SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Names: Cardiac Resynchronization Therapy Pacemaker (CRT-P)
Cardiac Resynchronization Therapy Defibrillator (CRT-D)

Device Trade Names:
Consulta® CRT-P Model C4TR01
Syncra® CRT-P Model C2TR01
Consulta® CRT-D Model D224TRK
Consulta® CRT-D Model D204TRM
Maximo® II CRT-D Model D284TRK
Maximo® II CRT-D Model D264TRM
Concerto® II CRT-D Model D274TRK
Protecta® CRT-D Model D334TRG
Protecta® CRT-D Model D334TRM
Protecta® XT CRT-D Model D314TRG
Protecta® XT CRT-D Model D314TRM
Viva™ XT CRT-D Model DTBA1D1
Viva™ XT CRT-D Model DTBA1D4
Viva™ S CRT-D Model DTBB1D1
Viva™ S CRT-D Model DTBB1D4
Brava™ CRT-D Model DTBC1D1
Brava™ CRT-D Model DTBC1D4

Device Procodes: NKE (CRT-P) and NIK (CRT-D)

Applicant's Name and Address:
Medtronic, Inc.
Cardiac Rhythm Disease Management
8200 Coral Sea Street
Mounds View, MN 55112

Date of Panel Recommendation: October 8, 2013

Premarket Approval Application (PMA) Numbers: P010015/S205 & P010031/S381

Date of FDA Notice of Approval: April 10, 2014

Priority Review: Granted priority review status on August 16, 2013 because the expansion of indications for use requested addresses an unmet medical need and is in the best interest of the indicated population.

The original indications statements for the subject CRT-P and CRT-D devices as well as the major changes to those statements are provided in the text below.

The original PMA P010015, InSync Model 8040, was approved on August 28, 2001 with an indication statement as follows:

> The InSync Model 8040 is indicated for the reduction of the symptoms of moderate to severe heart failure (NYHA Functional Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy (as defined in the clinical trials section), and have a left ventricular ejection fraction ≤ 35% and a QRS duration ≥ 130 ms.

The SSED to support the indication is available on the CDRH website and is incorporated by reference here: http://www.accessdata.fda.gov/cdrh_docs/pdf/P010015b.pdf.

PMA supplement P010015/S005, (InSync III Model 8042) was approved on February 25, 2003 where the indication statement was modified to add rate adaptive pacing and dual chamber modes and read:

> The Medtronic InSync III Model 8042 is indicated for the reduction of the symptoms of moderate to severe heart failure (NYHA Functional Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy (as defined in the clinical trials section), and have a left ventricular ejection fraction ≤ 35% and a QRS duration ≥ 130 ms. Rate adaptive pacing is provided for those patients developing a bradycardia indication who might benefit from increased pacing rates concurrent with increases in activity. Dual chamber and atrial tracking modes are indicated for patients who may benefit from maintenance of AV synchrony.

PMA supplement P010015/S016, (InSync III Model 8042) was approved on March 7, 2005 where the indication statement was modified to a prolonged QRS duration and read:

> The Medtronic InSync III Model 8042 is indicated for the reduction of the symptoms of moderate to severe heart failure (NYHA Functional Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy (as defined in the clinical trials section), and have a left ventricular ejection fraction ≤ 35% and a prolonged QRS duration. Rate adaptive pacing is provided for those patients developing a bradycardia indication who might benefit from increased pacing rates concurrent with increases in activity. Dual chamber and atrial tracking modes are indicated for patients who may benefit from maintenance of AV synchrony.

PMA supplement P010015/S084, (Consulta CRT-P and Syncra CRT-P) was approved on March 22, 2011 where the Consulta CRT-P indication statement was further expanded to include atrial therapies and atrial rhythm management features and read:

> The **Consulta CRT-P system** is indicated for NYHA Functional Class III or IV patients who remain symptomatic despite stable, optimal medical therapy, and have a left ventricular ejection fraction of ≤ 35% and a prolonged QRS duration. Rate adaptive pacing is provided for those patients developing a bradycardia indication who might benefit from increased pacing rates concurrent with increases in activity. Dual

chamber and atrial tracking modes are indicated for patients who may benefit from maintenance of AV synchrony. Antitachycardia pacing (ATP) is indicated for termination of atrial tachyarrythmias in patients with one or more of the above pacing indications. Atrial rhythm management features such as Atrial Rate Stabilization (ARS) and Post Mode Switch Overdrive Pacing (PMOP) are indicated for the suppression of atrial tachyarrhythmias in patients with atrial septal lead placement and one or more of the above pacing indications.

The **Syncra CRT-P system** is indicated for NYHA Functional Class III or IV patients who remain symptomatic despite stable, optimal medical therapy, and have a left ventricular ejection fraction of ≤ 35% and a prolonged QRS duration.

Rate adaptive pacing is provided for those patients developing a bradycardia indication who might benefit from increased pacing rates concurrent with increases in activity. Dual chamber and atrial tracking modes are indicated for patients who may benefit from maintenance of AV synchrony.

PMA supplement P010015/S162, (Consulta CRT-P) was approved on February 20, 2013 removing the atrial rhythm management feature from the indication statement and read:

The **Consulta CRT-P system** is indicated for NYHA Functional Class III or IV patients who remain symptomatic despite stable, optimal medical therapy, and have a left ventricular ejection fraction of ≤ 35% and a prolonged QRS duration. Rate adaptive pacing is provided for those patients developing a bradycardia indication who might benefit from increased pacing rates concurrent with increases in activity. Dual chamber and atrial tracking modes are indicated for patients who may benefit from maintenance of AV synchrony. Antitachycardia pacing (ATP) is indicated for termination of atrial tachyarrythmias in patients with one or more of the above pacing indications.

The original PMA P010031, InSync ICD Model 7272, was approved on June 26, 2002 with an indication statement as follows:

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

The SSED to support the indication is available on the CDRH website and is incorporated by reference here: http://www.accessdata.fda.gov/cdrh_docs/pdf/P010031b.pdf.

PMA supplement P010031/S018, (InSync III Marquis Model 7279, InSync Maximo Models 7303 and 7304, and InSync Sentry Models 7297 and 7299) was approved on April 8, 2005 where the indication statement was modified to read:

> The [name of the system] is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias. The system is also indicated for the reduction of the symptoms of moderate to severe heart failure (NYHA Functional Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy, and have a left ventricular ejection fraction less than or equal to 35% and a prolonged QRS duration.

PMA supplement P010031/S057, (Concerto CRT-D Models C154DWK and C164AWK) was approved on April 17, 2007 where the indication statement was further expanded to include atrial tachyarrhythmias and reads as follows:

> The [name of the system] is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias. In addition, the device is indicated for use in patients with atrial tachyarrhythmias, or those patients who are at significant risk of developing atrial tachyarrhythmias. The system is also indicated for the reduction of the symptoms of moderate to severe heart failure (NYHA Functional Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy and have a left ventricular ejection fraction ≤35% and a prolonged QRS duration.
>
> Atrial rhythm management features such as Atrial Rate Stabilization (ARS), Atrial Preference Pacing (APP), and Post Mode Switch Overdrive Pacing (PMOP) are indicated for the suppression of atrial tachyarrhythmias in ICD-indicated patients with atrial septal lead placement and an ICD indication.

PMA supplement P010031/S232, (Concerto CRT-D Model C154DWK, Consulta CRT-D Model D224TRK, Concerto II CRT-D Model D274TRK, Protecta XT CRT-D Model D314TRM, Protecta CRT-D Model D334TRM, Protecta XT CRT-D Model D314TRG, Protecta CRT-D Model D334TRG, and Consulta CRT-D Model D204TRM) was approved on April 4, 2012 where the indication statement was further expanded to include: Left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II and reads as follows:

> The [name of device] CRT-D system is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias and for providing cardiac resynchronization therapy in heart failure patients who remain symptomatic despite optimal medical therapy, and meet any of the following classifications:
>
> - New York Heart Association (NYHA) Functional Class III or IV and who have a left ventricular ejection fraction ≤ 35% and a prolonged QRS duration.
>
> - Left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II.

