle branch block, a QRS ≥ 120 ms, and a left ventricular ejection fraction ≤ 30%*

FDA Comment

The panel is being asked to comment on the proposed labeling (indications and claims) that would be solely based on the clinical data and results from the REVERSE and RAFT studies submitted by the sponsor.

3. Device Description

All devices used in both studies were commercially available Medtronic CRT and ICD systems that included the following products: pulse generators, defibrillation leads, pacing leads, external programmers, programming software, and all other supporting

accessories. The pulse generators used in the REVERSE study were cardiac resynchronization therapy defibrillators (CRT-D) and cardiac resynchronization therapy pacemakers (CRT-P). The pulse generators used in the RAFT study were cardiac resynchronization therapy defibrillators (CRT-D) and implantable cardioverter defibrillators (ICD).

The sponsor's cardiac resynchronization therapy defibrillators (CRT-Ds) provide ventricular tachyarrhythmia and cardiac resynchronization therapies. Ventricular tachyarrhythmia therapy is for the treatment of ventricular tachycardia (VT) and ventricular fibrillation (VF), which are arrhythmias associated with sudden cardiac death (SCD). Cardiac resynchronization therapy is for the treatment of heart failure (HF) and uses biventricular electrical stimulation to synchronize right and left ventricular contractions.

The sponsor wishes to use the revised Indications for Use statement with the following devices, which were previously reviewed and approved by FDA:

- Concerto CRT-D Model C154DWK (P010031/S031, approved 5/12/2006)
- Consulta CRT-D Model D224DRK (P010031/S084, approved 3/17/2008)
- Maximo II CRT-D Model D284TRK (P010031/S084, approved 3/17/2008)
- Concerto II CRT-D Model D274TRK (P010031/S125, approved 10/23/2008)
- Protecta XT CRT-D Model D314TRG (P010031/S171, approved 3/25/2011)
- Protecta CRT-D Model D334TRG (P010031/S171, approved 3/25/2011)

Medtronic is not requesting to modify the indications for their ICD devices (used in the RAFT study) or their CRT-P devices (used in the REVERSE study). The modifications to the indications are solely for the CRT-D devices.

4. Pre-Clinical Studies

The application does not include any additional bench or animal testing. The devices used during the REVERSE and RAFT studies are all commercially available systems. The sponsor previously submitted non-clinical data including bench testing, biocompatibility evaluation, and animal studies. These test results were previously reviewed by FDA and found to be acceptable.

5. REVERSE Clinical Study Design

5.1 Overview

The REVERSE study was a prospective, randomized, double-blinded, multi-center global study conducted in the United States, Canada and Europe. It was designed to

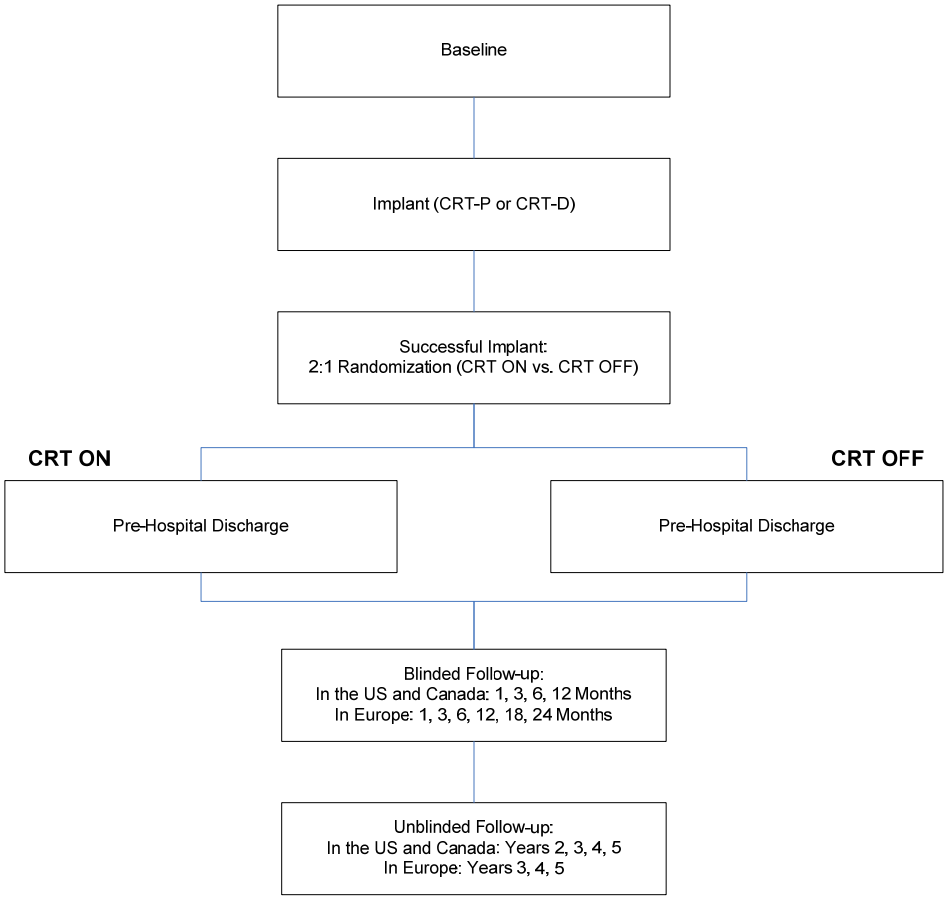
determine whether biventricular pacing limited the progression of heart failure as measured by the heart failure Clinical Composite Response as compared to optimal medical therapy alone in subjects with asymptomatic but previously symptomatic or mildly symptomatic heart failure (Stage C, NYHA Class I and Class II), ventricular dyssynchrony (QRS ≥120 ms), and reduced systolic left ventricular ejection fraction (LVEF ≤40%).

Enrolled subjects were implanted with a Medtronic CRT-P or CRT-D system (depending on ICD indication), and following successful implant were randomized in a 2:1 fashion to one of two study arms: biventricular pacing in conjunction with optimal medical therapy (CRT ON) or optimal medical therapy alone (CRT OFF). Randomization was stratified by center and type of device to be implanted (CRT-P or CRT-D).

In the U.S. and Canada, subjects were unblinded at 12 months and continued to be seen annually through 5 years of follow-up. European subjects were unblinded at 24 months and were seen annually thereafter until 5 years. It was recommended that all subjects have CRT programmed on at the conclusion of the blinded follow-up.

The following flowchart summarizes the study process.

Figure 1: REVERSE – Study Flowchart



Clinical assessments occurred at baseline, implant, pre-hospital discharge, 1 month, 6 months, 12 months, 18 months (Europe only), and then at 2, 3, 4 and 5 years. Clinical data was also collected for unscheduled follow-up visits, health care utilizations, subject

exit (including death) and system modifications. Adverse events were recorded at all visits. Visit descriptions are outlined in the table below.

Table 1: REVERSE – Description of Visits

Visit	Description
Baseline	Subject consent, subject history and symptoms, NYHA and ACC/AHA classification, echo, blood tests, 6-minute hall walk, QOL, ECG
Implant	System implant, testing and programming
Pre-hospital Discharge	Medications, chest x-ray, echo, final device programming, ECG, device interrogation save-to-disk
Blinded Follow-up	QOL, patient global assessment, 6-minute hall walk, physical assessment, NYHA and ACC/AHA classification, ECG, device interrogation save-to-disk, lead electrical data, medications, healthcare utilization, adverse events, previous blood tests (if available), echo at 6, 12, 18 (Europe only) and 24 months (Europe only)
Unblinded Follow-up	QOL, 6-minute hall walk, physical assessment, NYHA and ACC/AHA classification, device interrogation save-to-disk, healthcare utilization, adverse events, echo

5.2 Medication Stability and Optimization

The inclusion criteria included the following requirement:

> "Stable optimal medical regimen, which minimally includes an Angiotensin Converting Enzyme- Inhibitor (ACE-I) or Angiotensin Receptor Blockers (ARB) at therapeutic dose for 30 days prior to enrollment, if tolerated, and a beta blocker (BB) that is approved and indicated for HF within the geography for 90 days prior to enrollment, if tolerated, with a stable dosage for 30 days prior to enrollment. If the subject is intolerant of ACE-I or BB, documented evidence must be available. If anti-aldosterone therapy is needed in the NYHA Functional Class II subjects, it must be initiated and optimized prior to enrollment. Eplerenone requires dosage stability for 30 days prior to enrollment. Diuretics may be used as necessary to keep the subject euvolemic. Therapeutic equivalence for ACE-I substitutions is allowed within the enrollment stability timelines."

The REVERSE study recommended that subjects be placed on the target doses of optimal therapy prior to enrollment per discretion of the physician. The ACC/ESC/CCS guidelines were used as the guidance for defining optimal pharmacological therapy including optimal dosing. The REVERSE protocol did not require that subjects be on the target dose prior to enrollment and discouraged up titration. The following table provides the target dosages.

Table 2: REVERSE – Target Daily Dosage of Cardiovascular Medications

ACE Inhibitors (ACEI)	Aldosterone Receptor Blockers (ARB)	Beta Blockers (BB)
Captopril 300 mg	Candesartan 32 mg	Bisoprolol 10 mg
Enalapril 40 mg	**Losartan 100** mg	**Carvedilol 50** or 100 mg (weight based)
Fosinopril 40 mg	Valsartan 320 mg	
Lisinopril 40 mg		Metoprolol succinate 200 mg
Perindopril 16 mg		Metoprolol tartrate 200 mg
Quinapril 80 mg		
Ramipril 20 mg		
Trandolapril 8 mg		
For the analysis, ACE and ARB are combined with 40 mg of Lisinopril equivalent to 100 mg of Losartan and Lisinopril being the index drug.		

5.3 Study Oversight

The REVERSE study included the following oversight:

- **Steering Committee** – Provide scientific guidance to study design and protocol updates. Consult on clinical interpretation of study results.
- **Data Monitoring Committee** – Assess progress and accumulated safety data during the randomized period of the study. Provides recommendation on study continuation from a safety standpoint. Only Oversight Committee that reviews data in non-blinded fashion.
- **Adverse Event Advisory Committee** – Independently assess, review and classify the safety, death, healthcare utilization, and crossover data collected during study. Committee is blinded to subject's randomization arm, thus reducing bias in their adjudication.
- **Echo Core Laboratories** – Independently analyze echo data from study centers.

5.4 Heart Failure Hospitalization Definition and Adjudication

Definition

An overnight hospital admission, where the admission date and discharge date are different, and the Adverse Event Advisory Committee (AEAC) adjudicated the event as heart failure related.

Adjudication Committee Criteria

A hospitalization due to or associated with worsening heart failure. The primary reason for admission must be one of the following, or one of the following must have occurred, contributing to a prolonged hospital stay:

- Worsening HF defined as increased signs and symptoms requiring administration or augmentation of intravenous HF therapy (diuretics, inotropes, and/or vasodilators)
- Severe dehydration or hypovolemia in the absence of obvious hemorrhagic or gastrointestinal fluid loss and in the presence of diuretics
- Presumed worsening heart failure in the presence of any of the following:
  - signs and symptoms of heart failure without the requisite therapies to be categorized as worsening heart failure as described above,
  - acute coronary syndrome or myocardial infarction, or
  - atrial or ventricular arrhythmias, or electrolyte disturbances

Emergency Room Visits

Emergency room visits were collected for the purpose of understanding healthcare utilization and healthcare economic analyses. ER visits were not included in any REVERSE hospitalization analyses and were not adjudicated by the Adverse Event Advisory Committee. Unscheduled visits to the heart failure clinic were also not included in the analyses of heart failure hospitalizations.

5.5 Inclusion Criteria

Patients who met the following key inclusion criteria were given consideration for enrollment:

- NYHA Functional Class I or II with current American College of Cardiology/ American Heart Association (ACC/AHA) Stage C classification as confirmed by the documented consensus of two qualified individuals within 30 days prior to enrollment or during the baseline assessment. Stage C classification includes subjects who have current or prior symptoms of heart failure associated with underlying structural heart disease. Qualified individuals must include at least one cardiologist and another physician or a heart failure clinician/ nurse. A minimum of one classifying individual must be recorded on the Blinding Log. If the two qualified individuals assessing the NYHA Functional classification do not reach a consensus, the subject is not eligible.

- Ventricular dyssynchrony by QRS duration ≥120 ms (at Baseline or within the 30 days prior to enrollment)

- History of a left ventricular ejection fraction ≤40%, which is confirmed at the baseline echo

- Stable optimal medical regimen, which minimally includes an Angiotensin Converting Enzyme- Inhibitor (ACE-I) or Angiotensin Receptor Blockers (ARB) at therapeutic dose for 30 days prior to enrollment, if tolerated, and a beta blocker (BB) that is

approved and indicated for HF within the geography for 90 days prior to enrollment, if tolerated, with a stable dosage for 30 days prior to enrollment. If the subject is intolerant of ACE-I or BB, documented evidence must be available. If anti-aldosterone therapy is needed in the NYHA Functional Class II subjects, it must be initiated and optimized prior to enrollment. Eplerenone requires dosage stability for 30 days prior to enrollment. Diuretics may be used as necessary to keep the subject euvolemic. Therapeutic equivalence for ACE-I substitutions is allowed within the enrollment stability timelines.

- History of a left ventricular end diastolic diameter (LVEDD) ≥55 mm or the equivalent value via LVEDD Index (i.e., LVEDDi ≥ 2.8 cm/m2), which is confirmed at the baseline echo

- Indicated for an ICD as defined by the associated geography current at the time of enrollment, for those subjects that will be implanted with a CRT-D system

Note that these bullets include only the most relevant items. A complete list is available within the sponsor's materials.

5.6 Exclusion Criteria

Patients who met any of the following key exclusion criteria were <u>not</u> given consideration for enrollment:

- Classified as NYHA Functional Class III or IV in the 90 days prior to enrollment
- Decompensation of heart failure requiring hospitalization for the treatment of heart failure within the 90 days prior to enrollment
- Unstable angina, acute MI, CABG or PTCA within the 90 days prior to enrollment
- Requires permanent cardiac pacing
- Continuous or intermittent (i.e., more than two infusions per week) intravenous inotropic drug therapy
- Chronic (permanent) or persistent atrial arrhythmias. Chronic (permanent) atrial arrhythmias are defined as cases of long-standing atrial fibrillation (e.g., greater than 1 year) in which cardioversion has not been indicated or attempted. Persistent atrial arrhythmias are defined as recurrent atrial fibrillation (i.e., 2 episodes or more) that does not self terminate
- Cardioversion for atrial fibrillation or paroxysmal atrial fibrillation event within the past 30 days
- CRT-P, pacemaker, ICD or CRT-D device implanted previously or currently, except in cases where previously implanted non-CRT ICD device lifetime counters indicate the device is 95% free of ventricular and atrial pacing. If the ICD device or the subject records cannot provide this data, the subject is not eligible.

Note that these bullets include only the most relevant items. A complete list is available within the sponsor's materials.

5.7 Primary Effectiveness Endpoint

The primary effectiveness endpoint was the heart failure Clinical Composite Response measured at 12 months. The Clinical Composite Response utilizes mortality, hospitalizations for heart failure, crossover due to lack of sufficient therapeutic response secondary to worsening heart failure, NYHA Functional Class and the Patient Global Assessment.[7] The REVERSE study evaluated the proportion of subjects in each randomization group who were characterized as "Worsened" at 12 months as compared to baseline.

Success of the primary effectiveness endpoint was defined as a significantly greater percentage of subjects with a worsened Clinical Composite Response in the CRT OFF group compared to the CRT ON group.

Statistical Hypothesis and Study Success Criterion

The null and alternative hypotheses for the primary Clinical Composite Response endpoint are

H_0: $p_t = p_c$
H_a: $p_t \neq p_c$

where, p_t and p_c are the proportion of subjects with 'worsened' HF clinical composite response at 12 months post-randomization in the CRT ON and CRT OFF groups respectively. The Pearson Chi-Square test will be used to test this hypothesis. If p-value from the chi-square test is <0.05 and pt < pc then the treatment group (CRT ON) will be claimed to be superior to the control group (CRT OFF).

Clinical Composite Response Definitions

Subject deaths, hospitalizations, follow-up status and NYHA Class were collected on case report forms. NYHA Class was determined by a healthcare provider. In addition, a subject global assessment was performed in which subjects were asked at each visit how they felt in reference to their heart failure symptoms compared to before their CRT system implant. They were asked to rate their symptoms as markedly improved; moderately improved; mildly improved; unchanged; slightly worse; moderately worse; or markedly worse.

Subjects with subject global assessment scores of "mildly improved", "unchanged", or "slightly worse" received a clinical composite score of "unchanged", unless any of the improved or worsened conditions are met.

The categories of improved, unchanged, and worsened were classified as described in the following sections.

Worsened

[7] Packer, M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. Journal of Cardiac Failure. 2001; 7: 176- 182.

A subject was considered "Worsened" if he/she experienced any of the following between randomization and the earlier of 365 days post-implant or his/her 12-month follow-up:

- Death from any cause.

- Overnight hospitalization due to or associated with worsening heart failure (i.e. the admission date and discharge date must be different).

- Discontinuation of double-blind treatment due to or associated with worsening heart failure, treatment failure, or lack of/insufficient therapeutic response. This was considered to have occurred when a subject was an intentional crossover due to worsening heart failure, where "intentional crossover due to worsening heart failure" was defined to be when a study physician determine a subject had a chronically worsened (compared to baseline) NYHA classification despite exhausting all medical and surgical therapeutic intervention options and deliberately programmed the subject's CRT device to settings inconsistent with their randomization assignment for more than 72 consecutive hours. The subject's medical condition was discussed with the steering committee representative to ensure all medical options had been exhausted prior to crossover. All intentional crossovers were required to be pre-approved by the steering committee representative, unless in the case of medical emergency.

- Permanent discontinuation of double-blind treatment due to withdrawal of consent or other administrative reason with worsening heart failure at the time of study discontinuation. This was considered to have occurred when a subject exited the study and had a worse NYHA classification at that time compared to baseline.

A subject was also considered "Worsened" if either of the following occurred:

- A worsening in NYHA Class at 12 months (as compared to baseline), or if missing, the last observation carried forward (LOCF).

- Moderate or marked worsening of the subject global assessment score at 12 months, or if missing, the LOCF.

Improved

A subject was considered "Improved" if he/she was not "Worsened" and one of the following was true:

- An improvement in NYHA Class at 12 months (as compared to baseline), or if missing, LOCF.

- Moderate or marked improvement of the subject global assessment score at 12 months, or if missing, the LOCF.

Unchanged

If a subject was neither worsened nor improved, then he/she was considered "Unchanged".

FDA Comment

- **Clinical Composite Response Endpoint** – The Clinical Composite Response combines a variety of different measures including objective measures like deaths and hospitalizations as well as more subjective measures such as NYHA Class and a patient global assessment completed by the patient. As part of the global assessment, patients were asked at each visit how they felt compared to before their CRT system implant in reference to their heart failure symptoms. The results of this assessment are highly variable as a result of the highly subjective nature of terms such as "moderately improved" as compared to terms like "slightly improved." In addition, inconsistency was noted between the investigator's assessments of the patient's status (NYHA Class) as compared to the patient's self assessment (Patient Global Assessment).