The system is also indicated for use in patients with atrial tachyarrhythmias, or those patients who are at significant risk for developing atrial tachyarrhythmias.

Atrial rhythm management features such as Atrial Rate Stabilization (ARS), Atrial Preference Pacing (APP), and Post Mode Switch Overdrive (PMOP) are indicated for the suppression of atrial tachyarrhythmias in implantable cardioverter defibrillator (ICD)-indicated patients with atrial septal lead placement and an ICD indication.

PMA supplement P010031/S232 (Maximo II CRT-D Model D284TRK and Maximo II CRT-D Model D264TRM) was approved on April 4, 2012 where the indication statement was further expanded to include: Left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II and reads as follows:

The Maximo II CRT-D system is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias and for providing cardiac resynchronization therapy in heart failure patients who remain symptomatic despite optimal medical therapy, and meet any of the following classifications:

- New York Heart Association (NYHA) Functional Class III or IV and who have a left ventricular ejection fraction ≤ 35% and a prolonged QRS duration.
- Left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II.

The SSED to support the indication is available on the CDRH website and is incorporated by reference here: http://www.accessdata.fda.gov/cdrh_docs/pdf/P010031S232b.pdf.

PMA supplement P010031/S310, (Concerto CRT-D Model C154DWK, Consulta CRT-D Model D224TRK, Concerto II CRT-D Model D274TRK, Protecta XT CRT-D Model D314TRM, Protecta CRT-D Model D334TRM, Protecta XT CRT-D Model D314TRG, Protecta CRT-D Model D334TRG and Consulta CRT-D Model D204TRM) approved on March 26, 2013 removed the atrial rhythm management features and reads as follows:

The [name of device] CRT-D system is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias, for use in patients with atrial tachyarrhythmias, or those patients who are at significant risk for developing atrial tachyarrhythmias and for providing cardiac resynchronization therapy in heart failure patients who remain symptomatic despite optimal medical therapy, and meet any of the following classifications:

- New York Heart Association (NYHA) Functional Class III or IV and who have a left ventricular ejection fraction ≤ 35% and a prolonged QRS duration.

- Left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II.

The current supplements (P010015/S205 & P010031/S381) was submitted to expand the indication for all currently marketed Medtronic CRT-P and CRT-D devices to include NYHA Functional Class I, II, or III patients who have a left ventricular ejection fraction (LVEF) ≤ 50%, are on stable, optimal heart failure medical therapy if indicated, and have atrioventricular block (AV block) that is expected to require a high percentage of ventricular pacing that cannot be managed with algorithms to minimize right ventricular pacing.

The U.S. Food and Drug Administration (FDA) approval history for the Medtronic CRT-P and CRT-D devices subject of this submission is provided in **Table 1**.

Table 1: Initial FDA Approval History for Medtronic CRT-P and CRT-D Devices Under Review for this Submission

Name of Product	FDA Number	Date of FDA Approval
Consulta® CRT-P Model C4TR01	P010015/S084	March 22, 2011
Syncra® CRT-P Model C2TR01	P010015/S084	March 22, 2011
Consulta™Model D224TRK	P010031/S084	March 17, 2008
Maximo® II Model D284TRK	P010031/S084	March 17, 2008
Concerto® II Model D274TRK	P010031/S125	October 23, 2008
Protecta™ XT Model D314TRG	P010031/S171	March 25, 2011
Protecta™ Model D334TRG	P010031/S171	March 25, 011
Protecta™ XT Model D314TRM	P010031/S178	November 9, 2011
Protecta™ Model D334TRM	P010031/S178	November 9, 2011
Consulta® Model D204TRM	P010031/S176	January 9, 2012
Maximo® II Model D264TRM	P010031/S176	January 9, 2012
Viva™ XT Model DTBA1D1	P010031/S318	January 29, 2013
Viva™ XT Model DTBA1D4	P010031/S318	January 29, 2013
Viva™ S Model DTBB1D1	P010031/S318	January 29, 2013
Viva™ S Model DTBB1D4	P010031/S318	January 29, 2013
Brava™ Model DTBC1D1	P010031/S318	January 29, 2013
Brava™ Model DTBC1D4	P010031/S318	January 29, 2013

II. INDICATIONS FOR USE

The indications for use for the Consulta CRT-P Model C4TR01 and Syncra CRT-P Model C2TR01 is as follows:

The **Consulta CRT-P system** is indicated for:

- NYHA Functional Class III and IV patients who remain symptomatic despite stable, optimal heart failure medical therapy and have a LVEF ≤ 35% and a prolonged QRS duration.

- NYHA Functional Class I, II, or III patients who have a LVEF ≤ 50%, are on stable, optimal heart failure medical therapy if indicated and have atrioventricular block (AV block) that are expected to require a high percentage of ventricular pacing that cannot be managed with algorithms to minimize right ventricular pacing. Optimization of heart failure medical therapy that is limited due to AV block or the urgent need for pacing should be done post implant.

Rate adaptive pacing is provided for those patients developing a bradycardia indication who might benefit from increased pacing rates concurrent with increases in activity.

Dual chamber and atrial tracking modes are indicated for patients who may benefit from maintenance of AV synchrony.

Antitachycardia pacing (ATP) is indicated for termination of atrial tachyarrythmias in patients with one or more of the above pacing indications.

The **Syncra CRT-P system** is indicated for:

- NYHA Functional Class III and IV patients who remain symptomatic despite stable, optimal heart failure medical therapy and have a LVEF ≤ 35% and a prolonged QRS duration.

- NYHA Functional Class I, II, or III patients who have a LVEF ≤ 50%, are on stable, optimal heart failure medical therapy if indicated and have atrioventricular block (AV block) that are expected to require a high percentage of ventricular pacing that cannot be managed with algorithms to minimize right ventricular pacing. Optimization of heart failure medical therapy that is limited due to AV block or the urgent need for pacing should be done post implant.

Rate adaptive pacing is provided for those patients developing a bradycardia indication who might benefit from increased pacing rates concurrent with increases in activity.

Dual chamber and atrial tracking modes are indicated for patients who may benefit from maintenance of AV synchrony.

The indications for use is as follows for the Consulta CRT-D Model D224TRK, Concerto II CRT-D Model D274TRK, Consulta CRT-D Model D204TRM, Protecta XT CRT-D Model D314TRM, Protecta CRT-D Model D334TRM, Protecta XT CRT-D Model D314TRG, Protecta CRT-D Model D334TRG, Viva XT CRT-D Model DTBA1D4, Viva XT CRT-D Model DTBA1D1, Viva S CRT-D Model DTBB1D4, Viva S CRT-D Model

DTBB1D1, Maximo II CRT-D Model D284TRK, Maximo II CRT-D Model D264TRM, Brava CRT-D Model DTBC1D1 and Brava CRT-D Model DTBC1D4.

Consulta CRT-D Model D224TRK, Concerto II CRT-D Model D274TRK, Consulta CRT-D Model D204TRM, Protecta XT CRT-D Model D314TRM, Protecta CRT-D Model D334TRM, Protecta XT CRT-D Model D314TRG, Protecta CRT-D Model D334TRG, Viva XT CRT-D Model DTBA1D4, Viva XT CRT-D Model DTBA1D1, Viva S CRT-D Model DTBB1D4, and Viva S CRT-D Model DTBB1D1:

The [name of device] CRT-D system is indicated for patients who require ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias, for use in patients with atrial tachyarrhythmias, or those patients who are at significant risk for developing atrial tachyarrhythmias and for providing cardiac resynchronization therapy in heart failure patients on stable, optimal heart failure medical therapy if indicated, and meet any of the following classifications:

- New York Heart Association (NYHA) Functional Class III or IV and who have a left ventricular ejection fraction ≤ 35% and a prolonged QRS duration.

- Left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II.