5.8 Primary Safety Endpoint

The study did not have a pre-specified primary safety endpoint. A secondary objective of the REVERSE study was a comparison of adverse events between CRT ON and CRT OFF groups. However, no statistical hypothesis or test was pre-specified. Adverse events and deaths were collected in the study and adjudicated by a blinded Adverse Event Advisory Committee (AEAC). All events were classified as either complications or observations. The following definitions were used:

- Complication: An adverse event that results in invasive intervention, or the termination of significant device function regardless of other treatments. Intravenous (IV) and intramuscular (IM) drug therapies are considered invasive treatment.

- Observation: Any adverse event that is not a complication.

An Adverse Event Advisory Committee (AEAC) was established to assess, review and classify all adverse events and deaths during the clinical study. The committee also reviewed and adjudicated HF relatedness of all-cause healthcare utilization data excluding Emergency Room visits. Committee members were blinded to the randomization assignment of the subjects. The committee determined the relatedness of all adverse events and deaths to the system, procedure, therapy and heart failure (for hospitalizations). The committee also adjudicated heart failure relatedness of all crossovers.

A Data Monitoring Committee (DMC) was convened at six month intervals during the blinded period of the study to review adverse events, to address potential safety issues, and to provide recommendations for study continuation.

5.9 Selected Secondary Objective

Left ventricular end systolic volume index (LVESVi) was selected by the sponsor as a prospectively powered secondary endpoint to assess its relationship to outcomes in the NYHA I, II Stage C heart failure population. The change in LVESVi from baseline to 12 months was compared between the CRT ON group and CRT OFF group. Success of the key secondary endpoint was defined as a greater reduction in LVESVi at 12 months compared to baseline in the CRT ON group than the CRT OFF group, with the difference being statistically significant. To reduce bias, echocardiographic data were interpreted at core laboratories that were not informed of subjects' randomization assignment. There were two geographical echo core laboratories. Centers in the U.S. and Canada sent echo recordings to the U.S. Echo Core Lab and centers in Europe sent echo data to the European Echo Core Lab.

6. REVERSE Clinical Study Results

The following sections provide a brief summary of the results from the full cohort of 684 enrolled subjects in the study. A total of 684 patients were enrolled between September 3, 2004 and September 11, 2006 at 73 investigational sites, with 621 patients successfully implanted and 610 patients undergoing randomization. All 610 randomized subjects were included in the study analyses following completion of the randomized period of the study (the 12-month visit for U.S. and Canadian subjects, and the 24-month visit for European subjects). The following table summarizes the status of enrolled patients. Note that the sponsor also presented the results in a subset of subjects in order to support the proposed indication.

FDA Comment

- **Subset of REVERSE Study** – The proposed indications for use requested by the sponsor are not consistent with the enrollment criteria for the REVERSE study. The REVERSE study enrolled patients with an LVEF up to 40%, any QRS morphology, QRS duration ≥ 120 ms, and NYHA Class I and II patients. The proposed indications are in a subset of the total cohort limited to patients with LBBB, NYHA Class II, LVEF ≤ 30%, and QRS duration ≥ 120 ms. Only 31% (189 out of 610) of the original REVERSE study population would fulfill the indications for use proposed by the sponsor. As a result of concerns expressed by FDA, the sponsor proposed a modified indication statement and presented data from the subpopulations of the REVERSE and RAFT studies that were consistent with the proposed indications for use. These results are summarized in Section 9: Supporting Post-Hoc Analyses. In addition, REVERSE did not achieve significance for the pre-specified primary endpoint.

- **Post Hoc Analyses** – Many of the REVERSE results presented by the sponsor to support the proposed indications for use are not specified in the protocol or the pre-specified endpoint of Clinical Composite Response. All results presented looking at the combined endpoint of all cause mortality and heart failure hospitalizations are post hoc analyses.

- **Unable to Interpret P-Values** – For both the subgroup and post hoc analyses, p-values are un-interpretable. In other words, we do not know the type I error rate associated with these analyses.

Table 3: Compliance by Randomization

	CRT OFF (n=191)			CRT ON (n=419)		
	Visits Expected	Visits Completed	Visits In Window	Visits Expected	Visits Completed	Visits In Window
Pre-hospital Discharge	191	191 (100%)	177 (92.7%)	419	419 (100%)	376 (89.7%)
1-month Follow-up	191	191 (100%)	166 (86.9%)	417	415 (99.5%)	369 (88.5%)
3-month Follow-up	191	189 (99.0%)	173 (90.6%)	416	411 (98.8%)	380 (91.3%)
6-month Follow-up	191	191 (100%)	185 (96.9%)	413	410 (99.3%)	402 (97.3%)
12-month Follow-up	188	188 (100%)	179 (95.2%)	409	406 (99.3%)	385 (94.1%)
18-month Follow-up (Europe Only)	77	77 (100%)	72 (93.5%)	175	172 (98.3%)	166 (94.9%)
24-month Blinded Follow-up (Europe Only)	73	73 (100%)	67 (91.8%)	172	172 (100%)	157 (91.3%)

6.1 Patient Characteristics

The general characteristics of the 610 randomized patients are presented in the following table. The patients were predominantly male (78.5%) with an average age of 62.5 years, an average LVEF of 26.7%, an average LVEDD of 66.9 mm, and NYHA Class II functional status (82.5%).

Table 4: REVERSE – Baseline Patient Demographics

Subject Characteristic	CRT OFF (n= 191)	CRT ON (n= 419)
Male	79.6%	78.0%
Age (yrs)	61.8	62.9
LVEF (%)	26.4	26.8
LVEDD (mm)	67.4	66.7
QRS Duration (ms)	154	153
QRS Morphology Type		
Right bundle branch block	10%	9%
Left bundle branch block	59%	62%
IVCD	30%	30%
Ischemic	50.8%	56.3%
Device		
CRT-D	85.3%	82.3%
CRT-P	14.7%	17.7%
NYHA Classification		
Class I	16.8%	17.9%
Class II	83.2%	82.1%

The following table compares the baseline characteristics of subjects enrolled outside of the US (OUS) and subjects enrolled in the US.

Table 5: REVERSE – Baseline Patient Demographics – OUS vs. US

Subject Characteristic	OUS (n= 267)	US (n= 343)
Male	81%	76%
Age (yrs)	61.4	63.4
LVEF (%)	27.1	26.3
QRS Duration (ms)	156	151
QRS Morphology Type		
Right bundle branch block	5%	13%
Left bundle branch block	72%	52%
IVCD	22%	36%
Ischemic	44%	63%
NYHA Classification		
Class II	82%	83%

FDA Comment

- **Differences in Patient Characteristics Between US and OUS Patients** – In the REVERSE study, 610 subjects were randomized. Out of 610 subjects, 343 (56%) were from the U.S., and 267 (44%) were from outside the U.S. (OUS). There are significant differences in the baseline characteristics when comparing patients enrolled outside the US (OUS) to patients enrolled in the US. Significant differences were noted in a variety of variables including ischemic etiology, QRS morphology, QRS duration, and history of hypertension. As an example, 63% of the subjects enrolled at US sites were ischemic as compared to only 44% at OUS sites.

6.2 Evaluation of Optimal Medical Therapy

The following tables summarize the baseline medication usage for the REVERSE study for the full cohort of 610 randomized patients. All patients were included in the mean and target dose medication calculations, even patients who were not on the medication.

Table 6: REVERSE – Baseline Heart Failure Medication Use: U.S. vs. OUS

	OUS (n=267)	U.S. (n=343)
Beta Blocker		
% using	91% (243)	93% (318)
% at or above target dose	25% (66)	22% (74)
Mean daily dose (mg)	25.8 ± 20.0	22.7 ± 17.8
ACE-I/ARB		
% using	97% (259)	88% (302)
% at or above target dose	6% (15)	15% (50)
Mean daily dose (mg)	16.3 ± 9.0	15.9 ± 14.5

Table 7: REVERSE – Baseline Heart Failure Medication Usage (% to target)

Target Dose	≥100% target	≥75% target	≥50% target	≥25% target
Carvedilol 50 mg/day equivalent	23.0%	25.7%	53.9%	76.6%
Lisinopril 40 mg/day equivalent	7.2%	8.5%	35.9%	63.3%
Losartan 100 mg/day equivalent	3.4%	3.6%	12.3%	16.9%

The following figures summarize the mean dosages over time for the CRT-ON and CRT-OFF groups, distinguishing between US and OUS subjects.

Figure 2: REVERSE – Heart Failure Medication (Beta Blocker Doses Over Time)

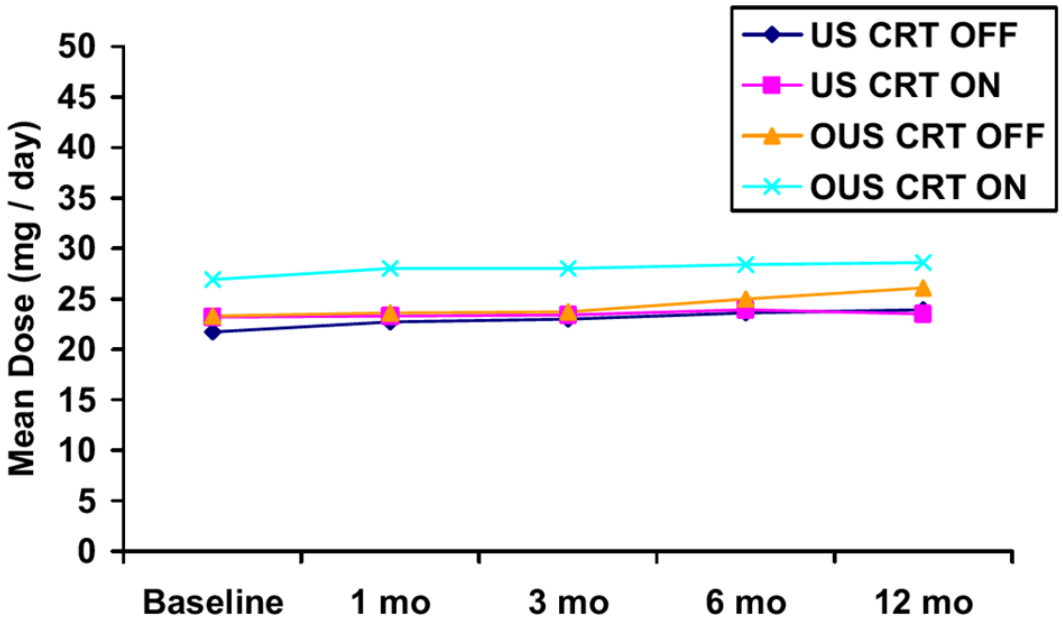
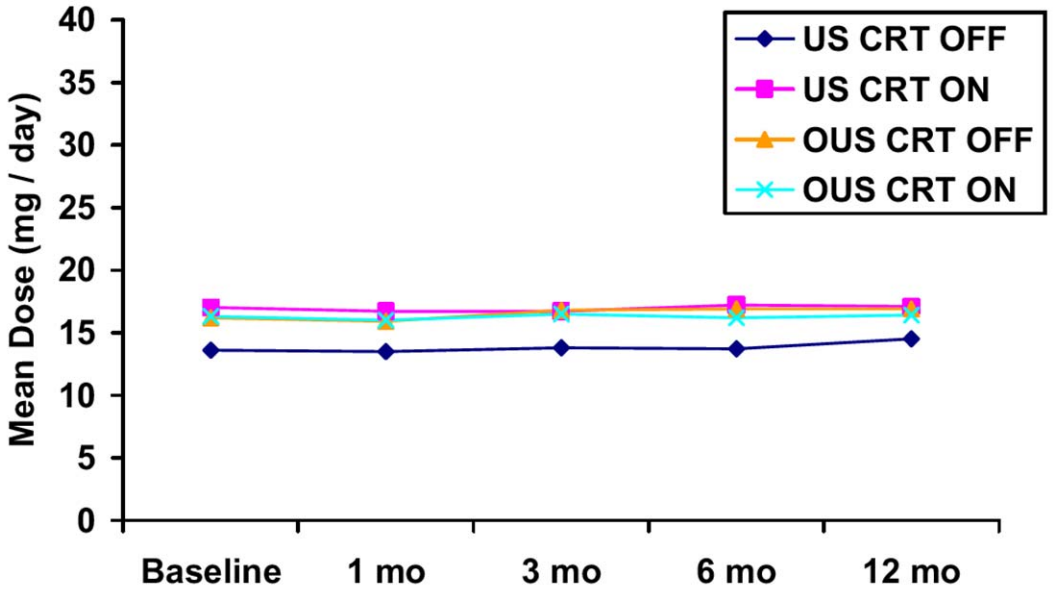


Figure 3: REVERSE – Heart Failure Medication (ACE-I/ARB Doses Over Time)



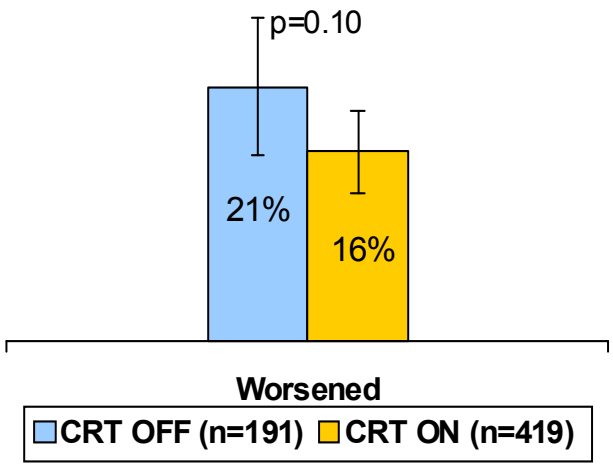
FDA Comment

- **Lack of Optimal Medical Therapy** – Consistent with the previous indication statement for NYHA Class III / IV patients, the sponsor has proposed to expand the indications to NYHA Class II patients "who remain symptomatic despite stable, optimal medical therapy." FDA is concerned about the lack of true optimization and low doses of heart failure drug therapy prior to enrollment. Only 23% were on target beta-blocker dose and 10.6% on target ACE-I/ARB at baseline. Although beta-blocker doses were fairly stable during the trial, the CRT-ON arm consistently had a higher mean dose of ACE-I/ARB and more subjects on targets dose of ACE-I/ARB. There was also a differential dosing at baseline and up to 12 months with the CRT-ON having higher doses of ACE-I/ARB.

6.3 Primary Effectiveness Endpoint

The analysis of effectiveness was based on the Clinical Composite Response at the 12-month time point. The primary endpoint for the study was the Clinical Composite Response (CCR). A CCR was recorded at 12 months for all 610 randomized subjects. The Clinical Investigation Plan (CIP) pre-specified that a comparison would be made between the two groups based on the percentage of subjects worsened. Figure 4 shows that 21% of the CRT OFF group subjects worsened versus 16% of the CRT ON group subjects. Although CRT ON resulted in a more favorable response, it did not achieve statistical significance at 12 months (p=0.10).

Figure 4: REVERSE – Primary Effectiveness Endpoint



The following tables show the contribution of the components of the Clinical Composite Response. The first table combines both US and OUS patients, while the second table differentiates the results between US and OUS patients.

Table 8: Detailed Clinical Composite Response (US and OUS Combined)

Clinical Composite Response	CRT OFF (n=191)	CRT ON (n=419)
WORSENED	41 (21%)	67 (16%)
Death	3 (2%)	9 (2%)
Hospitalized for worsening HF	14 (7%)	14 (3%)
Crossover due to worsening HF	5 (3%)	1 (<1%)
Moderately or Markedly Worse Patient Global Assessment and Worsened NYHA	0 (0%)	2 (<1%)
Worsened NYHA	18 (9%)	38 (9%)
Moderately or Markedly Worse Patient Global Assessment	1 (1%)	3 (1%)

Table 9: Detailed Clinical Composite Response (US and OUS Differentiated)

	OUS		US	
Clinical Composite Response Variable	**CRT OFF (n=83)**	**CRT ON (n=184)**	**CRT OFF (n=108)**	**CRT ON (n=235)**
WORSENED	18 (22%)	20 (11%)	23 (21%)	47 (20%)
Death	3 (4%)	3 (2%)	0 (0%)	6 (3%)
Hospitalized for worsening HF	3 (4%)	4 (2%)	11 (10%)	10 (4%)
Crossover due to worsening HF	3 (4%)	0 (0%)	2 (2%)	1 (<1%)
Moderately or Markedly Worse Patient Global Assessment and Worsened NYHA	0 (0%)	1 (1%)	0 (0%)	1 (<1%)
Worsened NYHA	9 (11%)	10 (5%)	9 (8%)	28 (12%)
Moderately or Markedly Worse Patient Global Assessment	0 (0%)	2 (1%)	1 (1%)	1 (<1%)

FDA Comment

- **Worst Case Analysis of Primary Effectiveness Endpoint** – As previously noted, the REVERSE study failed to meet the primary endpoint with a p-value of 0.10. There were 4 subjects with missing components (NYHA Class and Patient Global Assessment) of the primary endpoint, and all 4 subjects were in the CRT ON group. According to the protocol specified analysis, Last Observation Carried Forward (LOCF) was used to impute missing data in the ITT analysis. Results of sensitivity analysis to investigate the impact of using LOCF to impute missing data indicates that under a worst case scenario if all 4 subjects have a 'worsened' CCR at 12 months, the percentage of subjects with worsened CCR in the CRT ON group increases to 17%, with chi-square p=0.18 for the comparison between the treatment and control groups.
- **Differences in Results Between US and OUS Patients** Significant differences were also noted in the clinical results as measured by the clinical composite response. At US sites, 21% of the patients with CRT off worsened as compared to 20% of the patients with CRT on. At OUS sites, 22% of the patients with CRT off worsened in their clinical composite response as compared to 11% of the patients with CRT on. The beneficial effects of the therapy appear to be limited to OUS patients. Some differences in the mean dosages of heart failure medications such as beta-blockers were also noted between geographies. Primary endpoint data might not be poolable for the US and OUS populations. The p-value for interaction of treatment and geography was 0.11 using logistic regression model, and a p-value of less than 0.15 is used by FDA to determine that two groups are not poolable. Furthermore, the sponsor presented data through 24 months for the OUS patients. The results of the REVERSE study presented through 24 months are difficult to interpret and could be misleading. Patients enrolled at US sites were only followed through 12 months, while only patients enrolled at European sites were followed

through 24 months. The poolability analysis of US and OUS patients showed that the groups are not poolable with differences in baseline characteristics and results. Therefore, the 24 month results might not be applicable to US patients.

6.4 Primary Safety Endpoint

The study did not have a pre-specified primary safety endpoint. However, the sponsor provided adverse event and death information, which was evaluated by an Adverse Event Advisory Committee.

6.4.1 Adverse Events

There were 660 implant attempts in a total of 642 subjects. This included 621 successful implants and 39 unsuccessful implant attempts (16 subjects had two or more attempts). A total of 648 patients completed a baseline visit. In summary, a total of 608 adverse events were classified as procedure, system, or therapy-related at the time of the data cut-off, which are summarized in the table below.