- NYHA Functional Class I, II, or III and who have left ventricular ejection fraction ≤ 50% and atrioventricular block (AV block) that are expected to require a high percentage of ventricular pacing that cannot be managed with algorithms to minimize right ventricular pacing. Optimization of heart failure medical therapy that is limited due to AV block or the urgent need for pacing should be done post implant.

For the **Maximo II CRT-D Model D284TRK, Maximo II CRT-D Model D264TRM, Brava CRT-D Model DTBC1D1 and Brava CRT-D Model DTBC1D4**:

The [name of device] CRT-D system is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias and for providing cardiac resynchronization therapy in heart failure patients on stable, optimal heart failure medical therapy if indicated, and meet any of the following classifications:

- New York Heart Association (NYHA) Functional Class III or IV and who have a left ventricular ejection fraction ≤ 35% and a prolonged QRS duration.

- Left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II.

- NYHA Functional Class I, II, or III and who have left ventricular ejection fraction ≤ 50% and atrioventricular block (AV block) that are expected to require a high percentage of ventricular pacing that cannot be managed with algorithms to minimize

right ventricular pacing. Optimization of heart failure medical therapy that is limited due to AV block or the urgent need for pacing should be done post implant.

III. CONTRAINDICATIONS

Contraindications for Medtronic CRT-P and CRT-D devices are listed below:

CRT-P Devices:

- Concomitant implant with another bradycardia device
- Concomitant implant with an implantable cardioverter defibrillator

There are no known contraindications for the use of pacing as a therapeutic modality to control heart rate. The patient's age and medical condition, however, may dictate the particular pacing system, mode of operation, and implant procedure used by the physician.

- Rate-responsive modes may be contraindicated in those patients who cannot tolerate pacing rates above the programmed Lower Rate
- Dual chamber sequential pacing is contraindicated in patients with chronic or persistent supraventricular tachycardias, including atrial fibrillation or flutter
- Asynchronous pacing is contraindicated in the presence (or likelihood) of competition between paced and intrinsic rhythms
- Single chamber atrial pacing is contraindicated in patients with an AV conduction disturbance
- Anti-tachycardia pacing (ATP) therapy is contraindicated in patients with an accessory antegrade pathway

CRT-D Devices:

- Patients experiencing tachyarrhythmias with transient or reversible causes including, but not limited to, the following: acute myocardial infarction, drug intoxication, drowning, electric shock, electrolyte imbalance, hypoxia, or sepsis
- Patients who have a unipolar pacemaker implanted
- Patients with incessant ventricular tachycardia (VT) or ventricular fibrillation (VF)
- Patients whose primary disorder is chronic atrial tachyarrhythmia with no concomitant VT or VF. (Note: this contraindication does not apply to the Maximo II devices).

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Medtronic CRT-P and CRT-D devices labeling.

V. DEVICE DESCRIPTION

Medtronic CRT-P devices are multi-programmable, cardiac resynchronization therapy implantable pulse generators (IPG). The CRT-P systems provide biventricular pacing for cardiac resynchronization therapy and monitor and regulate a patient's heart rate by

providing dual chamber rate-responsive bradycardia pacing and atrial therapies if available. The devices also provide diagnostic and monitoring information that assist with system evaluation and patient care. A more detailed device description can be found in the SSED for P010015: http://www.accessdata.fda.gov/cdrh_docs/pdf/P010015b.pdf.

Medtronic CRT-D devices are multi-programmable, dual chamber implantable cardioverter defibrillators (ICD) with biventricular pacing features for cardiac resynchronization. The CRT-D systems are different from CRT-P systems in that they have the added functionality for automatically detecting ventricular tachyarrhythmias (VT/VF) and providing treatment with defibrillation, cardioversion, and antitachycardia pacing therapies. A more detailed device description can be found in the SSED for P010031: http://www.accessdata.fda.gov/cdrh_docs/pdf/P010031b.pdf

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The primary alternative practice and procedure for patients with atrioventricular block (AV block) that requires a high percentage of ventricular pacing that cannot be managed with algorithms to minimize ventricular pacing, who are NYHA Functional Class I, II, or III on stable optimal medical therapy and who have a LVEF $\leq$ 50% is implantation of a right ventricular pacing system. This alternative has its own advantages and disadvantages. A patient should fully discuss alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Medtronic CRT-P and CRT-D devices are marketed in over 50 countries throughout the world. Medtronic first received FDA approval for CRT-P devices on August 28, 2001 under PMA P010015. Medtronic first received approval for CRT-D devices on June 26, 2002 under PMA P010031. None of these devices have been withdrawn from marketing anywhere for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the transvenous leads and pacing systems:

- acceleration of tachyarrhythmias (caused by device)
- air embolism
- bleeding
- body rejection phenomena, including local tissue reaction
- cardiac dissection
- cardiac perforation
- cardiac tamponade
- chronic nerve damage
- constrictive pericarditis
- death
- device migration
- endocarditis
- erosion/erosion through the skin
- excessive fibrotic tissue growth

- extrusion
- fluid accumulation
- heart block
- hemothorax
- keloid formation
- lead migration/dislodgement
- muscle and/or nerve stimulation
- myocardial irritability
- pericardial effusion
- pneumothorax
- threshold elevation
- thrombosis
- transvenous lead-related thrombosis
- valve damage (particularly in fragile hearts)
- venous or cardiac perforation
- fibrillation or other arrhythmias
- formation of hematomas/seromas or cysts
- heart wall or vein wall rupture
- infection
- lead abrasion and discontinuity
- mortality due to inability to delivery therapy
- myocardial damage
- myopotential sensing
- pericardial rub
- poor connection of the lead to the device, which may lead to oversensing, undersensing or a loss of therapy
- thrombolytic embolism
- tissue necrosis
- venous occlusion

An additional potential adverse event associated with the use of transvenous left ventricular pacing leads is coronary sinus dissection.

Additional potential adverse events associated with the use of ICD systems include, but are not limited to, the following events:

- inappropriate shocks
- potential mortality due to inability to defibrillate
- shunting current of insulating myocardium during defibrillation

Patients susceptible to frequent shocks despite medical management could develop psychological intolerance to an ICD system that might include the following conditions:

- dependency
- depression
- fear of premature battery depletion
- fear of shocking while conscious
- fear that shocking capability may be lost
- imagined shocking (phantom shock)

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

Medtronic CRT-P and CRT-D systems are commercially available. These systems were previously evaluated via non-clinical laboratory testing including: bench testing (including hardware/software verification and validation), biocompatibility testing, and animal studies. Device design and system compatibility involved verification and validation of the system. The test procedures and results were previously reviewed and approved in the applications listed in **Table 1** above.

X. SUMMARY OF PRIMARY CLINICAL STUDY

This section includes a summary of the Medtronic-sponsored "Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block" (BLOCK HF) Clinical Study which was conducted under IDE G030156 as outlined in **Table 2**.

Table 2: BLOCK HF Clinical Study

Clinical Study	Study Design	Objective	# of Sites	Number of Subjects
BLOCK HF (IDE G030156)	Prospective, randomized, controlled, two-arm, double-blind, multi-center clinical trial	Evaluate the clinical benefit of CRT in NYHA Class I, II and III subjects with LVEF ≤ 50% and AV block	60	918 enrolled 758 successfully implanted 691 randomized and analyzed

Results from the BLOCK HF study were submitted to support the request for expanding the indication for use for Medtronic CRT-P and CRT-D systems to patients with atrioventricular block (AV block) that requires a high percentage of ventricular pacing that cannot be managed with algorithms to minimize ventricular pacing, who are NYHA Functional Class I, II, or III on stable, optimal medical therapy if indicated, and who have a LVEF ≤ 50%.

The following sections will provide an overview of the BLOCK HF clinical study and results.

BLOCK HF Clinical Study

A. Study Design

Patients were treated between December 30, 2003 and December 21, 2012. The database for these PMA supplements reflected data collected through December 21, 2012 and included 918 patients. There were 60 investigational sites.