Table 10: REVERSE – Adverse Events

	Complications		Observations		Total	
Event Description	**# Events**	**# Subjects**	**# Events**	**# Subjects**	**# Events**	**# Subjects**
Prior to Implant (n=648 baseline visits)	4	4 (0.6%)	0	0 (0.0%)	4	4 (0.6%)
During Implant (n=660 implant attempts)	20	20 (3.0%)	31	30 (4.5%)	51	46 (7.0%)
After Unsuccessful Implant (n=39 unsuccessful attempts)	1	1 (2.6%)	1	1 (2.6%)	2	2 (5.1%)
After Successful Implant (n=621 implanted patients)	318	214 (34.5%)	233	175 (28.2%)	551	315 (50.7%)

All subjects in the trial received a CRT-P or CRT-D device, depending on whether they were indicated for an ICD. Since the majority of REVERSE subjects were already indicated for an ICD at the time of enrollment (83%), the incremental risk for these subjects was the implantation of the LV lead and potential subsequent complications. All subjects in the trial received an LV lead, however the LV pacing feature was not activated for subjects in the CRT OFF group until the end of their randomization period (12 months in the U.S. and Canada, and 24 months in Europe).

Among the 621 subjects that were successfully implanted with the CRT system, 77 had a total of 92 LV lead-related complications after their successful implant. The two most common LV lead-related complications, accounting for 70% of these types of events, were LV lead dislodgement and diaphragmatic stimulation.

6.4.2 Deaths

During the randomized period, 19 deaths occurred in the study: 7 in the CRT OFF group (3.7%), and 12 in the CRT ON group (2.9%). There were 0 US deaths in the CRT OFF group and 6 US deaths in the CRT ON arm. All deaths were adjudicated by the Adverse Event Advisory Committee (AEAC). Per the Clinical Investigation Plan, if insufficient information was available to classify a death as sudden cardiac, non-sudden cardiac, or non-cardiac, the death was classified as unknown. The most common cause of death during the randomized period was progressive heart failure (4 of 19 deaths). At least 8 of the 19 (42.1%) deaths were from non-cardiac causes.

6.5 Selected Secondary Endpoint

Left ventricular end systolic volume index (LVESVi) was a prospectively powered secondary endpoint for the study. The table below shows the LVESVi results for the echo performed at 12 months post-implant as compared to baseline. CRT was programmed off for all subjects while the 12-month echo was performed in order to eliminate the potential acute effects of CRT on the LVESVi measurement. The CRT OFF subjects averaged a 1.6 ml/m^2 reduction in LVESVi over 12 months while the CRT ON subjects averaged an 18.2 ml/m^2 reduction. The following table summarizes the results. P-values are not presented because the study failed to meet the primary endpoint.

Table 11: REVERSE – Left Ventricular End Systolic Volume Index

	CRT OFF (n=191)	CRT ON (n=419)
Baseline		
n recorded	165	328
Mean ± Standard Deviation	102.3 ± 43.9	98.9 ± 34.9
Median	93.3	92.2
Range	40.2 - 384.2	31.3 - 242.4
12 Months (CRT programmed off)		
n recorded	165	328
Mean ± Standard Deviation	100.7 ± 49.5	80.8 ± 36.9
Median	94.9	71.8
Range	31.2 - 435.5	24.3 - 285.5
Paired Difference at 12 Months		
n recorded	165	328
Mean ± Standard Deviation	-1.6 ± 23.4	-18.2 ± 29.4
Median	-1.0	-15.8
Range	-85.5 - 68.1	-125.2 - 85.6

FDA Comment

- **Interpretation of Secondary Analyses** – According to the protocol, to control the type I error, secondary endpoints can be tested for statistical significance only if the primary endpoint is met. The REVERSE protocol (v10) states, "Provided the primary objective is met with a significant p-value, to keep the overall (familywise) Type I error rate at 0.05, a hierarchical test procedure will be applied to 8 of the secondary objective hypothesis tests. The goal of this hierarchical procedure is to make

statistically valid claims of significance." The sponsor has conducted statistical significance testing for secondary endpoints as well as other post-hoc endpoints and reported results of statistical inference for these analyses. The sponsor indicated in their summary that these analyses are post-hoc. It is important to note that these p-values are un-interpretable and conclusions are likely to be misleading (e.g., interpretation of changes in LVESVi).

- **Future Concern for LVESVi in IDE Letter** – FDA conditionally approved the REVERSE IDE clinical study in a letter on May 28, 2004. Within the letter, FDA asked the sponsor to give serious consideration to additional feedback regarding the analysis of the data for the purpose of determining safety and effectiveness for a future PMA application: "However, FDA believes that determining whether changes in LVESVi correlate with changes in patient clinical status will be more relevant to assessing the value of LVESVi as a useful surrogate in future CRT trials. FDA anticipates that all relevant clinical data, in addition to the criterion specified in the protocol, will be necessary to make this assessment." LVESVi does not appear to be a clear surrogate for clinical outcome, given that the REVERSE study did not fulfill the primary endpoint and did not show a reduction in mortality.

6.6 Protocol and Follow-Up Compliance

There were a total of 3522 protocol deviations with 658 deviations related to follow-up compliance. The following table outlines types and number of deviations.

Table 12: REVERSE – Protocol Deviations

Deviation	Number of Deviations in REVERSE (n=684) Events (subjects, %)
Informed consent	51 (46, 6.7%)
Inclusion/Exclusion criteria not met	121 (104, 15.2%)
Pharmacological change not related to inclusion/exclusion criteria	79 (66, 9.6%)
Randomization/Blinding	135 (120, 17.5%)
Visit compliance (early/late/missed)	658 (329, 48.1%)
Protocol required data collection and testing	1508 (525, 76.8%)
Protocol required implanted system - outside inclusion/exclusion criteria	2 (2, 0.3%)
Regulatory	132 (83, 12.1%)
Source documents	545 (194, 28.4%)
Protocol required training	80 (68, 9.9%)
Programming non-compliance	211 (170, 24.9%)
Total deviations	3522 (619, 90.5%)
Deviation Rate including Visit Compliance (Deviations / Total Patients)	5.14
Deviation Rate excluding Visit Compliance (Deviations / Total Patients)	4.18

The 3522 total deviations include 2864 unrelated to visit compliance and 658 related to visit compliance.

As a reminder, US patients were followed through 12 months while OUS patients were followed for 24 months.

FDA Comment

The collection and reporting of protocol deviations as well as the overall deviation rate appears to be typical.

7. RAFT Clinical Study Design

7.1 Overview

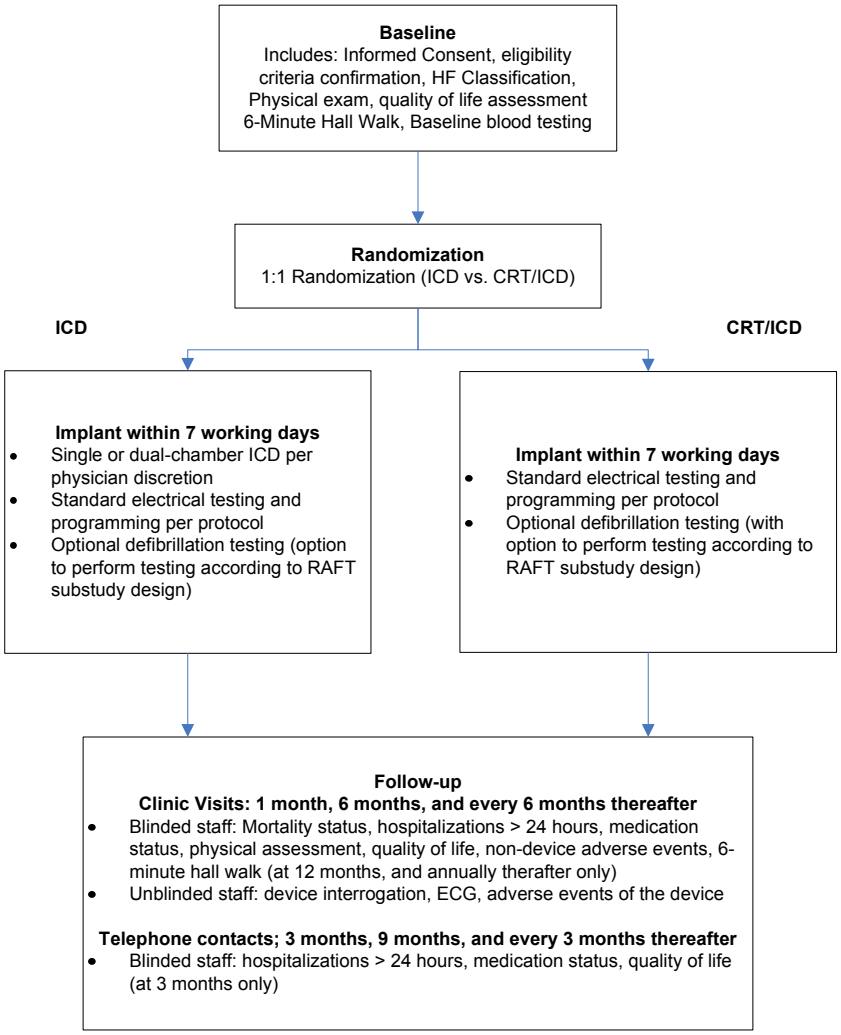
The study was a prospective, randomized, double-blind, multi-center, global post-market clinical study conducted in Canada, Europe, Turkey and Australia. The study was designed to determine whether biventricular pacing with an ICD (CRT-D) plus optimal medical therapy (OMT) reduces total mortality and heart failure hospitalizations as compared to ICD plus OMT, in subjects with mild to moderate heart failure (New York Heart Association (NYHA) Functional Class II and III), ventricular dyssynchrony (intrinsic QRS ≥ 120 ms), and reduced systolic left ventricular ejection fraction (EF ≤ 30%). The University of Ottawa Heart Institute functioned as the Coordinating Center and overall sponsor for the study.

Subjects received commercially available Medtronic devices and commercially available leads. Subjects were followed for a minimum of 18 months and remained blinded for the duration of the study. Eligible subjects who signed informed consent were randomized in a 1:1 fashion to either CRT-D or ICD arms. Randomization was stratified by center, chronic persistent atrial fibrillation (yes or no), and by type of ICD indicated (dual vs single chamber ICD).

As a reminder, the RAFT study was submitted to FDA as an IDE study but was subsequently withdrawn after FDA provided feedback. No patients were enrolled in the US. Because RAFT was conducted entirely outside of the United States, an IDE was not required.

The following flowchart summarizes the study process.

Figure 5: RAFT – Study Flowchart



Clinical assessments occurred at baseline, implant, 1 month, 6 months, and every 6 months thereafter until the last subject completed the 18-month follow-up visit. Clinical data were also collected for telephone contacts at 6-month intervals between clinic visits, hospitalizations greater than 24 hours, system modifications and subject exit (including death). Implant procedure and system-related complications were recorded at all visits.

7.2 Medication Stability and Optimization

The inclusion criteria included the following requirements:

All subjects were required to receive optimal medical therapy for 6 weeks prior to enrollment. This was defined to be:

- ACE Inhibitor / ARB: All patients were to receive ACE inhibitor whenever possible, limited by symptomatic hypotension, renal dysfunction, cough, allergic reaction, or significant other side effect. A target dosage of enalapril 10 – 20 mg bid (or equivalent ACE inhibitor and dosage) was recommended. For patients

unable to tolerate ACE inhibitor, an ARB or a hydralazine/nitrate combination was expected.

- Beta-blocker: All patients were to receive a beta-blocker whenever possible, limited by symptomatic bradycardia, allergic reaction, or significant side effect. A target dosage of metoprolol 75 mg BID, carvedilol 25 mg BID, or bisoprolol 10 mg QD was recommended unless limited by symptomatic bradycardia or hypotension, pulmonary wheeze, allergic reaction, or significant other side effect.

- Digoxin: Digoxin was allowed at the discretion of the treating physician.

- Nitrates: Any formulation of nitrates could be used for heart failure symptom control.

- Diuretic: Diuretics could be added or reduced according to patient's symptoms.

- Amiodarone: Amiodarone was allowed for the treatment of symptomatic atrial arrhythmias. Amiodarone was not to be started for asymptomatic or minimally symptomatic PVC or non-sustained VT. Amiodarone was allowed to be used for symptomatic ventricular arrhythmias developed after a subject's enrollment into the study, or frequent ICD shocks due to atrial or ventricular arrhythmias.

- Other anti-arrhythmic medications: Amiodarone was expected to be the drug of choice if anti-arrhythmic drug is necessary. In the event that a patient required an anti-arrhythmic drug and was intolerant to or had significant side effects from amiodarone, another anti-arrhythmic drug could be chosen at the discretion of the treating physician.

- Anti-coagulant: Anticoagulants could be prescribed as clinically indicated.

The RAFT study recommended that subjects be placed on the target doses of optimal therapy per discretion of the physician. The ACC/ESC/CCS guidelines were used as the guidance for defining optimal pharmacological therapy including optimal dosing. It was not required that subjects be on the target dose prior to enrollment. The following table provides the target dosages, with the medications listed being used for the subsequent discussions as the equivalent normalized dose.

Table 13: RAFT – Target Daily Dosage of Cardiovascular Medications

ACE Inhibitors (ACEI)	Aldosterone Receptor Blockers (ARB)	Beta Blockers (BB)
Captopril 300 mg	Candesartan 32 mg	Bisoprolol 10 mg
Enalapril 40 mg	**Losartan** 100 mg	**Carvedilol 50** or 100 mg (weight based)
Fosinopril 40 mg	Valsartan 320 mg	
Lisinopril 40 mg		Metoprolol succinate 200 mg
Perindopril 16 mg		Metoprolol tartrate 200 mg
Quinapril 80 mg		
Ramipril 20 mg		
Trandolapril 8 mg		
For the analysis, ACE and ARB are combined with 40 mg of Lisinopril equivalent to 100 mg of Losartan and Lisinopril being the index drug.		

Heart failure medication was allowed to be adjusted post-randomization during the study as indicated with the intention to provide optimal medical care for each patient. In fact, up-titration of heart failure medications, especially beta-blockers and ACE inhibitors, was encouraged as this trial tested optimal therapy including device support for drug dosing. It was understood that drug imbalance would occur, but the result of the trial would be more applicable to the reality of heart failure patient care. Down-titration of heart failure medication was discouraged.

FDA Comment

- **Differing Medication Requirements** – The optimization of heart failure therapy differed between the two studies during the randomized period. Both the REVERSE and RAFT trials encouraged optimal therapy prior to enrollment. The RAFT trial encouraged up titration during the study. It is difficult to compare these 2 trials for similarities in medical background therapy. FDA is concerned that differences in baseline dosages and changes in dosages during the trials might have influenced the perceived benefits of CRT in this expanded patient population.

7.3 Study Oversight

The RAFT study included the following oversight:

- **Executive Committee** – Initiated study concept and provided consultant guidance throughout study. Responsible for conduct of trial, interpretation of results, and publication. Blinded to study results throughout study.

- **Data and Safety Monitoring Board** – Assess progress and accumulated non-blinded efficacy and safety data during the study. Provide recommendation on study continuation. Only Oversight Committee that reviews data in non-blinded fashion.
- **Event (Adjudication) Committee** – Independently assess, review and classify the safety and death data, as well as hospitalizations >24 hours. Committee is blinded to subject's randomization arm, thus reducing bias in their adjudication.
- **Coordinating Center (University of Ottawa Heart Institute)** – Responsible for study coordination, database management, and statistical analysis.

7.4 Heart Failure Hospitalization Definition and Adjudication

Definition

An admission to a healthcare facility lasting more than 24 hours with symptoms of congestive heart failure and subsequent treatment for heart failure, and the RAFT Event Committee adjudicated the event as heart failure exacerbation.

Adjudication Committee Criteria

Adjudication of the RAFT Study Event case report form (CRF) by the Event Committee members will be the determinant of the cause of hospitalization. Determination of the above will be based upon review of the CRF and accompanying pertinent source documentation. Heart Failure Definitions to include:

- Evidence of heart failure as noted on chest x-ray
- IV diuretic use
- Oral diuretic use
- Increase in BNP
- Sudden weight gain
- Marked peripheral edema

7.5 Inclusion Criteria

Patients who met the following key inclusion criteria were given consideration for enrollment:

- NYHA Class II or III [revised to NYHA Class II only during later versions of the protocol]
- LVEF ≤ 30% by MUGA/Catheterization OR LVEF ≤ 30% and LV end diastolic dimension ≥ 60 mm (by echocardiogram) within 6 months prior to randomization
- Intrinsic QRS Complex Width ≥ 130 ms [revised to ≥ 120 ms during later versions of the protocol] OR Paced QRS measurement ≥ 200 ms [added in latter versions of the protocol]

- ICD indication for primary or secondary prevention
- Optimal heart failure pharmacological therapy
- Normal Sinus Rhythm or Chronic persistent Atrial Tachyarrhythmia with resting Ventricular Heart Rate ≤ 60 bpm and 6 Minute Hall Walk Ventricular Heart Rate of ≤ 90 bpm OR Chronic persistent Atrial Tachyarrhythmia with resting Ventricular Heart Rate > 60 bpm and 6 Minute Hall Walk Ventricular Heart Rate of > 90 bpm and booked for Atrio-Ventricular Junction Ablation

FDA Comment

- **Multiple Revisions to the Protocol Inclusion Criteria** – Note that the inclusion criteria were modified during the study. First, NYHA Class II and III subjects were initially considered for enrollment in the initial version of the protocol until the inclusion criteria were modified to include only NYHA Class II subjects. Second, the QRS duration was modified from ≥ 130 ms in the initial version to ≥ 120 ms in later versions. Note that only 3% of the patients were enrolled under the initial version of the protocol, which required a QRS duration ≥ 130 ms. Patients were enrolled under 5 different versions of the protocol. The enrollment criteria related to NYHA Class and QRS duration were modified during the study. The initial versions of the protocol allowed enrollment of NYHA Class II & III patients and used a QRS duration cut-off of 130 milliseconds. Nearly half (46%) of the patients were enrolled into the study under the initial 3 versions of the protocol, using enrollment criteria inconsistent with the final requirements for NYHA Class II patients and a QRS duration cut-off of 120 milliseconds. These differences in the inclusion criteria could have biased the results, especially with regard to the enrollment of patients that were not truly NYHA Class II functional status.

7.6 Exclusion Criteria

Patients who met any of the following key exclusion criteria were not given consideration for enrollment:

- Intravenous inotropic agent in the last four days
- Patients with an acute coronary syndrome including MI can be included if the patient has had a previous MI with LV dysfunction (LVEF ≤ 30%)
- In-hospital patients who have acute cardiac or non-cardiac illness that requires intensive care
- Restrictive, hypertrophic or reversible form of cardiomyopathy
- Patients with an existing ICD (Patients with an existing pacemaker may be included if the patients satisfies all other inclusion/exclusion criteria)
- Coronary revascularization (Coronary Artery Bypass Graft (CABG) or Percutaneous Coronary Intervention (PCI)) < 1 month if previously determined LVEF > 30%

- Patients with a more recent revascularization can be included if a previous determined LVEF was ≤ 30%

Note that these bullets include only the most relevant items. A complete list is available within the sponsor's materials.

7.7 Primary Effectiveness Endpoint

The primary effectiveness endpoint was a composite of all-cause mortality and hospitalization for heart failure (time to first event). Hospitalization for heart failure (HF) was defined as an admission to a hospital with a diagnosis of worsening HF for greater than 24 hours. Emergency room visits for heart failure were not included. Success of the primary effectiveness endpoint was defined as a reduction in the composite endpoint of all-cause mortality and HF hospitalization for CRT-D subjects as compared to ICD subjects with the difference being statistically significant. The primary objective of this study was to determine if the addition of CRT to optimal medical therapy and ICD is effective in reducing morbidity or mortality in patients with poor LV function, wide QRS and heart failure symptoms. The log-rank test was used to compare the time to first HF hospitalization or all-cause death between the CRT-D group and the ICD group.

Statistical Hypothesis and Study Success Criterion

The RAFT protocol does not explicitly state the statistical hypothesis or study success criterion.

The implied null and alternative hypotheses from the protocol are:

H_0: $S_{CRT\text{-}D} = S_{ICD}$
H_a: $S_{CRT\text{-}D} \neq S_{ICD}$

Where, S_{ICD} and $S_{CRT\text{-}D}$ are the time to death or CHF hospitalization. The two-sided log-rank test will be used to test this hypothesis. If p-value <0.05 and $S_{CRT\text{-}D} < S_{ICD}$ then the treatment group (CRT-D) will be claimed to be superior to the control group (ICD).

FDA Comment

- **Sample Size Calculations and Analysis Plan –** The study sample size, estimates of the treatment effect, crossover rates, lost-to-follow up rate, minimum follow up duration and desired study power all underwent modifications during the course of the study. Patients were enrolled under 5 different versions of the protocol. According to the original study protocol, 1500 subjects were to be enrolled in the study and followed for a minimum of 24 months. This was revised to 1800 subjects and minimum follow up duration of 18 months (Note: In the IDE protocol submitted for agency approval the study sample size was specified as 2222 subjects). The interim analyses plan was revised multiple times during the course of the study. Initially the study had three planned interim analyses (when 25%, 50% and 75% of patients have been followed for 2 years). Two interim analyses were conducted by the DSMB (when 33% and 66% of subjects had been followed for 18 months). The DSMB recommended study continuation after both interim analyses. The RAFT

study protocol did not explicitly state statistical hypothesis for the primary endpoint or the study success criteria. The study specified several secondary endpoints but no multiplicity adjustment strategy was pre-specified in the protocol to control the type I error. Due to all these unplanned changes the statistical conclusions may not be valid.

7.8 Primary Safety Endpoint

The study did not have a pre-specified primary safety endpoint. However, basic safety data (procedure and system-related complications and patient deaths) were collected as part of the study.

FDA Comment

Evaluation of Safety – The RAFT study did not have any pre-specified safety endpoints or goals. No statistical hypothesis or test was pre-specified. FDA expressed concern about the collection of supporting safety data when the RAFT study was submitted as an IDE. The sponsor withdrew the IDE submission without addressing these concerns.

8. RAFT Clinical Study Results

The following sections outline a brief summary of the results from the full cohort of 1798 randomized patients enrolled in the RAFT study. The first RAFT subject was enrolled on January 13, 2003. A total of 1798 patients signed an informed consent form at 34 clinical study centers in Canada, Western Europe, Turkey, and Australia. There were no US patients. Enrollment was completed on February 27, 2009. Nine hundred and four (904) patients were randomized to the ICD arm, and 894 patients were randomized to CRT-D. Patients were followed for a mean 40 months ± 20 months. The following figure summarizes the status of enrolled patients.

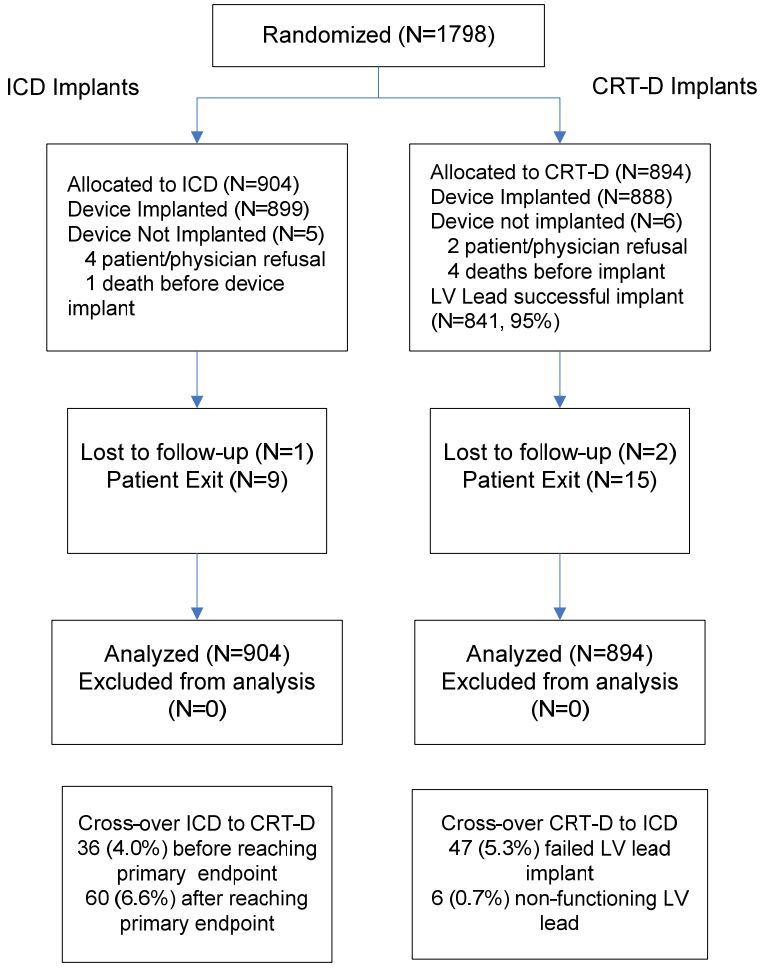
FDA Comment

- **General RAFT Concerns** – As a reminder, the RAFT data was submitted by the sponsor as additional supporting data to supplement the REVERSE study results. The sponsor elected to use the data from RAFT after REVERSE failed its primary endpoint. Furthermore, the proposed indications for use requested by the sponsor are not consistent with the enrollment criteria for the RAFT study. The proposed indications are in a subset of the total cohort limited to patients with LBBB, NYHA class II and LVEF ≤ 30%. Only 53% of the original RAFT study population fulfills the indications for use proposed by the sponsor. Therefore, the sponsor also presented additional post-hoc analyses on the subset of patients in the RAFT study that would be consistent with the proposed indications for use. These analyses are discussed in Section 9: Supporting Post-Hoc Analyses.

- **RAFT as Non-IDE Study** – RAFT was submitted to FDA as an IDE study (G060248). FDA expressed a number of concerns including a lack of a safety

endpoint and limited evaluation and collection of adverse events. The sponsor elected to withdraw the IDE application. FDA is specifically concerned about some critical elements including the subject's NYHA Class, the prevalence or timing of heart failure hospitalizations, and the medication doses of BB and ACE-I/ARB.

Figure 6: RAFT – Patient Status



8.1 Patient Characteristics

The general characteristics of the 1798 randomized patients are presented in the following table. The patients were predominantly male (82.9%) with an average age of 66.1 years, an average LVEF of 22.6%, and NYHA Class II functional status (80.0%). The following tables summarize the patient characteristics at baseline.

Table 14: RAFT – Baseline Patient Demographics

	All Patients	
	ICD (n=904)	**CRT-D (n=894)**
Age (yrs)	66.2 ± 9.4	66.1 ± 9.3
Male	81.0%	84.8%
Ischemic	64.9%	68.7%
NYHA Class II	80.8%	79.2%
LVEF (%)	22.6 ± 5.1	22.6 ± 5.4
Permanent AF	12.7%	12.8%
QRS duration (ms)	158 ± 24	157 ± 24
QRS Morphology LBBB RBBB IVCD Paced	 71.1% 10.3% 11.2% 7.4%	 72.9% 7.6% 11.9% 7.6%
Beta blockers	89.0%	90.4%
ACE-I / ARB	97.1%	96.1%
Diuretics	83.6%	84.7%

Table 15: RAFT – Baseline Functional Status

Subject Characteristic	**ICD (n= 904)**	**CRT-D (n= 894)**
NYHA Classification		
Class II	730 (80.8%)	708 (79.2%)
Class III	174 (19.2%)	186 (20.8%)
6-Minute Hall Walk Distance (m)		
n	765	789
Mean	354.9	351.3
Standard Deviation	110.1	106.7

FDA Comment

- **Less Stringent Screening of Patients Prior to Enrollment in RAFT** – REVERSE study excluded patients who were hospitalized for HF or classified as NYHA III or IV in the 90 days prior to enrollment while RAFT did not specifically exclude these patients. The NYHA class at baseline had to be confirmed by two qualified individuals in REVERSE, but this process was not used in RAFT. The enrollment criteria for REVERSE were more specific and probably limited the enrollment of sicker patients: those patients currently with NYHA Class II symptoms but with previous recent heart failure hospitalizations or NYHA Class III or IV symptoms.

- **Choices for NYHA Class on Case Report Forms** – The initial 3 versions of the RAFT protocol allowed the enrollment of NYHA Class II & III patients, while the final 2 versions of the protocol only allowed the enrollment of NYHA Class II patients. The baseline case report form includes a section for the blinded physician exam. This section only included a choice of NYHA Class II in the later protocol versions. As a result, there was no way for the blinded physician to record any other NYHA Class on the case report form, even if the blinded physician believed that the patient was not NYHA Class II. This limitation could have created bias in the classification of patients at enrollment.

Table 16: RAFT – Baseline Cardiovascular Medical History

Subject Characteristic	ICD (n= 904)	CRT-D (n= 894)
Atrial Rhythm		
Permanent atrial fibrillation or flutter	115 (12.7%)	114 (12.8%)
Sinus or atrial paced	789 (87.3%)	780 (87.2%)
Hypertension	397 (43.9%)	402 (45.0%)
Diabetes Mellitus	313 (34.6%)	293 (32.8%)
Peripheral Vascular Disease	90 (10.0%)	88 (9.8%)
Previous Percutaneous Coronary Intervention	208 (23.0%)	220 (24.6%)
Previous CABG	313 (34.6%)	293 (32.8%)
Hospitalized for HF in previous 12 months	223 (24.7%)	238 (26.6%)
Current Cigarette Smoking	127 (14.0%)	121 (13.5%)
Estimated Glomerular Filtration Rate		
n	897	885
Mean	60.8%	59.5%
Standard Deviation	21.9	19.8
Rate (ml/min/1.73 m²)		
<30	63 (7.0%)	57 (6.4%)
30-59	383 (42.7%)	398 (45.0%)
≥60	451 (50.3%)	430 (48.6%)

8.2 Evaluation of Optimal Medical Therapy

The following tables summarize the baseline medication usage for the RAFT NYHA Class II subgroup. All patients were included in the mean and target dose medication calculations, even patients who were not on the medication.

Table 17: RAFT – Baseline Heart Failure Medication Usage (% to target) (NYHA II)

Target Dose	≥100% target	≥75% target	≥50% target	≥25% target
Carvedilol 50 mg/day equivalent	15.7%	21.9%	49.1%	74.2%
Lisinopril 40 mg/day equivalent	6.0%	8.1%	44.3%	66.8%
Losartan 100 mg/day equivalent	3.6%	4.1%	10.5%	16.3%

The following figures summarize the proportion at the target dosage for each medication.

Figure 7: RAFT – Percent on Target Dose Beta Blocker Over Time (NYHA II)

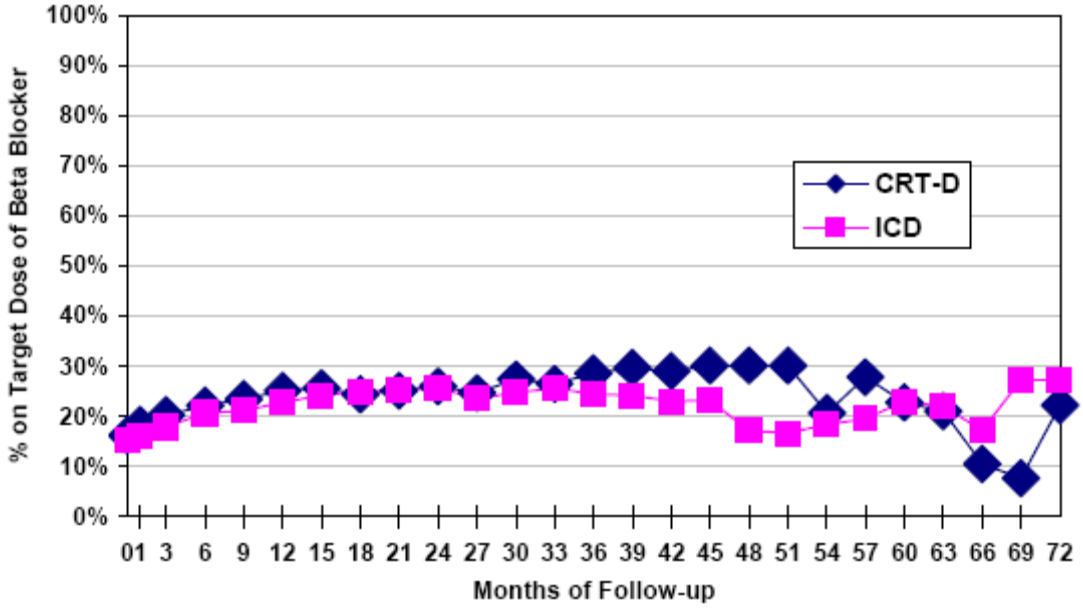
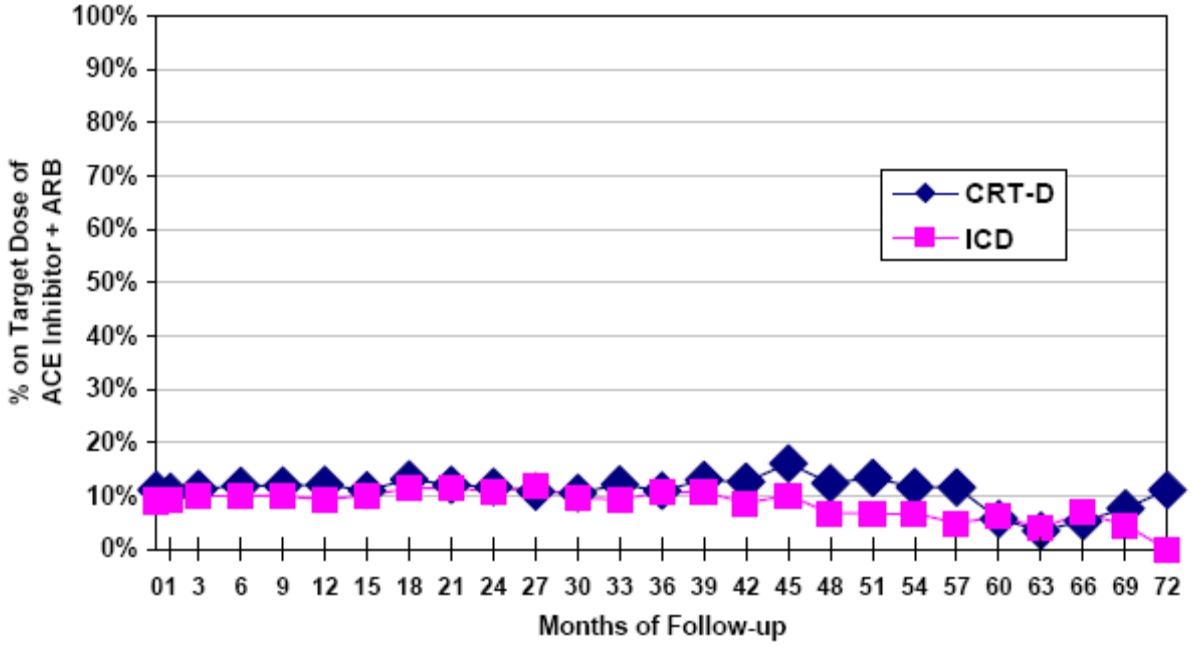


Figure 8: RAFT – Percent on Target Dose ACE-I/ARB Over Time (NYHA II)



FDA Comment

- **Lack of Optimal Medical Therapy** – Consistent with the previous indication statement for NYHA Class III / IV patients, the sponsor has proposed to expand the indications to NYHA Class II patients "who remain symptomatic despite stable, optimal medical therapy." FDA is concerned about the lack of true optimization of drug therapy prior to enrollment. The percent of patients on each of the drugs is not representative of the actual doses. Only 15.7% were on target beta-blocker dose and 9.6% were on target ACE-I or ARB at baseline. Although medication doses remained fairly stable, the CRT-D arm saw an increase in percentage of subjects on target dose compared to the ICD arm. The up titration of dosages during the study could account for the perceived benefit of CRT.

8.3 Primary Safety Endpoint

The study did not have a pre-specified primary safety endpoint. However, the sponsor provided adverse event and death information.

8.3.1 Adverse Events

Adverse event collection was limited in RAFT to implant procedure and system-related complications, which were collected at implant and each follow-up visit. Complications are a subset of adverse events, requiring invasive intervention or significant loss of device function. These complications were reviewed at DSMB meetings to ensure patient safety and were adjudicated by a blinded Event Committee. No specific objective was pre-specified surrounding adverse events. Of the 1798 randomized patients, 1787 had an attempted device implant and accrued 5974 years of follow-up

(ICD: n=899, 2923 years; CRT-D: n=888, 3051 years). During the study, 894 procedure or system-related complications were reported in 583 patients.

At FDA's request, the sponsor provided the following adverse event summary table. The sponsor's original presentation included "Upgrade to BiV ICD" as an adverse event in the ICD group. These events resulted from crossovers and were therefore excluded from the following table. The table provides a high-level summary of all RAFT procedure or system related complications collected for the duration of the study, excluding CRT-D upgrades, by relatedness. Note that of the 330 device-related complications, 292 were device replacements.

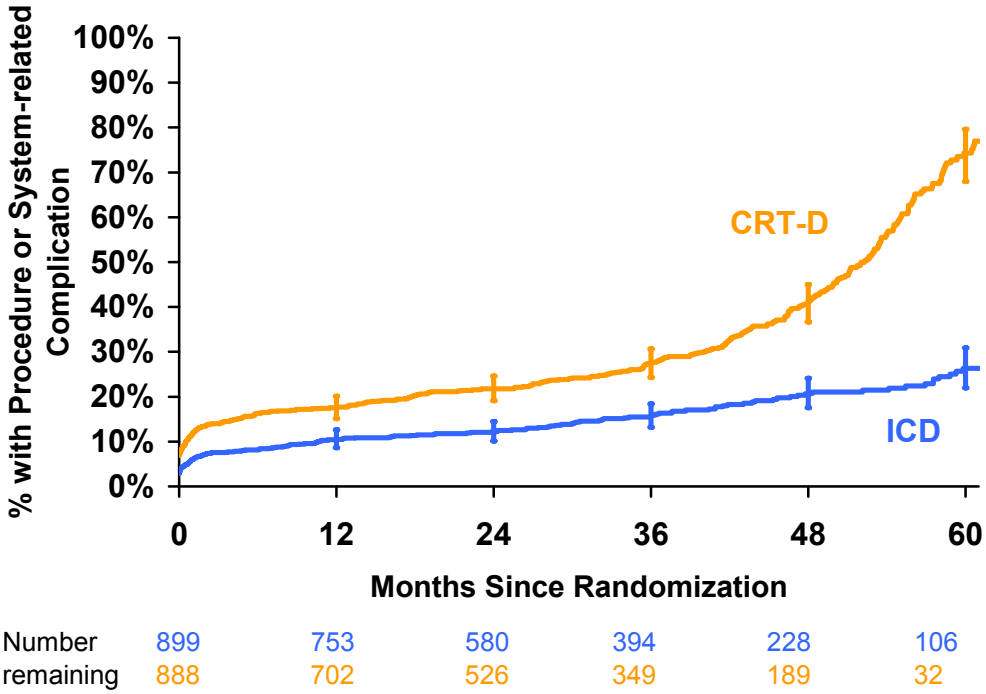
Table 18: RAFT Procedure or System Related Complications (excluding CRT-D upgrades)

	ICD N=899		**CRT-D N=888**	
Relatedness*	**No. AEs (%)**	**No. Subjects (%)**	**No. AEs (%)**	**No. Subjects (%)**
LV Lead-related	5 (2.2%)	5 (0.6%)	106 (18.7%)	90 (10.1%)
RV Lead-related	90 (40%)	80 (8.9%)	111 (19.5%)	103 (11.6%)
RA Lead-related	26 (11.6%)	24 (2.7%)	45 (7.9%)	38 (4.3%)
Implant Procedure-related (defined as any event within 30 days of implant)	56 (24.9%)	54 (6.0%)	113 (19.9%)	104 (11.7%)
System Modification Procedure-related (defined as any event within 30 days of a system modification)	23 (10.2%)	21 (2.3%)	43 (7.6%)	35 (3.9%)
Device-related	68 (30.2%)	65 (7.2%)	262 (46.1%)	238 (26.8%)
Total	**225**	**164 (18.2%)**	**568**	**359 (40.4%)**

*Relatedness categories are not mutually exclusive. Events could be related to more than one component/activity.