BLOCK HF was a prospective, multi-site, randomized, double-blinded, parallel-controlled Investigational Device Exemption (IDE) clinical study. Subjects were randomized in a 1:1 ratio to biventricular pacing or right ventricular pacing.

Randomization occurred 30-60 days after a successful implant procedure which allowed for initial pharmacological therapy to be managed. A successful implant was defined as implantation of market-released right ventricular (RV) and left ventricular (LV) leads, and a Medtronic Cardiac Resynchronization Therapy (CRT-P) or a CRT with defibrillation capabilities (CRT-D) device. Right atrial leads were implanted at the discretion of the physician.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the Block HF study was limited to patients who met the following inclusion criteria:

   - Subject had a standard Class I or Class IIa indication for pacemaker in accordance with current ACC/AHA/HRS guidelines at time of the implant
   - Subject had been diagnosed with at least one of the following:
     - Third degree AV block
     - Symptomatic or asymptomatic second degree AV block
     - First degree AV block with symptoms similar to pacemaker syndrome
     - Documented Wenckebach or PR interval $\geq$ 300ms when paced at 100 ppm
   - Subject is receiving a first-time device implant
   - Subject is indicated for ICD implantation for the automated treatment of life-threatening arrhythmias *(required only if the subject was to receive a CRT-D device)*
   - Subject has been classified as NYHA functional class I, II or III within 30 days prior to study enrollment
   - Subject's most recent documented left ventricular ejection fraction (by any methodology) was less than or equal to 50% and documented within 90 days prior to enrollment
   - Subject was at least 18 years old at the time of consent
   - Subject or authorized legal guardian or representative had signed and dated the Subject Informed Consent
   - Subject could receive a pectoral implant

- Subject was expected to remain available for follow-up visits at the trained study center

- Subject was willing and able to comply with the protocol

Patients were not permitted to enroll in the Block HF study if they met any of the following exclusion criteria:

- Subject had ever had a previous or existing pacemaker, ICD or CRT device

- Subject had unstable angina, acute myocardial infarction (MI), coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within 30 days prior to study enrollment

- Subject had a valve replacement or repair within six months (180 days) prior to study enrollment

- Subject had valvular disease and was indicated for a valve repair or replacement

- Subject had a mechanical right heart valve

- Subject was indicated for a biventricular pacing device (CRT-P or CRT-D)

- Subject was enrolled in a concurrent study that may have confounded the results of BLOCK HF

- Subject was pregnant, or a childbearing potential and not on a reliable form of birth control

- Subject was status post heart transplant

- Subject was classified as NYHA functional class IV within 90 days prior to study enrollment

- Subject, legal guardian or authorized representative was unable or unwilling to cooperate or give written informed consent

2. Follow-up Schedule

Clinical data were collected at baseline, implant, post-implant baseline/randomization, and follow-up visits occurring at 3, 6, 9, 12, 15, 18, 21 and 24 months post-randomization, with further follow-up visits required every three (3) months thereafter until sufficient data were collected for evaluation of the primary objective.

Data were also collected upon system modification, notification of adverse events and hospitalizations, (including adverse event-related emergency department and urgent care visits), interim follow-up visits, study exits, crossovers, deviations, and deaths.

Data collected included case report forms to capture demographics, medical history, device interrogations, echocardiograms (echo), assessment of clinical and functional status, as well as quality of life. Device data files and echocardiographic recordings were used as electronic data.

The key timepoints are shown below in the tables and figures summarizing safety and effectiveness.

3. Clinical Endpoints

The primary objective of the BLOCK HF study was to demonstrate the time until the first event of all-cause mortality, heart-failure-related urgent care, or a significant increase in left ventricular end systolic volume index (LVESVI) for subjects programmed to biventricular pacing is superior to that of subjects programmed to right ventricular pacing. This composite of endpoint event types was used to evaluate both safety and effectiveness of the device in the new population.

Heart failure-related urgent care was defined as experiencing one of the following:

- A heart failure-related hospitalization requiring intravenous heart failure therapy,
- An emergency department visit for heart failure requiring intravenous heart failure therapy, or
- A visit in which the subject presents with signs or symptoms consistent with heart failure or heart failure exacerbation, and intravenous therapy is required.

A significant increase in LVESVI was defined as a 15% or more increase in the normalized left ventricular end systolic volume from post-implant baseline/randomization to the time point of interest where the normalized systolic volume is systolic volume divided by body surface area. The clinical meaning of this increase in LVESVI was discussed during Panel deliberations (see Section XI for additional information).

Secondary objectives were intended to provide additional information on subject response, system performance and corroborate the results of the primary objective. The following were pre-specified for evaluation; however, since the statistical plan did not control for Type I error for any secondary objectives, all results are considered observational and hypothesis generating.

- Hazard rate for time to all-cause mortality
- Hazard rate for time to all-cause mortality or first heart failure-related hospitalization
- Hazard rate for time to all-cause mortality or significant increase (>15%) in LVESVI
- Hazard rate for time to first heart failure hospitalization; number of days hospitalized for heart failure per month

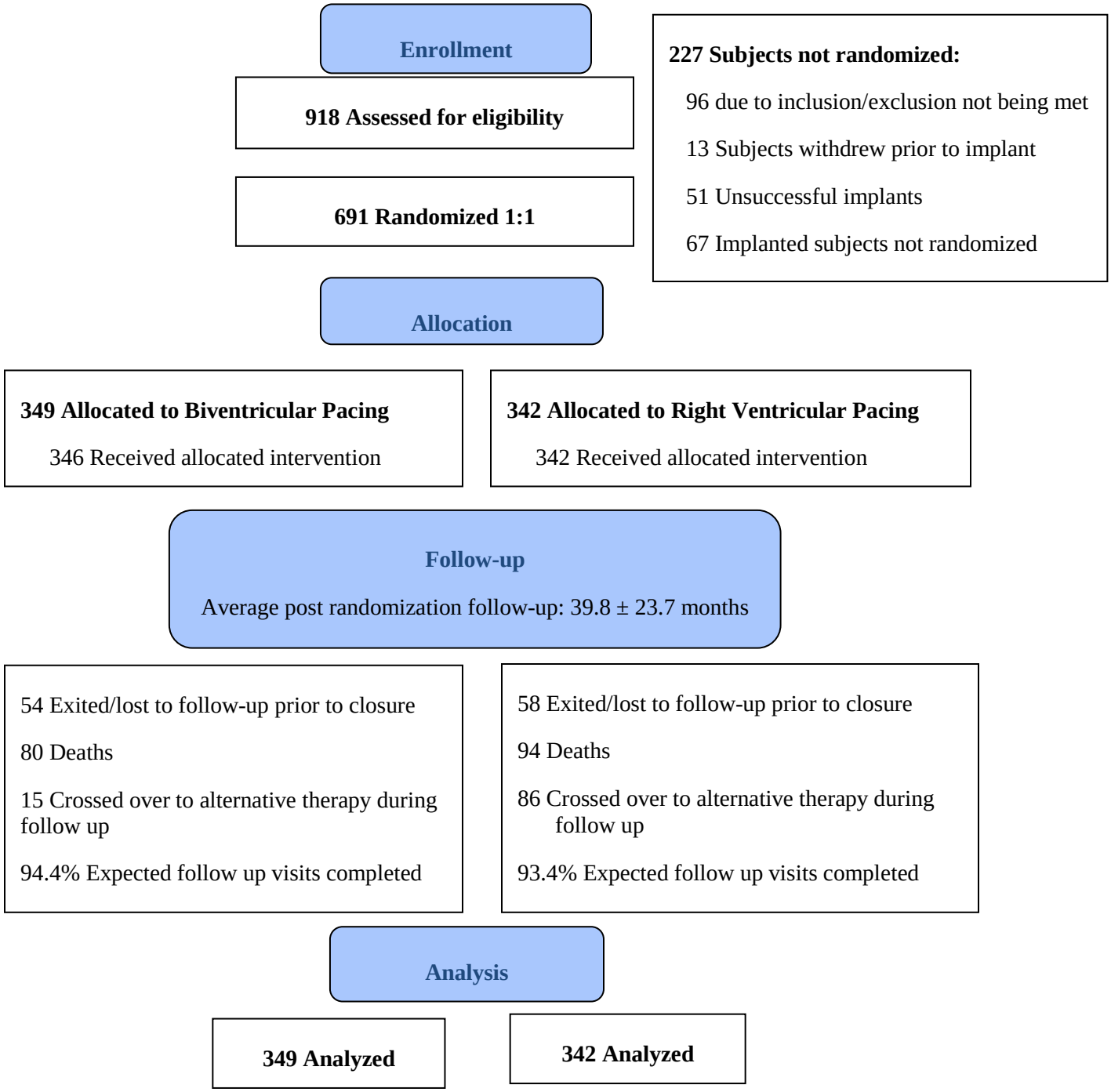
- Changes in NYHA functional classification
- Changes in heart failure stage
- Change in the use of cardiovascular medications over time
- Assess the frequency of occurrence of all trial reportable adverse events
- Assess the frequency of occurrence of cardiovascular health care utilizations
- Changes in quality of life scores as measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ)
- Changes in cardiac structure and function per echocardiography (LVEF, LVESVI, Left Ventricular End Diastolic Volume Index (LVEDVI), LV dimension in diastole, LV dimension in systole, LV mass, mitral regurgitation, cardiac index, interventricular mechanical delay, and E-wave/A-wave ratio)
- Changes in the Heart Failure Clinical Composite scores
- Proportion of subjects with a successful implant of a biventricular pacing system (CRT-P/CRT-D)
- For subjects implanted with a CRT-D: Compare the hazard rate for time to first VT/VF episodes