RAFT allowed complications to be classified to more than one component or activity. For instance, a LV lead dislodgement which occurred shortly after implant could be counted as both LV lead related and implant procedure related. This does lead to double-counting of events within the table.

Figure 9: RAFT – Time to First Procedure or System-Related Complication (post-hoc) (excluding CRT-D upgrades in ICD group)



Left Ventricular Lead-Related Complications

As all patients in the RAFT study were indicated for an ICD, the incremental risk between the CRT-D group and the ICD group was the left ventricular (LV) lead and potential subsequent complications. There were 106 LV lead-related complications reported in the CRT-D group. The table below displays the complications classified as related to the LV lead.

Table 19: RAFT – Left Ventricular Lead-Related Complications (post-hoc)

	CRT-D (n=894)	
Key Term	**# AEs**	**# AEs within 30 days of implant**
Lead dislodgement - intervention	83 (72, 8.1%)	34 (31, 3.5%)
Sensing/pacing issues	15 (14, 1.6%)	3 (3, 0.3%)
Lead fracture	3 (2, 0.2%)	0 (0, 0%)
Prophylactic lead replacement	3 (3, 0.3%)	0 (0, 0%)
Loose set screw	2 (2, 0.2%)	1 (1, 0.1%)
Total	**106 (90, 10.1%)**	**38 (34, 3.8%)**

Discussion on Procedure and System-Related Complications

As anticipated, the rate of procedure and system-related adverse events in RAFT was higher for the CRT-D arm as compared to the ICD arm (17.5% versus 10.5% at 12

months, based on the Kaplan-Meier estimates). This is due to the addition of the LV lead for the CRT-D group.

For those patients indicated for an ICD, the incremental risk is associated with the implantation of a LV lead and potential subsequent complications. The LV lead adverse event rate in RAFT was 7.4% at 12 months post-implant. This is comparable to the rate of 9.1% observed in REVERSE at 12 months. As in REVERSE, LV lead dislodgement was the most common LV lead-related event, occurring in 8.1% of CRT-D patients.

FDA Comment

- **Adverse Events (Crossovers)** – The sponsor's initial presentation of adverse events included "upgrade to BiV ICD" (crossovers) as adverse events in the ICD control group. These upgrades occurred in 101 patients out of 899 ICD subjects (11.2%) in the total RAFT cohort of 1798 subjects. FDA asked the sponsor to exclude these events from the analysis. In addition, these crossovers may represent a heart failure endpoint, but FDA does not feel they are truly representative of the safety profile for ICD devices.

- **Adverse Events (Pulse Generator Changes)** – During the study, 216 subjects (12.1%) required a pulse generator change as a result of normal battery depletion. This event occurred more frequently in the CRT-D group (188 or 21.2% of the subjects) than in the ICD group (28 or 3.1% of the subjects). This difference is anticipated but clinically relevant when comparing the devices. CRT-D devices would typically deplete the battery faster as a result of the increased current drain required for continuous pacing on both the right ventricular and left ventricular leads. This effect results in a divergence of the curves past 4 years of follow-up (Figure 9).

8.3.2 Patient Deaths

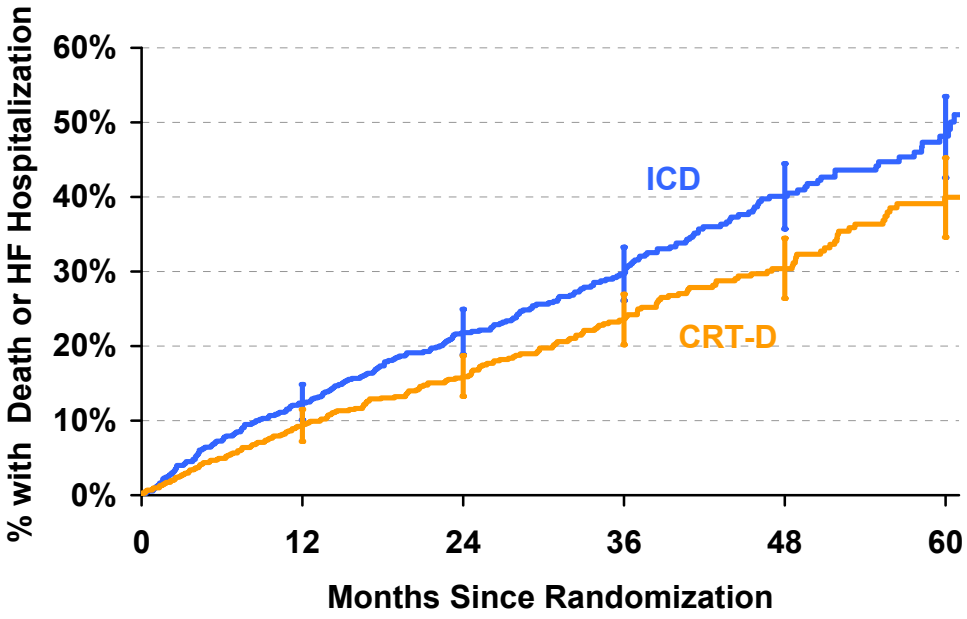
Patient deaths are included in the primary effectiveness endpoint discussion results below.

8.4 Primary Effectiveness Endpoint

The primary effectiveness endpoint was the time to first heart failure hospitalization or all-cause mortality for all randomized patients. All hospitalizations greater than 24 hours were adjudicated by the blinded Adjudication Committee to be either heart failure related or not heart failure related. The primary outcome occurred in 364 of 904 patients (40.3%) in the ICD group and 297 of 894 (33.2%) in the CRT-D group, for the full cohort. The time to occurrence of the primary endpoint was significantly prolonged in the CRT-D group (p=0.0002). This p-value is not adjusted for the two interim looks that were conducted. The adjusted p-value is 0.014. Based on the Cox proportional-hazards model the hazard ratio was 0.75. Both components of the primary endpoint, the time to death (p=0.003, HR=0.75) and the time to first HF hospitalization (p<0.0001, HR=0.68) were also individually prolonged by CRT-D. At 5 years, the observed rates of the primary endpoint were 51.3% in the ICD group and 42.4% in the CRT-D group.

The following sections present data from the NYHA Class II population, not the full cohort, as this subgroup is more relevant to subsequent discussions. The Kaplan-Meier curve and endpoint components of NYHA Class II subgroup is presented below (p=0.001, HR=0.73).

Figure 10: RAFT – Combined HF Hospitalization and All-Cause Mortality (NYHA Class II)



Number	730	638	465	299	146	57
remaining	708	640	488	315	181	70

Table 20: RAFT – Primary Effectiveness Endpoint Components (NYHA Class II)

	Number of Patients (% of All Patients in Treatment Group)		
	ICD (n=730)	**CRT-D (n=708)**	**Hazard Ratio (95% C.I.)**
Patients with Primary Endpoint Event	253 (35%)	193 (27%)	0.73 (0.61, 0.88)
Patients with All-Cause Mortality*	154 (21%)	110 (16%)	0.71 (0.56, 0.91)
Patients with HF Hospitalization	159 (22%)	115 (16%)	0.70 (0.55, 0.89)

* This category includes all deaths, including those that occurred after the first heart-failure event.

Table 21: RAFT – Primary Effectiveness Endpoint Components (Full Cohort)

Cause of Death Category	ICD (n=904)	CRT-D (n=894)	Total (n=1798)
Non Cardiovascular	70 (30%)	54 (29%)	124 (29%)
Unexpected death presumed to be cardiovascular disease, occurring within 24 hrs of the onset of symptoms without confirmation of cardiovascular cause, and without clinical or post mortem evidence of etiology	25 (11%)	20 (11%)	45 (11%)
Myocardial Infarction: Death within 7 days of the onset of documented MI	4 (2%)	3 (2%)	7 (2%)
Congestive Heart Failure: Death due to clinical, radiological or post-mortem evidence of CHF, without clinical or postmortem evidence of other cause, such as ischemia, infection, dysrhythmia	95 (40%)	81 (44%)	176 (42%)
Post cardiovascular intervention: Death associated with the intervention: within 30 days of cardiovascular surgery, or within 7 days of cardiac catheterization/angioplasty	1 (<1%)	0 (0%)	1 (<1%)
Documented Arrhythmia: Death due to brady or tachyarrhythmias, not induced by an acute ischemic event	24 (10%)	23 (12%)	47 (11%)
Stroke: Death due to stroke occurring within 7 days of the signs and symptoms of stroke	13 (6%)	4 (2%)	17 (4%)
Other cardiovascular diseases: Death due to other vascular diseases such as pulmonary embolism, aortic aneurysm, etc.	0 (0%)	1 (1%)	1 (<1%)
Presumed cardiovascular death: Suspicion of CV death that does not fulfill other criteria	4 (2%)	0 (0%)	4 (1%)
Total	236 (100%)	186 (100%)	422 (100%)

FDA Comment

- **RAFT Survival Rate** – The sponsor reported a reduction in all cause mortality in the CRT-D group as compared to the ICD group. However, the observed mortality rate in the ICD control group in the RAFT study is higher than other similar heart failure trials such as REVERSE. If the observed rate of mortality in the study is significantly higher than similar previous studies, then the reduction in mortality might be a result of the type of patients enrolled in the study, rather than the effect of CRT. The all-cause mortality rate for the NYHA Class II cohort of the ICD control group in RAFT (5.4% at 12 months) was higher than the rate observed in REVERSE (1.6% at 12 months) and MADIT-CRT (2.0% at 12 months). RAFT is the only CRT trial in NYHA Class II patients that demonstrated a mortality benefit, and FDA is concerned this outcome may be due to a sicker population than the other trials. The sponsor provided a few studies with similar or higher rates of mortality in NYHA Class II patients. However, FDA believes that these studies are not comparable to RAFT because the patient population is different.

- **Revisions to the Interim Analysis Plan and Sample Size Calculations** – Patients were enrolled under 5 different versions of the RAFT protocol. The planned study enrollment was 1500 subjects according to the original protocol but this was subsequently modified to 2222 patients (protocol version 4), which was again modified to 1800 subjects (protocol version 5). Two interim analyses were planned originally, the first when 50% of patients enrolled have been followed for 2 years and a second analysis when 75% of patients enrolled have been followed for 2 years. This was subsequently changed to 3 interim analyses (protocol version 4), the first, second and third analysis to be conducted when 25%, 50% and 75% of patients enrolled have been followed for 2 years. According to the sponsor, when 24.5% of the enrolled subjects had been followed for 2 years and just before the first interim analysis was to be conducted, it was decided to change the interim analyses plan to 2 interim analyses (protocol version 5 dated June 28, 2007), the first and second analysis when 33% and 66% of patients enrolled have been followed for 2 years. However, it should be noted that the first interim analysis was conducted on March 21, 2007 before the interim analysis plan change was reflected in the protocol. The event rate for the primary endpoint in the ICD arm was originally assumed to be 25% per year but this was changed to 11.2% per year after it was decided to limit inclusion to NYHA class II (protocol version 4) and it was subsequently changed to 12.6% per year (protocol version 5, which is dated after the first interim analysis was conducted). Additionally the relative risk reduction due to treatment and the study power also underwent modifications.

8.5 Secondary Objectives

The sponsor provided data to support a number of secondary objectives. The sponsor's presentation limited the results to patients with NYHA Class II (n = 1438) and excluded the NYHA Class III patients, which were 20.0% of the total RAFT cohort. The secondary objectives included

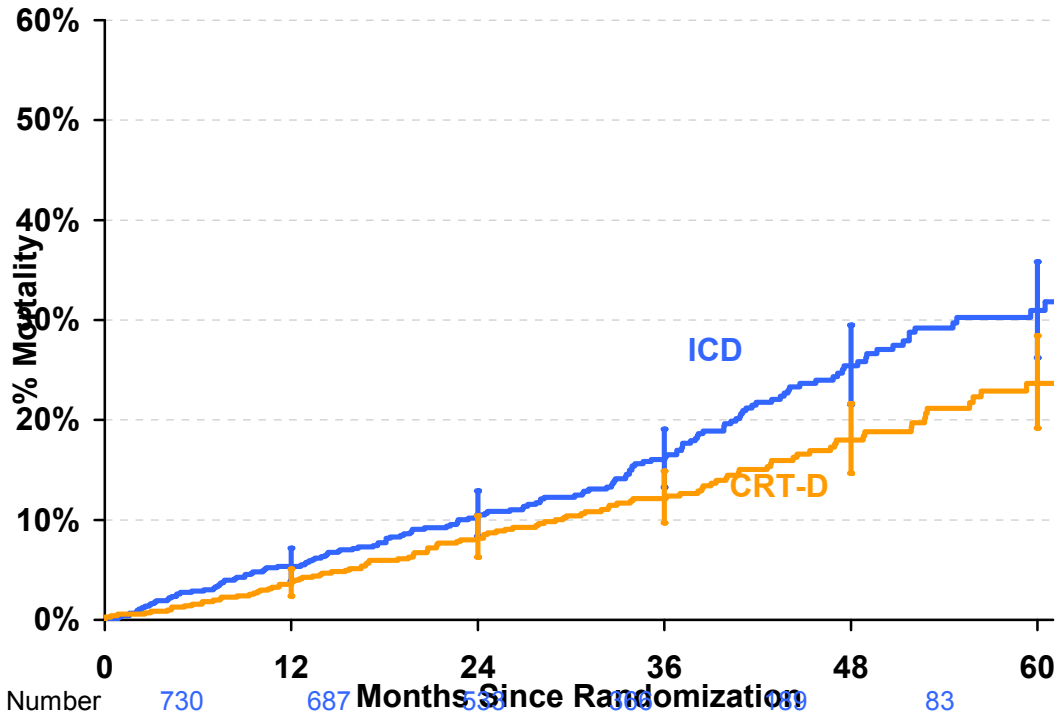
- Total mortality
- All-cause hospitalization rate
- HF hospitalization rate

The following text and figures present this data.

All-Cause Mortality

The figure below shows the time to all-cause mortality for the NYHA Class II patients only. Of the 730 NYHA Class II patients in the ICD group, 154 of them died, while in the CRT-D group, 110 of 708 died. The hazard ratio was 0.71 (95% Confidence Interval: 0.56–0.91) in favor of CRT-D. At 5 years, the mortality rates were 31.0% in the NYHA Class II ICD group, and 23.7% in the NYHA Class II CRT-D group.

Figure 11: RAFT – All-Cause Mortality (NYHA Class II)



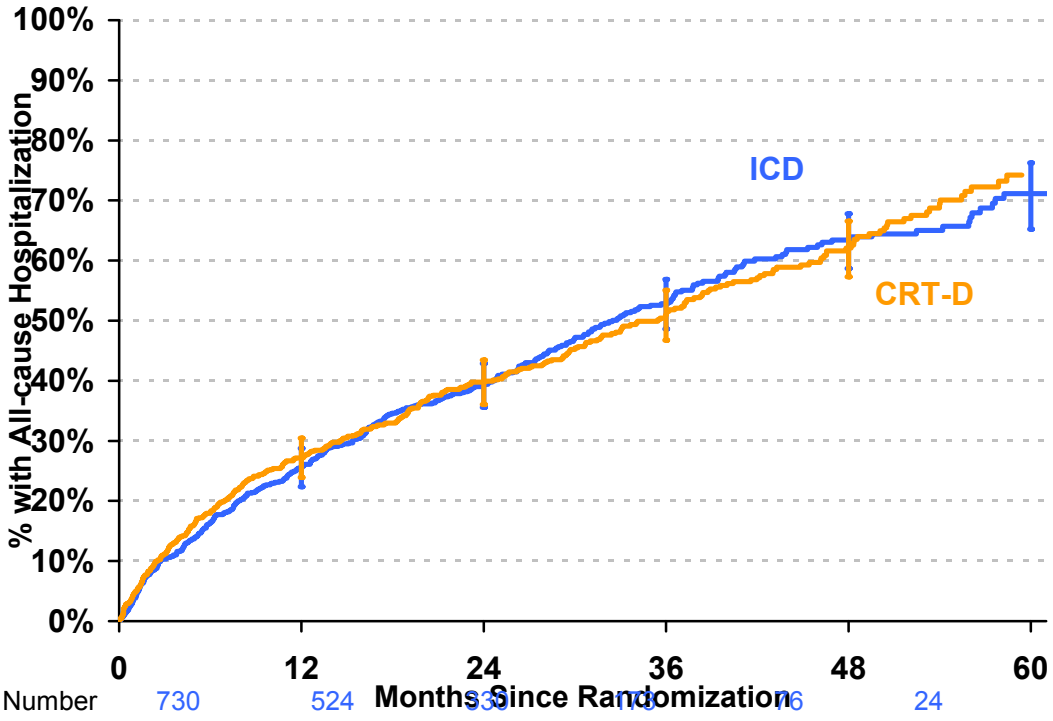
FDA Comment

- **Patient Death Classifications** – There appear to be some issues with the classification of patient deaths. Some deaths appear to be cardiac to FDA and were classified as cardiac by the investigator but were then adjudicated as non-cardiac by the Event (Adjudication) Committee. The RAFT protocol called for strokes to be adjudicated as cardiovascular by the committee. Cardiovascular could be confused with cardiac. Although the primary endpoint included all-cause mortality, a high percentage of non-cardiac deaths could affect one's interpretation of the primary endpoint results.
- **Strokes as Cardiovascular Deaths** - Among the NYHA Class II cohort of RAFT, there were 181 cardiovascular deaths, which included 14 strokes classified as cardiovascular deaths. FDA noted that strokes were counted as "cardiovascular deaths". Although this classification was pre-specified in the RAFT clinical protocol, FDA believes that this classification might be misinterpreted. One might confuse cardiovascular deaths, which would include strokes, with cardiac deaths, which would typically exclude strokes.

All-Cause Hospitalization

The figure below shows the Kaplan-Meier graph for time to first hospitalization (for any cause) for NYHA Class II patients. No difference was observed between the ICD and CRT-D groups. The overall hazard ratio = 1.01 (95% Confidence Interval: 0.87-1.16).

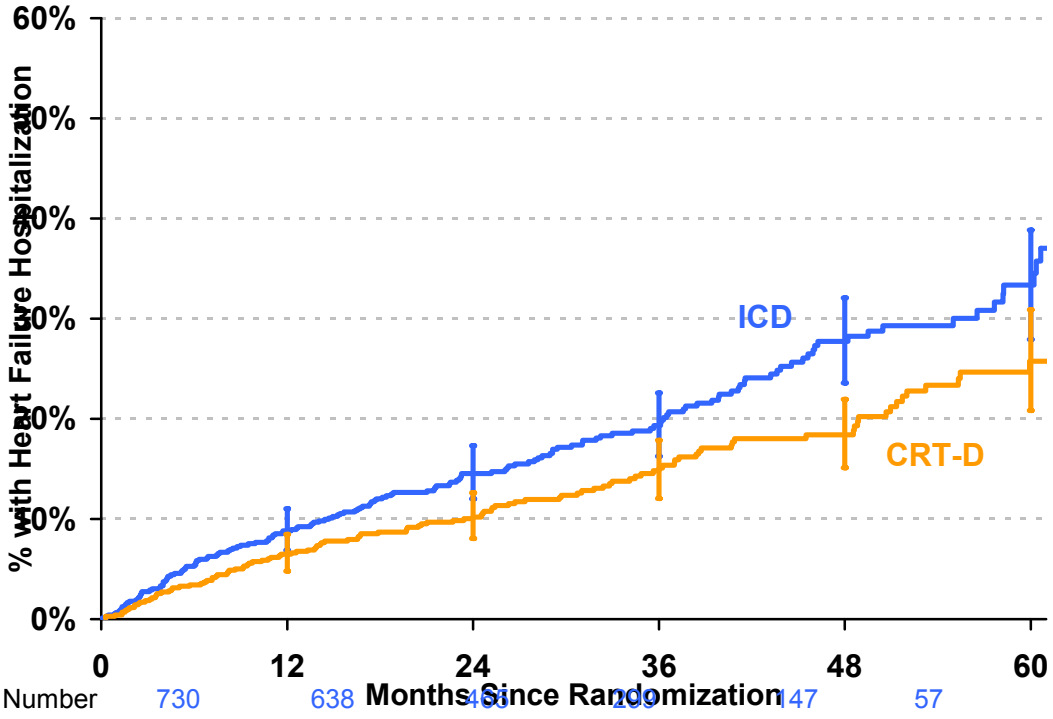
Figure 12: RAFT – All-Cause Hospitalization (NYHA Class II)



Heart Failure Hospitalization

The figure below shows the time to first HF hospitalization for the NYHA Class II patients only. At 12 months, the rate of patients with a heart failure hospitalization in the ICD group was 8.8% (95% Confidence Interval: 7.0-11.1%), and the rate in the CRT-D group was 6.5% (95% Confidence Interval: 4.9-8.6%). At 24 months, the rates were 14.6% (95% Confidence Interval: 12.1-17.4%) in the ICD group and 10.2% (95% Confidence Interval: 8.1-12.7%) in the CRT-D group. The overall hazard ratio is 0.70 (95% Confidence Interval: 0.55-0.89) in favor of the CRT-D group.

Figure 13: RAFT – HF Hospitalization (NYHA Class II)



FDA Comment

- **No Multiplicity Adjustment** – No multiplicity adjustment strategy was pre-specified in RAFT to control type I error so p-values are uninterpretable for the secondary objectives and other analyses.
- **MLWHF, NYHA, and 6MWT and Other Outcomes** – The change in Minnesota Living with Heart Failure (MLWHF) score, NYHA Class, and 6-Minute Walk Test (6MWT) distance were pre-specified secondary outcomes. There were no differences in any of these measures during the trial. There appears to be no effect of CRT in improving any of these measures. There was no effect of treatment for other secondary outcomes including time to first all-cause hospitalization or heart failure related emergency room visit, time to sudden arrhythmic death, and time to progressive congestive heart failure death.

8.6 Previous Hospitalizations

At FDA's request, the sponsor provided additional information about previous heart failure hospitalizations. In the RAFT study, the data collected about previous hospitalizations was limited due to issues in the way that the data was recorded on the case report forms. Subjects were asked at baseline how many times in the previous 12 months they had been hospitalized for congestive heart failure. The sponsor discovered that the data collected on the baseline form regarding previous hospitalizations are a mix of heart failure hospitalizations and other types of hospitalizations, as some centers listed all hospitalizations. Based on the limited information on the CRF, it is not possible to definitively determine whether the

hospitalizations listed were heart failure related or not. Therefore, the analyses were performed based on the available information.

In addition, the RAFT protocol didn't specifically exclude patients with recent hospitalization or recent NYHA Class III / IV status. In the NYHA Class II cohort and the proposed patient population cohort of RAFT, approximately 25% of the subjects were hospitalized for HF in the previous 12 months. The tables below summarize the outcomes in patients with and without a heart failure hospitalization within the previous 12 months for both the NYHA II cohort and proposed patient population cohort of the RAFT subjects. The treatment appears to be consistently less effective in patients without a previous heart failure hospitalization.

Table 22: RAFT – Previous HF Hospitalization Subgroup Analysis (NYHA II Cohort) (post hoc)

			Hazard ratio	95% confidence interval
Time to first HF hospitalization or all-cause death	Hosp for HF in previous 12 months	ICD (n=168)	0.53	0.38 - 0.74
		CRT-D (n=177)		
	Not Hosp for HF in previous 12 months	ICD (n=562)	0.83	0.66 - 1.04
		CRT-D (n=531)		
Time to first HF hospitalization	Hosp for HF in previous 12 months	ICD (n=168)	0.48	0.31 - 0.73
		CRT-D (n=177)		
	Not Hosp for HF in previous 12 months	ICD (n=562)	0.81	0.60 - 1.09
		CRT-D (n=531)		
Time to death	Hosp for HF in previous 12 months	ICD (n=168)	0.51	0.33 - 0.79
		CRT-D (n=177)		
	Not Hosp for HF in previous 12 months	ICD (n=562)	0.81	0.60 - 1.09
		CRT-D (n=531)		

In addition, the following table provides the same analysis, using the sponsor's proposed patient population, which is described in more detail in Section 9: Supporting Post-Hoc Analyses.

Table 23: RAFT – Previous HF Hospitalization Subgroup Analysis (Proposed Population) (post hoc)

			Hazard ratio	95% confidence interval
Time to first HF hospitalization or all-cause death	Hosp for HF in previous 12 months	ICD (n=110)	0.45	0.30 - 0.69
		CRT-D (n=129)		
	Not Hosp for HF in previous 12 months	ICD (n=360)	0.69	0.51 - 0.93
		CRT-D (n=348)		
Time to first HF hospitalization	Hosp for HF in previous 12 months	ICD (n=110)	0.39	0.24 - 0.66
		CRT-D (n=129)		
	Not Hosp for HF in previous 12 months	ICD (n=360)	0.68	0.47 - 0.995
		CRT-D (n=348)		
Time to death	Hosp for HF in previous 12 months	ICD (n=110)	0.48	0.28 - 0.83
		CRT-D (n=129)		
	Not Hosp for HF in previous 12 months	ICD (n=360)	0.72	0.48 - 1.07
		CRT-D (n=348)		

FDA Comment

- **Previous Hospitalizations** – FDA is concerned about the lack of more detailed information about previous heart failure hospitalizations and how enrollment of patients with previous heart failure hospitalizations might have biased the study results. The panel is being asked to comment on this issue.

8.7 Protocol and Follow-Up Compliance

There were a total of 3865 protocol deviations with 3157 deviations related to follow-up compliance. The following table outlines types and number of deviations.

Table 24: RAFT – Protocol Deviations

Deviation	Number of Deviations in RAFT (n=1798) Events (subjects, %)
Informed consent	2 (2, 0.1%)
Inclusion/Exclusion criteria not met	46 (44, 2.4%)
Pharmacological change not related to inclusion/exclusion criteria	N/A
Randomization/Blinding	233 (202, 11.2%)
Visit compliance (early or late deviations / missed visit forms)	131 (124, 6.9%) 3026* (983, 54.7%)
Protocol required data collection and testing	385 (329, 18.3%)
Protocol required implanted system - outside inclusion/exclusion criteria	28 (27, 1.5%)
Regulatory	0
Source documents	0
Protocol required training	0
Programming non-compliance	14 (0.8%)
Total deviations and Missed Visits	839 (616, 34.3%) 3865 (1257, 69.9%)
Deviation Rate including Visit Compliance (Deviations / Total Patients)	2.22
Deviation Rate excluding Visit Compliance (Deviations / Total Patients)	0.47

*Missed visits (n=3026) were recorded on a Missed Visit CRF instead of a Protocol Deviation CRF. There were 131 early or late visits and 3026 missed visits for a total of 3157 visit compliance events.

Only 28 of 894 (3.1%) CRT-D subjects and 21 of 883 (2.3%) ICD subjects exited the study. Additionally, 11 of the 28 CRT-D exits and 10 of the 21 ICD exits were after the primary endpoint of the study (HF hospitalization) had occurred.

FDA Comment

- **Unblinding and Crossovers** – Nearly 25% of the RAFT patients were unblinded during the course of the study. The reasons included discussions pertaining to upgrading of the device (48 pts), receipt of the Medtronic ID card in the mail (44 pts), viewing of the chest x-ray or echocardiogram (36 pts), patients overheard conversations (18 pts), or patients were informed after unsuccessful attempts to implant the LV lead (17 pts). The time at which subjects were unblinded was not collected. The blinding assessment was performed at the end of the study. Unblinding of heart failure investigators was not collected during the study and could have been more common than unblinding of patients. A request for a subject to crossover in the RAFT study could potentially result in the blind being broken. In the RAFT study, 96 subjects (10.6%) crossed over from the ICD group to the CRT-D group with 36 (4%) crossing over prior to reaching a primary endpoint event and 60 (6.6%) crossing over after reaching a primary endpoint event. A total of 53 subjects (6%) in the CRT-D group crossed over to the ICD group. The large number of crossovers and limited information about unblinding presents a significant concern, especially in the RAFT study where adjustment of heart failure medications after enrollment was encouraged.

- **Reporting of Protocol Deviations** – The protocol deviation rate reported in RAFT (0.47 deviations per patient) appears to be low and inconsistent with the deviation rate reported in the REVERSE study (4.18 deviations per patient). FDA is concerned that compliance with the protocol was not being properly evaluated or that protocol deviations were not being reported. As compared to the REVERSE study, the RAFT study enrolled significantly more patients and followed these patients for a longer period of time. However, the number of reported protocol deviations in RAFT (839 deviations reported unrelated to visit compliance) is significantly lower than REVERSE (2864 deviations reported unrelated to visit compliance), especially after excluding deviations related to early, late, or missing follow-up visits. Only 46 deviations related to inclusion/exclusion criteria were reported in RAFT, and there was only 1 reported deviation where the patient's NYHA class was higher than allowed. As another example, there were only 3 patients with protocol deviations related to not being on optimal medical therapy at least 6 weeks before enrollment into the RAFT study. Identifying the actual scope of this issue is even more difficult because investigators were encouraged to up titrate doses of medications during the study, in contrast to REVERSE, where stabilizing the dosage before and during the trial was encouraged.
- **Collection of Baseline 6 Minute Walk Test Data** – When evaluating and comparing the baseline functional status of subjects enrolled in the RAFT study, FDA noted that 244 subjects (13.6%) did not have baseline 6 Minute Walk Test distances. This test is a relatively simple test intended to quantitatively measure a subject's functional status. In some cases, reasons such as time constraints or patient refusal were recorded on the case report form. Protocol deviations were not consistently reported for not following this protocol requirement. FDA is concerned that this example highlights the potential for other, more serious protocol compliance issues.

9. Supporting Post-Hoc Analyses

The sponsor's original submission included a request to expand the indications for Medtronic CRT-D systems to include "heart failure patients who remain symptomatic despite stable, optimal medical therapy, and who have a left ventricular ejection fraction ≤35% and a prolonged QRS duration." FDA believed that the proposed indication was not consistent with the supporting clinical data. For example, the sponsor proposed to use a left ventricular ejection fraction cutoff of ≤35%. This value is inconsistent with the cutoffs used for the RAFT and REVERSE clinical studies, which were 30% and 40% respectively. As a result of concerns expressed by FDA, the sponsor proposed a modified indication statement and presented data from the subpopulations of the REVERSE and RAFT studies that were consistent with this modified indication. In order to address feedback from FDA, the sponsor presented additional analyses of various subpopulations, in order to demonstrate benefit of the therapy in various subgroups. This section summarizes those data.

The sponsor is proposing to expand the indications for their CRT-D devices for a post-hoc subgroup of patients common to both studies as neither of the two studies was designed and conducted for the proposed expansion of indications. The sponsor is

proposing to expand the indications for their CRT-D devices to one subgroup of patients common to both studies and then further restricted to patients with Left Bundle Branch Block (LBBB). This labeling proposal was determined after the study results were known. This section describes that population in further detail. The following table shows how the population was chosen based on the common inclusion criteria in the studies. The one exception is the use of QRS morphology, which was based on the subgroup analyses of both studies, which demonstrated consistent benefit with CRT for LBBB subjects. Statistical inference (such as p-values) should be interpreted with extreme caution, because the type-I error rate would not be controlled due to the post-hoc nature of these analyses. In addition, treatment assignment was not stratified within any of the subgroups; consequently, the analysis results could be confounded.

Table 25: Comparison of Study Inclusion Criteria and Proposed Population

	REVERSE	RAFT	Proposed Patient Population
CRT Device	CRT-D; CRT-P	CRT-D	CRT-D
NYHA Class	I and II	II (initially II and III)	II
LVEF (%)	≤ 40	≤ 30	≤ 30
QRS (ms)	≥ 120	≥ 120 (initially 130 ms)	≥ 120
Permanent Atrial Fibrillation Allowed	No	Yes	No
Permanent Pacing Allowed	No	Yes	No
QRS Morphology	All	All	Left Bundle Branch Block

When considering the proposed population from the REVERSE and RAFT studies, 189 (31%) of REVERSE patients meet the criteria and 947 (53%) of RAFT patients meet the criteria (CRT-D, NYHA Class II, LVEF≤ 30%, QRS ≥120 ms, and LBBB).

The following table summarizes how many patients were eliminated from the full study cohorts to the proposed patient population. Patients only appear once and appear in the top row in which they are included. For example, a RAFT NYHA III patient with permanent AF counts only toward the 360 NYHA III patients and is not included in the 165 permanent AF patients.

Table 26: Accounting of Proposed Population

	Number Eliminated		Number Remaining	
	REVERSE	**RAFT**	**REVERSE**	**RAFT**
Full Cohort			**610**	**1798**
NYHA III	0	360	610	1438
Permanent AF	0	165	610	1273
Paced	0	65	610	1208
CRT-P	102	0	508	1208
NYHA I	86	0	422	1208
Non-LBBB	175	255	247	953
LVEF > 30%	58	5	189	948
QRS duration <120 ms	0	1	189	947
Proposed Patient Population			**189**	**947**

The following table compares the baseline characteristics of the proposed patient populations for the REVERSE and RAFT subgroups.

Table 27: REVERSE & RAFT – Baseline Characteristics of Proposed Population

	REVERSE		RAFT	
	CRT OFF (n= 64)	CRT ON (n= 125)	ICD (n= 470)	CRT-D (n= 477)
Age (yrs)	59.3 ± 12.6	63.2 ± 11.6	65.0 ± 9.1	65.0 ± 9.5
Male	72%	76%	80%	83%
Ischemic	34%	45%	58%	64%
LVEF (%)	22.9 ± 5.5	22.7 ± 5.2	22.6 ± 5.1	22.4 ± 5.3
Minnesota Living with HF Score	33.6 ± 21.2	27.2 ± 19.1	34.5 ± 21.6	34.6 ± 21.0
6-minute Hall Walk (m)	380.3 ± 125.3	410.3 ± 110.9	375.9 ± 105.6	369.8 ± 104.8
QRS Duration (ms)	165.7 ± 21.0	162.8 ± 20.5	162.3 ± 24.6	159.6 ± 24.6
On ACE-I/ARBs	97%	98%	97%	96%
On beta blocker	92%	97%	90%	92%
On diuretics	80%	80%	81%	82%
On aldosterone antagonist	38%	30%	41%	40%
On lipid-lowering agent	53%	60%	74%	75%
On Digitalis/cardiac glycosides	39%	26%	31%	29%
Coronary artery disease	34%	45%	49%	53%
Myocardial infarction	30%	37%	50%	56%
Hypertension	48%	49%	44%	47%
Previous CABG	19%	18%	30%	30%
Diabetes	30%	18%	33%	31%
Serum Creatinine (mg/dL)	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.7	1.2 ± 0.6
eGFR (mL/min/1.73m^2)	76.9 ± 27.8	71.8 ± 23.1	64.3 ± 22.7	62.5 ± 19.4
Systolic Blood Pressure (mmHg)	123.8 ± 18.4	125.0 ± 18.3	118.4 ± 17.0	118.6 ± 17.3
Diastolic Blood Pressure (mmHg)	71.5 ± 12.9	71.9 ± 10.8	68.8 ± 10.0	68.5 ± 10.3

There are some differences in baseline characteristics between REVERSE and RAFT patients who met the defined parameters of the proposed patient population. The RAFT patient population had a greater proportion of ischemic heart failure etiology, history of myocardial infarction, presence of dilated cardiomyopathy, and lower renal function (eGFR).

FDA Comment

- **Post-Hoc Subgroup for REVERSE and RAFT** – A total of 31% (189/610) of the original REVERSE study population and 53% (947/1798) of the original RAFT study

population would fulfill the indications proposed by the sponsor. The proposed indicated population is a post-hoc subgroup. The process of retrospectively selecting those subjects most likely to respond to the therapy introduces significant bias that must be considered when interpreting the results. Results of statistical inference, like p-values, based on post-hoc subgroup analyses are un-interpretable.

- **Use of Two Studies to Support Indication** – Despite some similarities, the REVERSE and RAFT studies had many differences in enrollment criteria, control group therapy, study conduct and endpoints, event adjudication, and data collection. RAFT was conducted entirely OUS and its applicability to the US population is not known. These differences are significant and present concerns for combining the data to support a single, unified, retrospectively selected indication.
- **Suboptimal Baseline Drug Therapy** – In the full cohort of REVERSE patients (n=610), only 23.0% of patients were at the target dose of 50 mg/day beta blockers at baseline. In the NYHA Class II subgroup of the RAFT patients (n=1438), only 15.7% of patients were at the target dose of 50 mg/day beta blockers at baseline. Similar trends were noted in angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) for the REVERSE study (7.2% and 3.4% at target dose at baseline, respectively) and the NYHA Class II subgroup of the RAFT study (6.0% and 3.6% at target dose at baseline, respectively). Although the underutilization of heart failure drug therapy was similar in REVERSE and RAFT, the observed low doses are not consistent with the guidelines and could have affected the results of the studies.
- **Selection of Proposed Indication** – The indication proposed by the sponsor appears to be based on published literature including the results of the MADIT-CRT study, though MADIT-CRT used a wider QRS duration of 130 ms. FDA is concerned that the patient population in RAFT and REVERSE are different from that enrolled in MADIT-CRT and that the sponsor has retrospectively identified a subgroup of patients in these studies that responded well to CRT. In addition, as previously stated, FDA is concerned that the patients enrolled in the RAFT study might not have been on optimal and stable medical therapy before enrollment and that patients might have had previous NYHA Class III symptoms, including previous hospitalizations, given that this was not an exclusion criterion for the RAFT study.