The prespecified statistical approach for the primary objective and stopping rules for data collection and trial completion was an adaptive Bayesian statistical design. Posterior probabilities and 95% credible intervals were the metrics generated in lieu of Frequentist statistical measures such as p-values and confidence intervals. A posterior probability that a parameter (e.g. BiV to RV hazard ratio for mortality) falls within a given range is a number between 0 and 1 that represents the likelihood, based on pre-trial assumptions and accumulated trial data, that the parameter falls in that range. The objective was met if the probability that the parameter fell within the rejection region exceeded the pre-specified threshold. The primary objective was met if the posterior probability (PP) that the combined hazard ratio was less than 1 exceeded 0.9775. A 95% credible interval is a range of values a parameter falls within with a posterior probability of 0.95. An intention-to-treat analysis served as the primary analysis for each objective. Similar models were used to assess several of the secondary objectives. However, Type I error was not controlled for the analysis of secondary objectives, so their results should be interpreted with caution.

B. <u>Accountability of PMA Cohort</u>

A total of 918 subjects were enrolled at 58 sites in the United States and two (2) sites in Canada. Of the 918 subjects enrolled, implants were attempted in 809. Implants were successful in 758 subjects: 531 received a CRT-P and 227 received a CRT-D. For a variety of reasons, a total of 227 subjects were not randomized from the enrolled 918, leaving 691 randomized subjects available for analysis. **Figure 1** shows the number of subjects included in the analysis of the primary objective.

Figure 1: CONSORT Flow Diagram of Subjects Analyzed for Primary Objective



C. <u>Study Population Demographics and Baseline Parameters</u>

The demographics of the study population are typical for a CRT study performed in the US. **Table 3** summarizes the baseline demographics for all 691 randomized subjects. Mean and standard deviation are presented for continuous variables.

Table 3: Baseline Demographics of All Randomized Subjects

Subject Characteristic	CRT-P (N= 484)		CRT-D (N=207)		Total (N=691)
	BiV Arm (N=243)	RV Arm (N=241)	BiV Arm (N=106)	RV Arm (N=101)	
Gender (N, %)					
Male	181 (74.5%)	168 (69.7%)	87 (82.1%)	81 (80.2%)	517 (74.8%)
Female	62 (25.5%)	73 (30.3%)	19 (17.9%)	20 (19.8%)	174 (25.2%)
Ethnic Origin (N, %)					
Subject did not offer ethnicity	6 (2.5%)	5 (2.1%)	4 (3.8%)	3 (3%)	18 (2.6%)
African American	8 (3.3%)	10 (4.1%)	4 (3.8%)	4 (4%)	26 (3.8%)
Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Caucasian	225 (92.6%)	224 (92.9%)	96 (90.6%)	90 (89.1%)	635 (91.9%)
Hispanic	3 (1.2%)	1 (0.4%)	2 (1.9%)	2 (2%)	8 (1.2%)
Native American	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	1 (0.1%)
Other	1 (0.4%)	0 (0%)	0 (0%)	2 (2%)	3 (0.4%)
Age (years)					
Mean ± Standard Deviation	74.4 ± 10.2	73.8 ± 10.8	72 ± 9.3	71 ± 10	73.3 ± 10.3
Minimum - Maximum	43.8 - 92.4	25.9 - 93.2	40.2 - 88.4	40.6 - 89.5	25.9-93.2
LVEF Measurement (%)					
Mean ± Standard Deviation	43.4 ± 6.5	42.5 ± 6.6	33 ± 7.8	32.9 ± 8	40.0 ± 8.3
Median	45	45	35	32	40
25^{th} Percentile - 75^{th} Percentile	40 - 49	40 - 47	29 - 38	29 - 35	35 - 45
NYHA Classification (N, %)					
Class I	35 (14.4%)	47 (19.5%)	11 (10.4%)	16 (15.8%)	109 (15.8%)
Class II	141 (58%)	126 (52.3%)	67 (63.2%)	58 (57.4%)	392 (56.7%)
Class III	66 (27.2%)	68 (28.2%)	28 (26.4%)	27 (26.7%)	189 (27.4%)
Class IV	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not Available	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Heart Failure Stage Classification (N, %)					
Stage A	1 (0.4%)	3 (1.2%)	0 (0%)	0 (0%)	4 (0.6%)
Stage B	34 (14%)	40 (16.6%)	9 (8.5%)	14 (13.9%)	97 (14.0%)
Stage C	207 (85.2%)	198 (82.2%)	97 (91.5%)	87 (86.1%)	589 (85.2%)
Stage D	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not Available	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)

The percent ventricular pacing was high, over 90% among at least 75% of subjects consistently across different intervals of follow-up, and consistently among both device and treatment arms. The overall median percent RV pacing for the study was over 98%. This supported the trial enrollment goal that subjects must have AV block that requires pacing. Of note, BLOCK HF enrolled very few ethnic minorities with more than 90% of enrollees having Caucasian ethnicity.

D. Safety and Effectiveness Results

1. Safety Results

In this study, all cardiovascular-related, pulmonary-related, renal-related, system-related, procedure-related, and any events in which the subject presents with symptoms compatible with fluid retention and/or decreased exercise tolerance were reported. Adverse events were classified for Seriousness, Complications/Observations, and Relatedness. A complication was defined as an adverse event that results in death, involves any termination of significant device function, or requires invasive intervention. An observation was defined as any adverse event that is not a complication. System relatedness was assessed with respect to device and the leads. The Adverse Event Adjudication Committee (AEAC) adjudicated relatedness for all adverse events.

Out of the 809 subjects in whom implants were attempted, 143 subjects (17.7%) experienced a serious adverse event within 30 days of the initial procedure and 207 subjects (25.6%) experienced a procedure, generator, or LV lead related complication. **Table 4** below summarizes the serious adverse events and complications observed by type.