The following sections present data from the REVERSE and RAFT studies looking at all-cause mortality as well as combined heart failure hospitalization and all-cause mortality.

9.1 Clinical Composite Response – Proposed Population

The sponsor provided the results of the REVERSE primary endpoint, Clinical Composite Response. The results of this post hoc analysis are provided below.

Table 28: REVERSE – Clinical Composite Response – Proposed Population (post hoc)

Clinical Composite Response	CRT OFF (n=64)	CRT ON (n=125)
Worsened	11 (17%)	7 (5.6%)
Death	2	2
Hospitalized for Worsening HF	5	2
Crossover due to worsening HF	1	0
Moderately or markedly worse patient global assessment and worsened NYHA	0	0
Worsened NYHA	3	1
Moderately or markedly worse patient global assessment	0	2

9.2 HF Hospitalization & All-Cause Mortality – Proposed Population

REVERSE

Due to the small number of HF hospitalizations and all-cause deaths in the proposed patient population in the REVERSE study only summary statistics are presented for the REVERSE study. In REVERSE randomized follow up for US subjects was 12 months and it was 24 months for OUS subjects so summary statistics are presented separately for US and OUS subjects.

The following table shows the proportion of US and OUS patients in the proposed population who died or were hospitalized for HF during the randomized follow up period.

Table 29: REVERSE – Combined HF Hospitalization and All-Cause Mortality – Proposed Population

Patients who died or were hospitalized for HF	CRT OFF	CRT ON
US (12 month follow up)	11% (n=36)	4% (n=72)
OUS (12 month follow up)	11% (n=28)	2% (n=53)
OUS (24 month follow up)	32% (n=28)	11% (n=53)

RAFT

The following figure and table show the combined heart failure hospitalization and all-cause mortality data for the RAFT study.

Figure 14: RAFT – Combined HF Hospitalization and All-Cause Mortality in the Proposed Population (post-hoc)

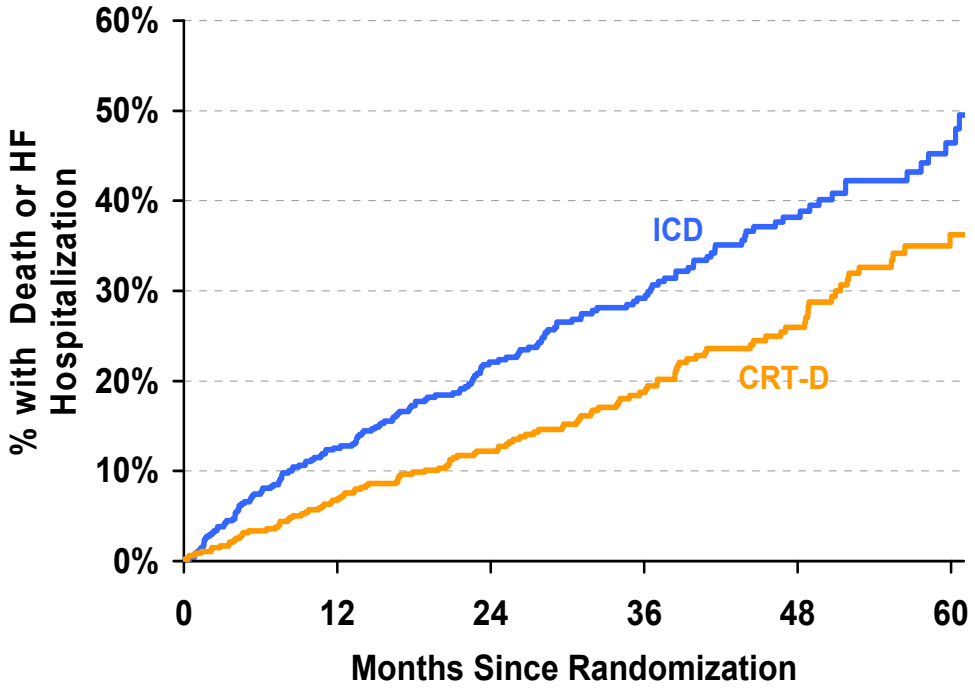


Table 30: RAFT – Primary Effectiveness Endpoint Components (Proposed Population) (post hoc)

Item	Number of Patients (% of All Patients in Treatment Group)		
	ICD (n=470)	CRT-D (n=477)	Hazard Ratio (95% C.I.)
Patients with Primary Endpoint Event	160 (34%)	112 (23%)	0.62 (0.48, 0.78)
Patients with All-Cause Mortality*	92 (20%)	63 (13%)	0.64 (0.46, 0.88)
Patients with HF Hospitalization	106 (23%)	70 (15%)	0.58 (0.43, 0.79)

* This category includes all deaths, including those that occurred after the first heart-failure event.

9.3 All-Cause Mortality – Proposed Population

REVERSE

The following table shows the proportion of US and OUS patients in the proposed population who died during the randomized follow up period. Randomized follow up for US subjects was 12 months and it was 24 months for OUS subjects in the REVERSE study. A Kaplan-Meier curve is not provided because of the small number of events.

Table 31: REVERSE – All-Cause Mortality – Proposed Population

Proportion of patient deaths	CRT OFF	CRT ON
US (12 month follow up)	0% (n=36)	3% (n=72)
OUS (12 month follow up)	7% (n=28)	0% (n=53)
OUS (24 month follow up)	18% (n=28)	0% (n=53)

RAFT

The following figure and table show the all-cause mortality data for the RAFT study.

Figure 15: RAFT – Mortality in the Proposed Population (post-hoc)

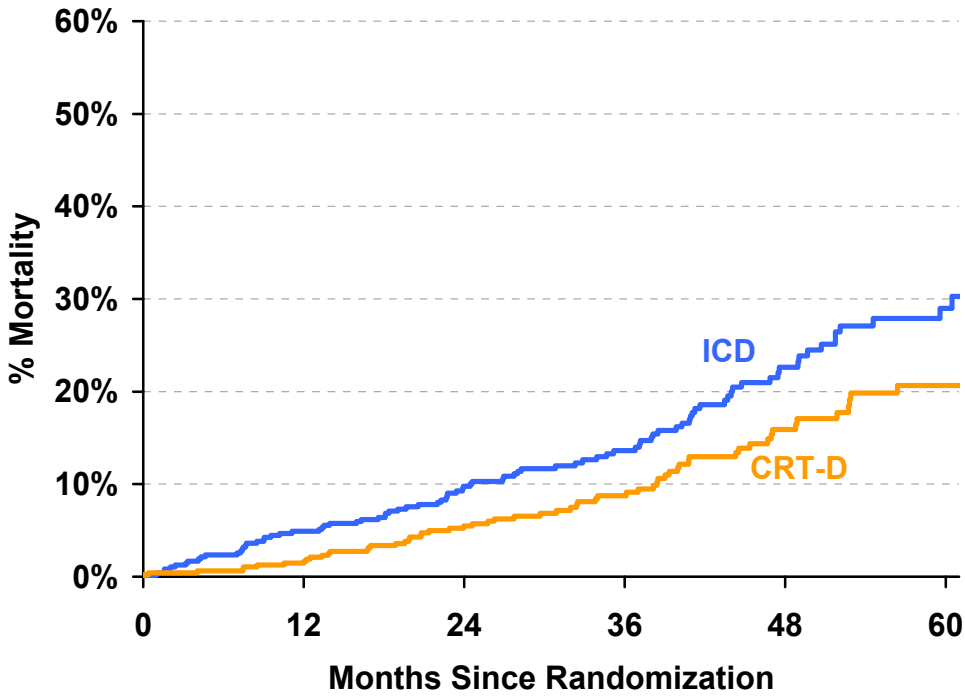


Table 18: RAFT – Cause of Death (Proposed Population) (post hoc)

Cause of Death Category	ICD (n=470)	CRT-D (n=477)	Total (n=947)
Non Cardiovascular	23 (25%)	19 (30%)	42 (27%)
Unexpected death presumed to be cardiovascular disease, occurring within 24 hrs of the onset of symptoms without confirmation of cardiovascular cause, and without clinical or post mortem evidence of etiology	10 (11%)	6 (10%)	16 (10%)
Myocardial Infarction: Death within 7 days of the onset of documented MI	2 (2%)	2 (3%)	4 (3%)
Congestive Heart Failure: Death due to clinical, radiological or post-mortem evidence of CHF, without clinical or postmortem evidence of other cause, such as ischemia, infection, dysrhythmia	40 (43%)	26 (41%)	66 (43%)
Documented Arrhythmia: Death due to brady or tachyarrhythmias, not induced by an acute ischemic event	8 (9%)	8 (13%)	16 (10%)
Stroke: Death due to stroke occurring within 7 days of the signs and symptoms of stroke	7 (8%)	1 (2%)	8 (5%)
Other cardiovascular diseases: Death due to other vascular diseases such as pulmonary embolism, aortic aneurysm, etc.	0 (0%)	1 (2%)	1 (1%)
Presumed cardiovascular death: Suspicion of CV death that does not fulfill other criteria	2 (2%)	0 (0%)	2 (1%)
Total	92 (100%)	63 (100%)	155 (100%)

9.3.1 Additional Subgroup Analyses

Due to the small number of events in the proposed patient population in the REVERSE study and the low power of the interaction test, further subgroup analyses of the proposed patient population in REVERSE is of limited value.

Hazard ratio charts which summarize other subgroups within NYHA class II patients and the proposed patient population are presented below for RAFT. P-values are nominal and represent the interaction term of subgroup*randomization.

The first two figures summarize the subgroup of RAFT patients with NYHA Class II (n = 1438). Figure 16 provides the combined heart failure hospitalization and all-cause mortality subgroup analysis. Figure 17 provides the all-cause mortality subgroup analysis.

The second two figures summarize the subgroup of RAFT patients that fulfill the proposed population (n = 947). Figure 18 provides the combined heart failure hospitalization and all-cause mortality subgroup analysis. Figure 19 provides the all-cause mortality subgroup analysis.

For NYHA class II subjects, there is a significant subgroup by treatment interaction (p-value of less than 0.15 being significant) for gender, prior hospitalization, left ventricular ejection fraction, QRS morphology and atrial rhythm.

Figure 16: RAFT – Combined HF Hospitalization or All-Cause Mortality – Subgroup Analysis in NYHA Class II (post-hoc)

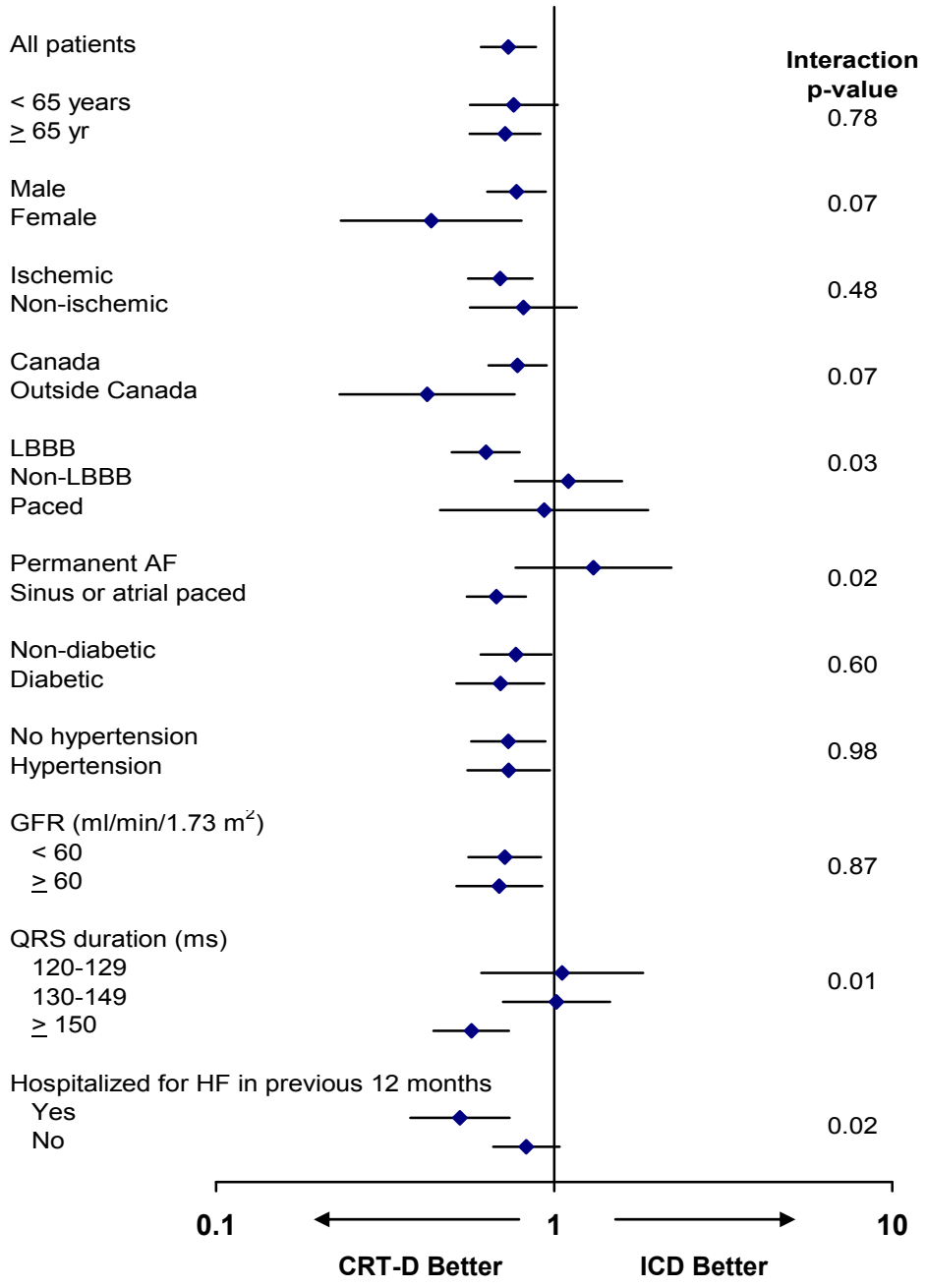


Figure 17: RAFT – All-Cause Mortality – Subgroup Analysis in NYHA Class II (post-hoc)