Table 4: Adverse Events in BLOCK HF Study

Event Type	# Subjects (%)				
	CRT-P (N=484)		CRT-D (N=207)		Others with Implant Attempt (N=118)
	BiV (N=243)	RV (N=241)	BiV (N=106)	RV (N=101)	
Serious Adverse Event ≤ 30 days	41 (16.9%)	28 (11.6%)	18 (17.0%)	15 (14.9%)	41 (34.7%)
Procedure-related complication	42 (17.3%)	26 (10.8%)	21 (19.8%)	16 (15.8%)	34 (28.8%)
Generator-related complication	11 (4.5%)	10 (4.1%)	34 (32.0%)	18 (17.8%)	8 (6.8%)
LV lead-related complication	14 (5.8%)	12 (5.0%)	6 (5.7%)	9 (8.9%)	10 (8.5%)

LV Lead-Related Safety

Given that the LV lead was required to function adequately only in the subjects assigned to BiV pacing, the LV lead related complication rate in the BiV arm of 5.7%

was used for evaluation of the additional LV lead-related risks of a CRT device over an RV pacemaker. This rate is comparable with recent CRT trials, including RAFT (7.4% LV lead related complications at 12 months post implant) and REVERSE (9.1% LV lead related complications at 12 months post implant). The main causes of the lead related complications in the BiV arm are shown in **Table 5** below.

Table 5: LV Lead Related Complications in BiV Arm (N=349)

	# Subjects (%)
All complications	20 (5.7%)
Diaphragmatic stimulation	12 (3.4%)
Lead dislodgement	4 (1.1%)
Failure to capture	1 (0.3%)

An additional consideration for safety is the ability to implant an LV lead. In 51 (6.3%) of the 809 subjects in which implants were attempted, an LV lead implant was not possible. Although increased surgical time is required for attempted, but unsuccessful LV lead implants, not all result in complications. No epicardial leads were used in this study.

Death Summary

Of the 691 subjects randomized, 25.2% died during their follow-up. The majority of deaths were non cardiac related (88/174 = 50.6%). The overall mortality rate was similar in study groups, trending lower for the BiV-randomized arm. No deaths were adjudicated to be procedure-related; one death was found to be system-related. The following table categorizes the deaths observed in the study.

Table 6: Deaths by Device Type and Treatment Arm

AEAC Classification	Number of Subjects (% of Subjects)				
	CRT-P (N=484)		CRT-D (N=207)		Total Randomized Subjects (N=691)
	BiV Arm (N=243)	RV Arm (N=241)	BiV Arm (N=106)	RV Arm (N=101)	
Sudden Cardiac	9 (3.7%)	11 (4.6%)	2 (1.9%)	2 (2.0%)	24 (3.5%)
Non-sudden cardiac	18 (7.4%)	12 (5.0%)	5 (4.7%)	10 (9.9%)	45 (6.5%)
Non-cardiac	25 (10.3%)	34 (14.1%)	14 (13.2%)	15 (14.9%)	88 (12.7%)
Unknown	5 (2.1%)	9 (3.7%)	2 (1.9%)	1 (1.0%)	17 (2.5%)
Heart Failure Related	16 (6.6%)	14 (5.8%)	5 (4.7%)	11 (10.9%)	46 (6.7%)
Total	**57 (23.5%)**	**66 (27.4%)**	**23 (21.7%)**	**28 (27.7%)**	**174 (25.2%)**

2. Clinical Endpoint Results

The primary objective was a composite endpoint that demonstrated the time to the first event of all-cause mortality, heart failure-related urgent care visit, or a ≥15% increase in LVESVI for subjects with BiV pacing is superior to that of subjects with RV pacing.

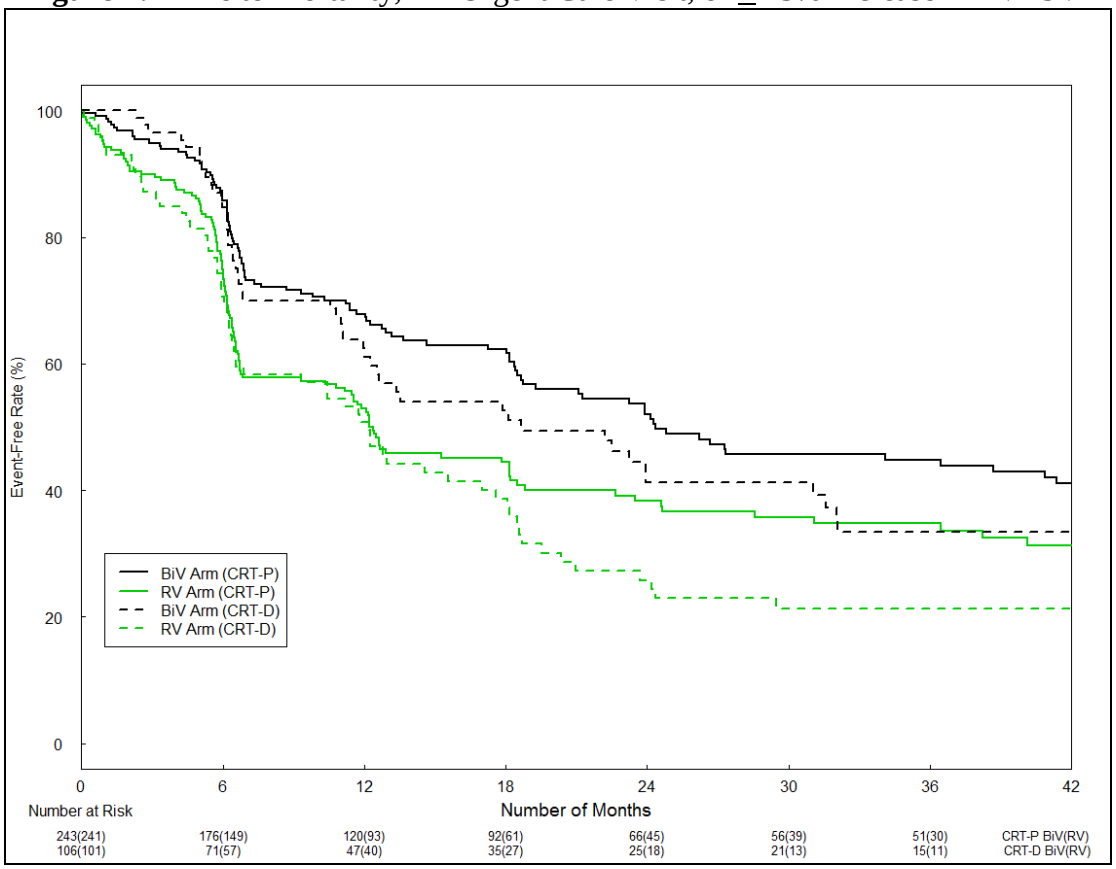
The primary endpoint was met in 186 of 349 (53%) subjects in the BiV pacing arm, compared to 219 of 342 (64%) subjects in the RV pacing arm. Subjects with missing LVESVI measures at the required timepoints of post-implant baseline, 6, 12, 18 and 24 months were censored at the last visit with a readable LVESVI measure prior to the visit with missing data, even if an endpoint was later met. Thus, some primary endpoint events did not contribute to the analysis of the primary objective. After accounting for censoring, 160 (45.8%) of subjects in the BiV pacing arm and 191 (55.8%) of subjects in the RV pacing arm experienced primary endpoints that were included in the primary objective analysis. See **Table 7** and **Figure 2**.

Table 7: Primary Endpoint Events for Analysis of Primary Objective

	Number of Subjects (% of Subjects)				
	CRT-P (N=484)		CRT-D (N=207)		Total Randomized Subjects (N=691)
	BiV Arm (N=243)	RV Arm (N=241)	BiV Arm (N=106)	RV Arm (N=101)	
Primary Endpoint Events	**109 (44.9%)**	**128 (53.1%)**	**51 (48.1%)**	**63 (62.4%)**	**351 (50.8%)**
LVESVI Events	55 (22.6%)	78 (32.4%)	30 (28.3%)	36 (35.6%)	199 (28.8%)
HF Urgent Care	40 (16.5%)	39 (16.2%)	16 (15.1%)	23 (22.8%)	118 (17.1%)
Deaths	14 (5.8%)	11 (4.6%)	5 (4.7%)	4 (4.0%)	34 (4.9%)

Among events that counted towards the primary objective analysis, the most common event type was an increase in LVESVI (28.8% of randomized subjects), followed by a heart failure-related urgent care visit (17.1% of randomized subjects), and death (4.9% of randomized subjects) (see Section 4 "Additional Analysis to Understand the Impact of LVESVI" below for further discussion). Among the LVESVI endpoints, LVESVI increased on average 33.5%.

Figure 2: Time to Mortality, HF Urgent Care Visit, or ≥ 15% Increase in LVESVI



Biventricular pacing resulted in an overall 27% reduction in the primary endpoint achieving Bayesian statistical significance (Posterior Probability = 0.999) of the Hazard Ratio (HR) < 1. Sensitivity analyses including censored data yielded similar findings and the observed relative benefit of biventricular pacing was comparable across device groups (see Section 3"Subgroup Analysis" below for further details). **Table 8** provides the results of the Bayesian primary objective for CRT-P and CRT-D devices and for all subjects.

Table 8: Statistical Analysis of Primary Objective

Subject Group	Hazard Ratio (95% CI)
CRT-P (N=484)	0.72 (0.57, 0.90)
CRT-D (N=207)	0.74 (0.56, 1.00)
All Subjects (N=691)	0.73 (0.59, 0.89)

Secondary Objectives

The results of all secondary objectives are provided below in **Table 9**. Since the statistical plan did not control for Type I error for any secondary objectives, all results below are considered observational and hypothesis generating.

Table 9: Analysis of Secondary Objectives

Secondary Objective	Results
Mortality	A mortality endpoint occurred in 80 (23%) of 349 subjects in the BiV group compared with 94 (27%) of 342 subjects in the RV pacing group.
Time to Mortality/HF-related Hospitalization	A mortality/first HF hospitalization endpoint occurred in 121(35%) of 349 subjects in the BiV group compared with 135 (39%) of 342 subjects in the RV pacing group.
Mortality/Change in LVESVI	A mortality/ ≥15% increase in LVESVI occurred in 158 (45.3%) of BiV subjects and 201 (58.8%) of RV subjects.
Change in Heart Failure-related Hospitalizations	There were 147 HF hospitalizations among 79 (22.6%) of 349 subjects in the BiV arm compared to 157 HF hospitalizations among 92 (26.9%) of 342 RV arm subjects. BiV arm subjects were observed to have overall lower mean rates of days hospitalized for HF per year than RV arm subjects.
Change in NYHA Functional Classification	The analyses comparing the observed mean change in NYHA from Post-implant baseline/randomization to 6, 12, 18, and 24 months post randomization showed similar results between arms.
Change in Heart Failure Stage	The analyses comparing the observed mean change in HF Stage from Post-implant baseline/randomization to 6, 12, 18, and 24 months post-randomization showed similar results between arms: most subjects were Stage C at randomization and remained at Stage C at the other time points of study.
Change in Cardiovascular Medications	The targets for medical therapy recommended in the trial were consistent with AHA/ACC Guidelines for Heart Failure. The observed, administered doses of heart failure medications were lower than the recommended targets. In spite of the lower EF in the CRT-D group, the ACE Inhibitor doses were low, but similar across groups. In addition, in spite of lower EF in the CRT-D group, 85% were on beta blockers with doses at approximately 35% of recommended by the study. After 6 months of pacing, however, beta blocker doses had changed only minimally to 38% of recommended doses.

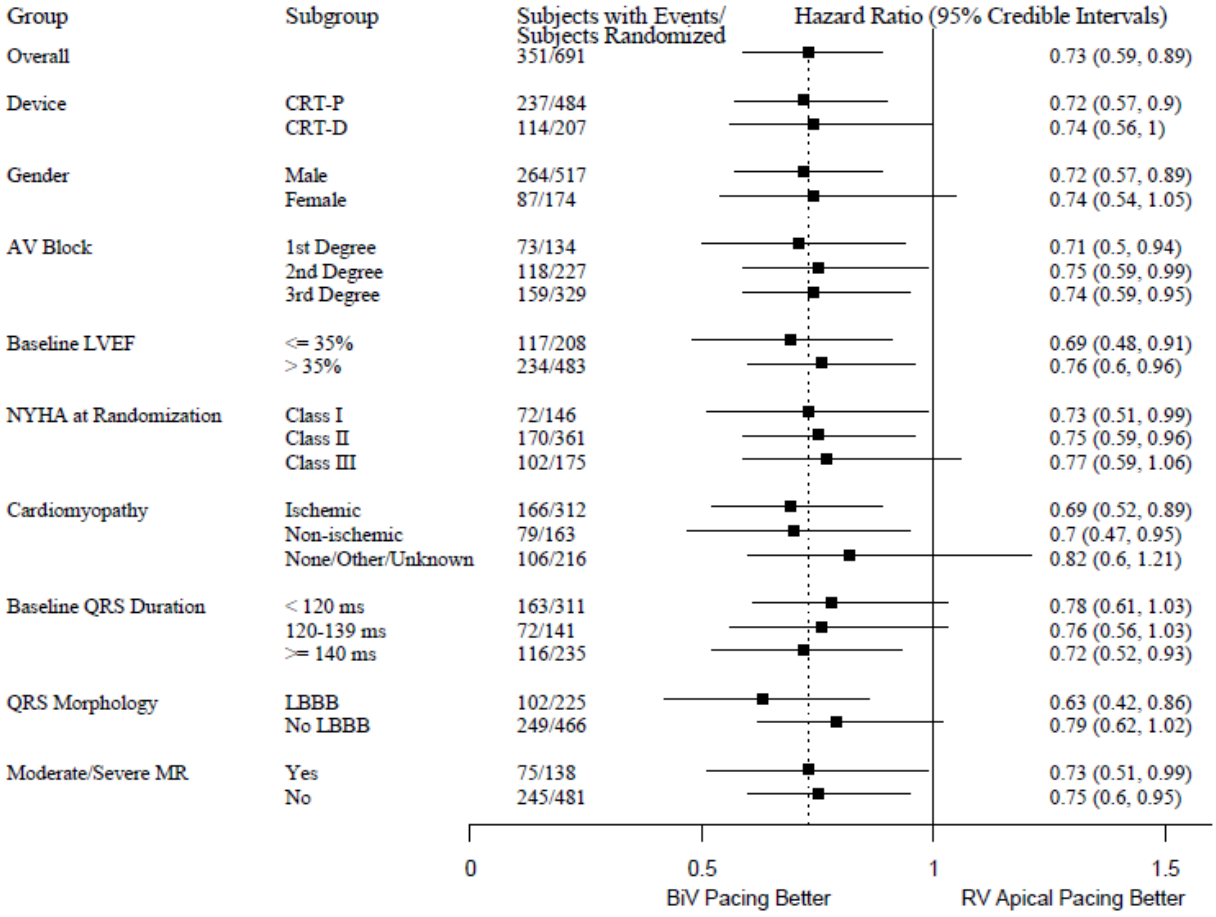
Secondary Objective	Results
Frequency of Adverse Events	There were 3064 adverse events (1669 complications, 1395 observations) experienced by 655 subjects. Observed rates of heart-failure related adverse events were observed to be lower in the BiV arm, while rates of inappropriate device stimulation of tissue were observed to be higher in the BiV arm. Among CRT-D subjects more generator-related complications were observed in the BiV arm. Most of these complications were device change-outs due to the device reaching end of life. The time frame for many of these events was four to five years post implant, corresponding to observed battery longevity.
Cardiovascular Health Care Utilizations	There were 2345 post-randomization CV healthcare utilizations among 527 randomized subjects. Observed rates of heart failure-related hospitalizations were lower in the BiV arm among CRT-P subjects and comparable between arms among CRT-D subjects. Observed CV-related urgent care/clinic visits were lower in the BiV arm across device groups, while rates of observed CV related hospitalizations for reasons other than HF (e.g. lead dislodgement, device changeouts) were higher in the BiV arm.
Change in Quality of Life	Change in Quality of Life score from randomization was compared between arms at 6, 12, 18, and 24 months post randomization. Subjects in the BiV arm were observed to have an average improvement in quality of life at 6 and 12 months, but saw less improvement at 18 and 24 months. Subjects randomized to RV pacing averaged little observed difference in their quality of life through 24 months.