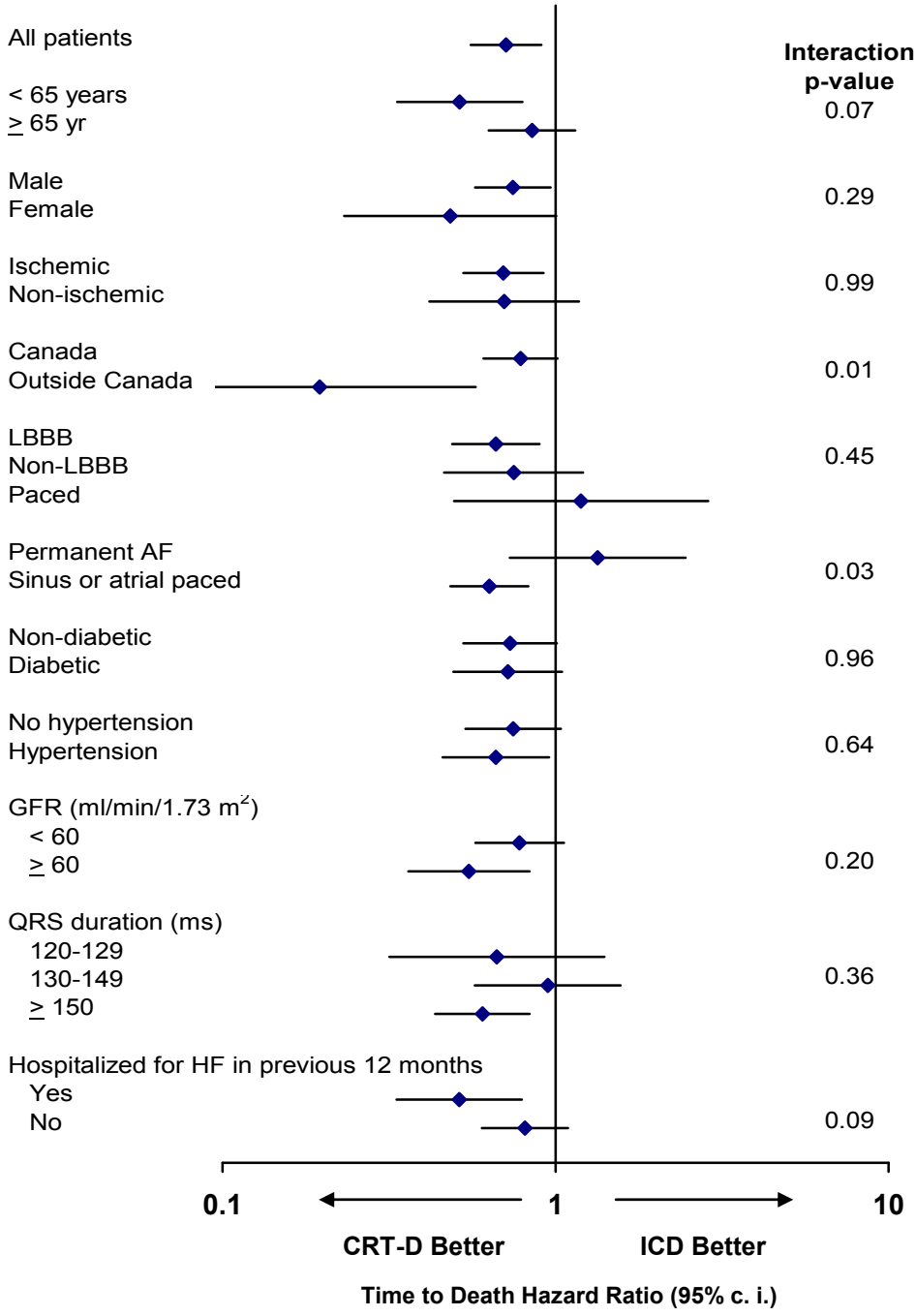
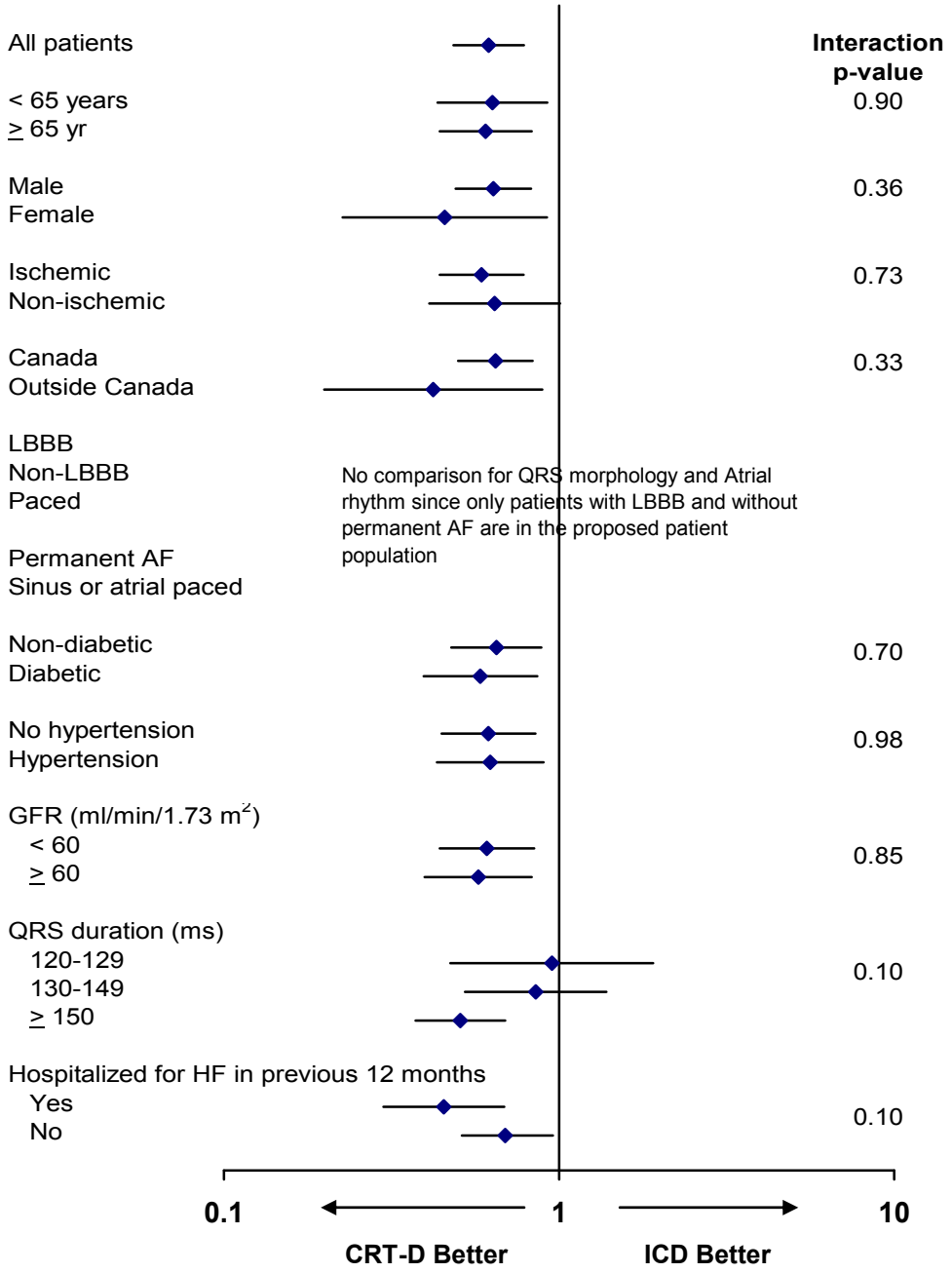
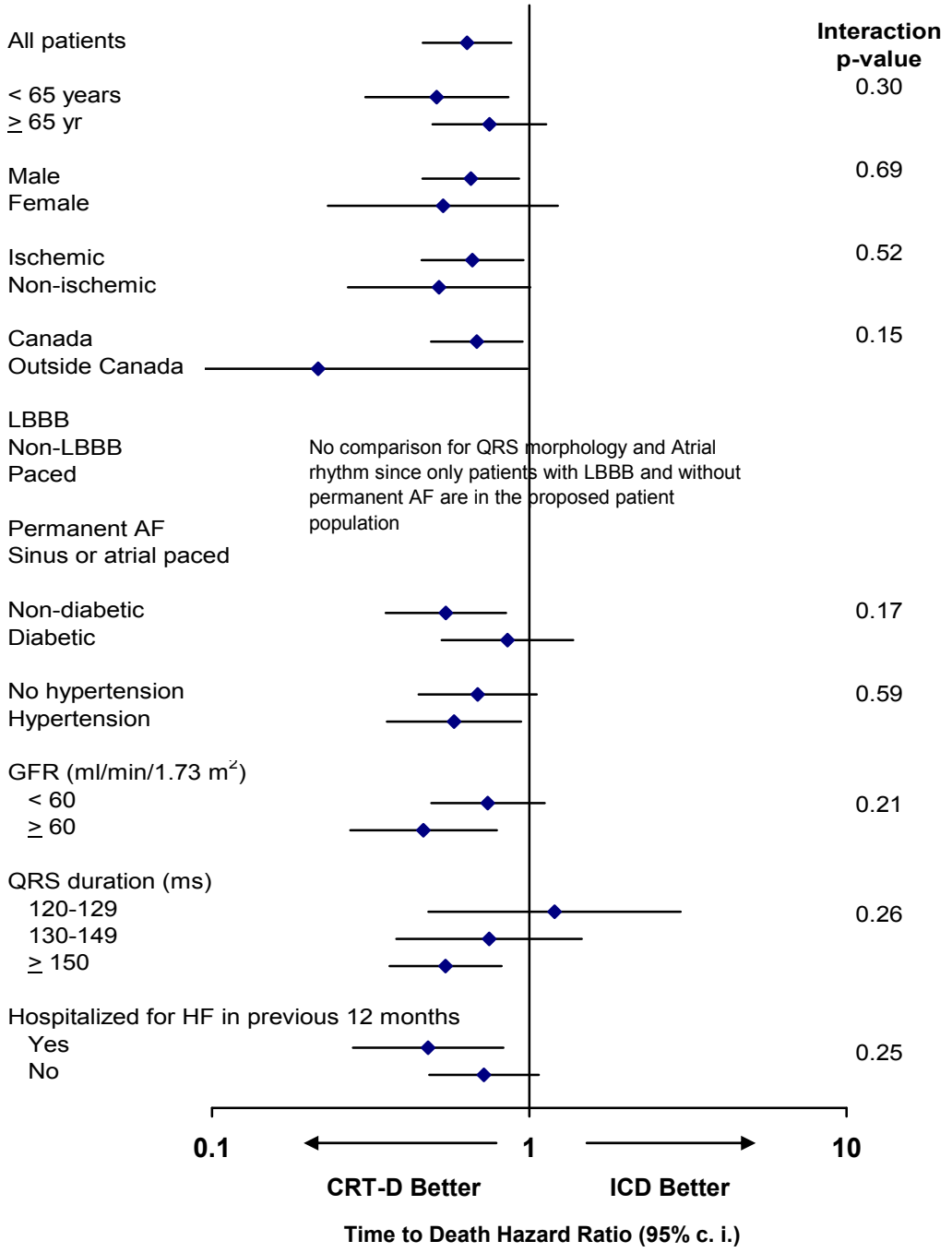


Figure 18: RAFT – Combined HF Hospitalization and All-Cause Mortality – Subgroup Analysis in Proposed Population (post-hoc)



Time to First HF Hospitalization or All-cause Death Hazard Ratio (95% c. i.)

Figure 19: RAFT – All-Cause Mortality – Subgroup Analysis in Proposed Population (post-hoc)



9.4 Proposed QRS Duration Cutoff

FDA requested additional analyses related to QRS duration. The sponsor has proposed a QRS duration of ≥ 120 ms. The REVERSE study used a QRS duration of 120 ms. The RAFT study initially used a QRS duration of ≥ 130 ms but then changed the inclusion criteria to allow use of ≥ 120 ms as a cut-off. Based on the data submitted

by the sponsor, the selected QRS duration does not seem appropriate. The published journal article with the RAFT study results included a pre-specified analysis of results with a QRS duration of 150 ms as a cutoff. The pre-specified analysis in the RAFT publication as well as subsequent analyses performed by the sponsor at FDA's request noted that patients with a QRS duration < 150 ms did not show a benefit from the therapy. The previous figures with the hazard ratio plots for the RAFT study further demonstrate that benefit is limited to those with QRS duration ≥ 150 ms even when QRS is divided into 3 groups; 120-129 ms, 130-149 ms, and ≥ 150 ms. The post-hoc analyses for the REVERSE and RAFT studies are provided in the following table. The RAFT patients included in this analysis met the following criteria: NYHA II, CRT-D, LVEF ≤ 30%, no chronic AF, and non-paced. The REVERSE patients included in this analysis met the following criteria: NYHA II, CRT-D, and LVEF ≤ 30%. Note that a benefit was not observed with QRS duration < 150 ms even in those patients with left bundle branch block.

Table 32: REVERSE – QRS Duration and Morphology

	Number of Patients / Events (Percent of Total Patients) HF Hospitalization or All-cause Death Hazard Ratio 95% Confidence Interval Post-Hoc P-value		
QRS Width	**Non-LBBB**	**LBBB**	**Total**
QRS < 150ms	90 / 15 (28.7%) HR = 1.01 (0.36-2.85) p=0.99	42 / 6 (13.4%) HR = 0.51 (0.09-2.91) p=0.44	132 (42%)
QRS ≥ 150ms	35 / 3 (11.1%) HR = 0.00 p=0.0008	147 / 16 (46.8%) HR = 0.24 (0.08-0.70) p=0.004	182 (58%)
Total	125 (39.8%)	189 (60.2%)	314

Table 33: RAFT – QRS Duration and Morphology

	Number of Patients / Events (Percent of Total Patients) HF Hospitalization or All-cause Death Hazard Ratio 95% Confidence Interval Post-Hoc P-value		
QRS Width	**Non-LBBB**	**LBBB**	**Total**
QRS < 150ms	133 / 48 (11.1%) HR = 1.24 (0.70-2.19) p=0.45	298 / 98 (24.9%) HR = 0.89 (0.60-1.32) p=0.55	431 (35.9%)
QRS ≥ 150ms	119 / 49 (9.9%) HR = 0.83 (0.47-1.47) p=0.52	649 / 174 (54.1%) HR = 0.51 (0.37-0.69) p<0.0001	768 (64.1%)
Total	252 (21%)	947 (79%)	1199

FDA Comment

FDA is concerned that subjects with QRS duration < 150 ms, even in the proposed patient population, did not benefit from CRT based on the data submitted.

10. Post-Approval Studies

The sponsor submitted an outline of the post-approval study plan. The following text summarizes the sponsor's proposal.

Purpose

The purpose of the REVERSE Post-Approval Study is to estimate the long-term (i.e. 5 years) patient survival probability in the real world after the approval of the newly expanded indications for Medtronic CRT-D devices. This study will be conducted utilizing patients enrolled in the NCDR® ICD Registry™ who meet the newly expanded indications for Medtronic CRT-D systems. The REVERSE and RAFT studies provided evidence that clinical outcome can be significantly improved for patients with mildly symptomatic heart failure conditions. The two multi-center, blinded, randomized controlled clinical trials are both designed to examine long term clinical outcome comparing patients with bi-ventricular pacing therapy (CRT) and without bi-ventricular pacing therapy. The results from this REVERSE Post-Approval Study utilizing the NCDR® ICD Registry™ will confirm the patient survival probability observed in the REVERSE and RAFT studies in the real world in the post approval environment.

Study Objectives

Primary Objective: To estimate 5-year survival probability for patients with newly expanded indications who are implanted with a Medtronic CRT-D device.

Statistical Analysis: The primary endpoint for this objective is all-cause mortality. The Kaplan-Meier method will be used to estimate patient survival probability at 5 years after implanting a Medtronic CRT-D device. The 2-sided 95% confidence interval will be calculated.

Secondary Objective: To characterize all cause mortality for the proposed population by gender.

Statistical Analysis: Based on recently conducted CRT studies.[8,9,10] in addition to the REVERSE and RAFT studies, it is estimated that about 25-30% (or 375-450) of the study subjects will be female. The Kaplan-Meier method will be used to estimate patient survival probability of each gender at 5 years after implanting a Medtronic CRT-D device.

The 2-sided 95% confidence intervals will be calculated. The purpose of this objective is to confirm the mortality rates seen in previous studies. There is no planned hypothesis testing to detect a gender difference.

Additional analysis will be conducted to characterize the association between patient baseline QRS duration (ms) and all-cause mortality for each gender group.

Study Population

All US patients who are implanted with a Medtronic CRT-D device after the approval date and who match the proposed indications will be included in the analyses for all clinical progress reports and the final report. The newly proposed indications are ICD indicated patients that are NYHA Class II, with a LVEF ≤ 30%, QRS ≥120ms, and a LBBB morphology.

Enrollment/Sample Size

A minimum of 1500 patients who meet the study inclusion criteria will be included in the analysis datasets. The RAFT study patients included in the proposed labeling population observed a 5-year mortality rate of 21% for patients with a CRT-D implanted, and 29% for patients with an ICD implanted. For the post-approval study, the sample size calculation assumes a 25% 5-year cumulative mortality rate. A total of 1500 patients will result in a 95% confidence interval width of 4.5% for the survival probability estimate at 5 years. A 5% total attrition is assumed to account for lost-to-follow up

[8] Moss, A. J., W. J. Hall, et al. (2009). "Cardiac-resynchronization therapy for the prevention of heart-failure events." *N Engl J Med* 361(14): 1329-1338.

[9] Cleland, J. G. F., J.-C. Daubert, et al. (2005). "The effect of cardiac resynchronization on morbidity and mortality in heart failure." N Engl J Med 352(15): 1539-1549.

[10] Bilchick KC, et al. Bundle-Branch Block Morphology and other Predictors of Outcome After Cardiac Resynchronization Therapy in Medicare Patients, Circulation 2010; 122:2022-2030.

(mainly due to inaccurate system implant information where patient records cannot be accessed). The Peto's formula was used for this calculation.[11]

Table PA-1

Sample Size	Projected 95% CI Width
1000	5.5%
1250	4.9%
1500	***4.5%***
1750	4.2%
2000	3.9%

Of the 1500 patients, approximately 25-30% will be female. Table PA-2 provides projected estimation precisions for the 5-year survival probability stratified by gender. This calculation assumed a survival probability of 75% at 5 years. The asymptotic method was used for estimating the 2-sided confidence interval for the survival probability. The confidence interval widths are within 10% for either gender group.

Table PA-2

Female		Male	
N (Proportion of total # of patients)	95% CI	n	95% CI
375 (25%)	(70.6%, 79.4%)	1125	(72.5%, 77.5%)
400 (27%)	(70.8%, 79.2%)	1100	(72.4%, 77.6%)
425 (28%)	(70.9%, 79.1%)	1075	(72.4%, 77.6%)
450 (30%)	(71.0%, 79.0%)	1050	(72.4%, 77.6%)
475 (32%)	(71.1%, 78.9%)	1025	(72.4%, 77.6%)
500 (33%)	(71.2%, 78.8%)	1000	(72.3%, 77.7%)

Data Collection

Patient baseline characteristics: patient age, gender, NYHA, LVEF, QRS, LBBB morphology, and cardiomyopathy etiology (i.e. ischemic vs nonischemic)

System information: Medtronic implanted devices

Follow-up / Study Duration

There is no defined protocol required follow-up post-implant for this study. Patient mortality data will be collected via the Social Security Death Index (SSDI). The estimated study subject accrual time is 10 months. The final analysis will be conducted at 5 years after the last qualified study subject is identified.

Study Milestones and Timelines

[11] Alan Cantor (1997) Extending SAS Survival Analysis Techniques for Medical Research, Cary, N: SAS Institute Inc.

Subject accrual start date and completion date: It is estimated that about 3600 - 4500 patients with mildly symptomatic heart failure conditions will be implanted with Medtronic ICDs annually under current CRT-D indications. The adoption rate of the new indications may not be 100% during the first year after the approval[21]. Therefore, we project approximately 50% (1800 – 2250) of those patients will potentially receive Medtronic CRT-D devices after the approval of the new indications. Consequently, the study subject accrual will take a minimum of 10 months after the indication approval date.

Expected date to complete follow-up of all study participants: The expected date of completing follow-up of all study participants will be 5 years after the last qualified study subject is identified.

Study Progress Reports: Study Progress Reports will be submitted to the FDA every 6 months for the first 2 years and annually thereafter until study completion.

Anticipated study completion and date for submitting Final Study Report: The final report analysis dataset will be retrieved 5 years after the last qualified study subject is identified. The study final report will be submitted to FDA within 3 months after the final database closure.

FDA Comment

FDA offers the following comments on each aspect of the proposed post approval study.

- Objective – The proposed objective of this PAS is to estimate 5-year survival probability for patients with newly expanded indications who are implanted with a Medtronic CRT-D device without assessment of device safety. The premarket trials demonstrated that CRT-D implant was associated with increased incidence of adverse events during the implant procedure and follow-up. Without safety data, it will be difficult to evaluate the long-term benefit-risk ratio for the CRT-D implant. The device should be carefully evaluated by assessing the degree of benefit and magnitude of risk of device in the indicated patient population.
- Study Design – The sponsor proposes to conduct a single-arm observational study to assess 5-year survival probability for patients with newly expanded indications who are implanted with a Medtronic CRT-D device. The proposed PAS did not include a study hypothesis or comparison group. Without a reference group and study hypothesis, it will be difficult to determine whether CRT-D implantation provides a long-term beneficial effect. A reference group and hypothesis is necessary to objectively evaluate effectiveness of CRT-D implantation in this postmarket study.
- Endpoints – The sponsor proposes that the primary study endpoint is to assess long-term effect of CRT-D on all cause mortality without evaluation of heart failure symptom progression. Without heart failure data, it will be difficult to evaluate the long-term effectiveness of CRT-D implant, which is a key issue of this PAS study. The assessment of heart failure events, such as heart failure hospitalization, should be included in the PAS at least as secondary endpoints.

- Statistical Plan – The sponsor proposes a secondary study endpoint to characterize all cause mortality for the proposed population by gender. Due to the expected, small proportion of the female patient subgroup (25-30%, n=375-450) in the PAS population, PAS will probably not have sufficient power to assess the potential difference in effectiveness between male and female patients. The PAS proposal should define the minimum of number of female patients necessary to assess the benefit of CRT in females.
- Timeline – The proposed PAS outline did not include the detailed study timelines. The information is needed for the FDA to objectively assess study conduct and progress.

11. Summary of FDA's Comments

The sponsor seeks to expand the indications for their CRT-D devices to include NYHA Functional Class II patients who remain symptomatic despite stable, optimal medical therapy, and who have left bundle branch block (LBBB) with a QRS duration ≥ 120 ms, and left ventricular ejection fraction ≤ 30%. This request to broaden the indications for use is based upon the results of Medtronic-sponsored REVERSE study (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction), which was conducted under IDE G040004, with supporting information from the University of Ottawa Heart Institute-sponsored RAFT study (Resynchronization / defibrillation for Ambulatory heart Failure Trial).

The sponsor conducted two separate large scale trials randomizing over 2400 patients in multiple countries in order to evaluate the benefits of CRT in an expanded population of patients. However, the indications proposed by the sponsor are a post hoc subset of the patients enrolled in either trial. Although some aspects of the overall results from the studies are compelling, FDA has identified a number of issues that require further discussion. For the REVERSE study, the key issues include the failed primary endpoint, differences between US and OUS patient characteristics and results, difficulty interpreting secondary analyses, and limitations in the evaluation of the Clinical Composite Response endpoint. For the RAFT study, the key issues include higher than expected mortality rate compared to similar CRT trials, multiple revisions to the inclusion criteria and statistical analysis plans, limited reporting of protocol deviations, high rate of unblinding and crossovers, collection and bias of previous hospitalizations, and biased collection of NYHA Class at enrollment. For both studies, the key issues include the post hoc analyses of the proposed patient population subgroup and the baseline dosage and changes in dosages of heart failure medications.

FDA would like to acknowledge the sponsor for providing the data and analyses necessary to prepare this summary and looks forward to a productive panel discussion.