Secondary Objective	Results
Change in Cardiovascular Structure and Function per Echocardiography	Changes in cardiovascular structure and function were assessed at 6, 12, 18, and 24 months post randomization. Subjects who received BiV pacing were observed to have better outcomes as measured by change in LVEF, LVESVI, LVEDVI, LV diastolic dimension, LV mass, and Interventricular Mechanical Delay compared to subjects with RV pacing through 24 months. No differences were observed between randomization groups for change in the following parameters between randomization and any subsequent time points: Cardiac Index, Mitral Regurgitation, LV systolic dimension, and E-Wave/A-Wave Ratio.
Change in Heart Failure Clinical Composite Score	Subjects who received BiV pacing were observed to achieve a better clinical composite score than subjects with RV pacing through 24 months of receiving the therapy.
CRT-P and CRT-D System Implant Success Rate	A CRT system (with or without an RA lead) was successfully implanted in 93.7% of the subjects who received an implant attempt. CRT-D system implant was successful in 227 (91.5%) of 248 attempts. An initial implant attempt of a CRT-P system was made in 561 subjects, and was successful in 531 (94.7%) of those subjects. In all 51 of the unsuccessful cases, the LV lead could not be successfully implanted.
Incidence of VT/VF	More subjects in the BiV arm experienced post-randomization VT/VF (37%) and non-VT/VF (55%) than subjects in the RV arm (31% experienced VT/VF and 47% experienced non-VT/VF).

3. Subgroup Analysis

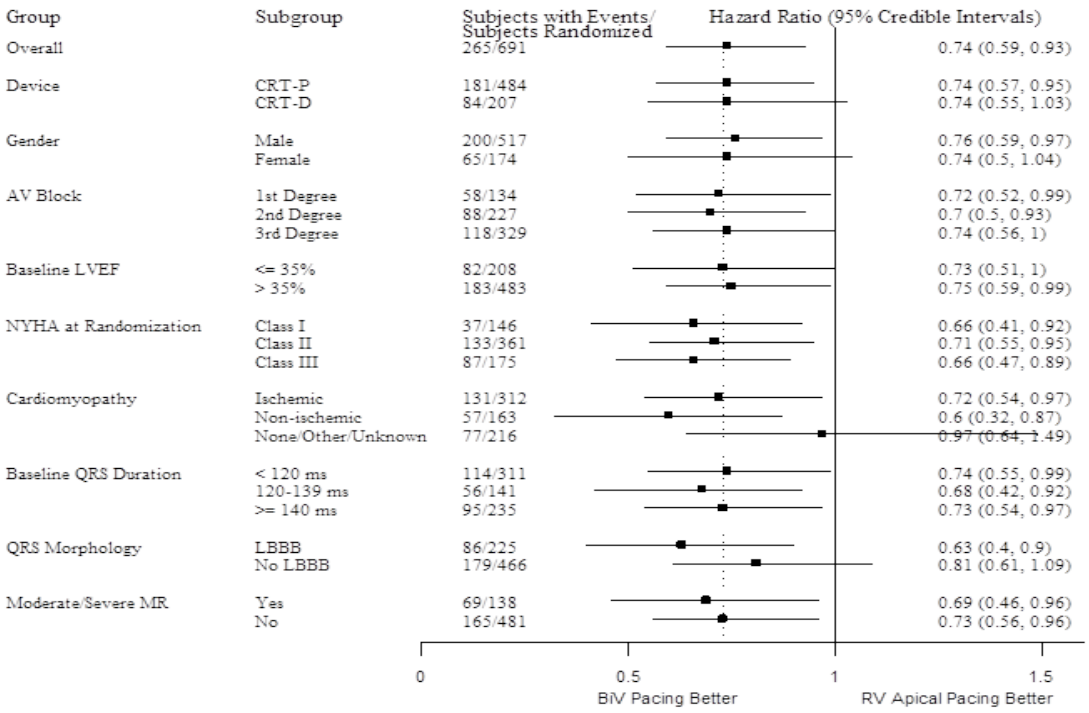
The treatment effect for key clinical subgroups was examined by calculating the hazard ratio in each group as shown in **Figure 3**.

Figure 3: Subgroup Analysis Forest Plot for Primary Objective



The treatment effect when LVESVI is excluded was also examined. See **Figure 4**.

Figure 4: Subgroup Analysis Forest Plot for Death of HF-Related Urgent Care Visit



The treatment effect was consistent across subgroups, noting that some subgroups had higher enrollment than others.

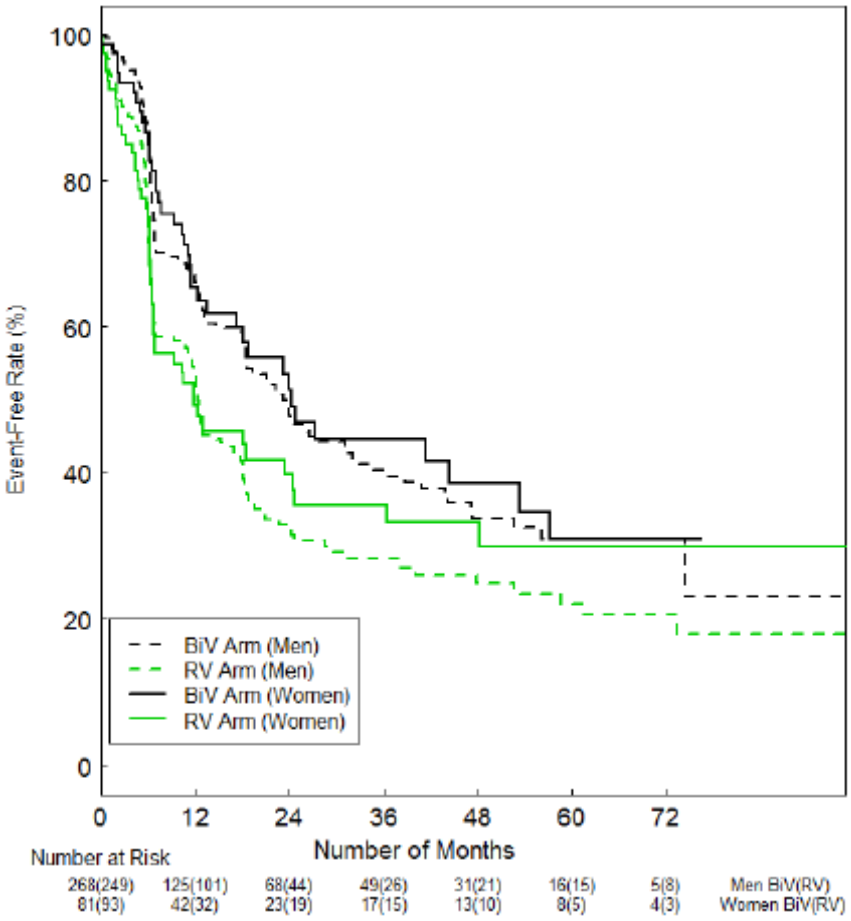
Additional subgroup analyses were performed by gender. The interpretability of these analyses is limited given the low enrollment of women in the BLOCK HF study, 174/691 (25.2%). Both men and women demonstrated similar improvement trends with BiV pacing compared to RV pacing which is discussed further below.

The proportion of female subjects enrolled in the BLOCK HF study is lower than the gender-specific incidence or prevalence of heart failure in this patient population. Of the 5.3 million Americans affected by heart failure, nearly 50% are women[1]. However, the proportion of women enrolled in BLOCK HF is similar to that observed in other trials of CRT and to that observed of AV block subjects with an ICD or pacemaker in the Medtronic Product Surveillance database.

To examine the results of the primary objective by gender, a hierarchical model similar to that used in the main analysis was used to generate the hazard ratios and corresponding 95% two sided credible intervals. In women, biventricular pacing results in an overall 26% reduction in the primary endpoint, while in men the reduction was more (28%). See

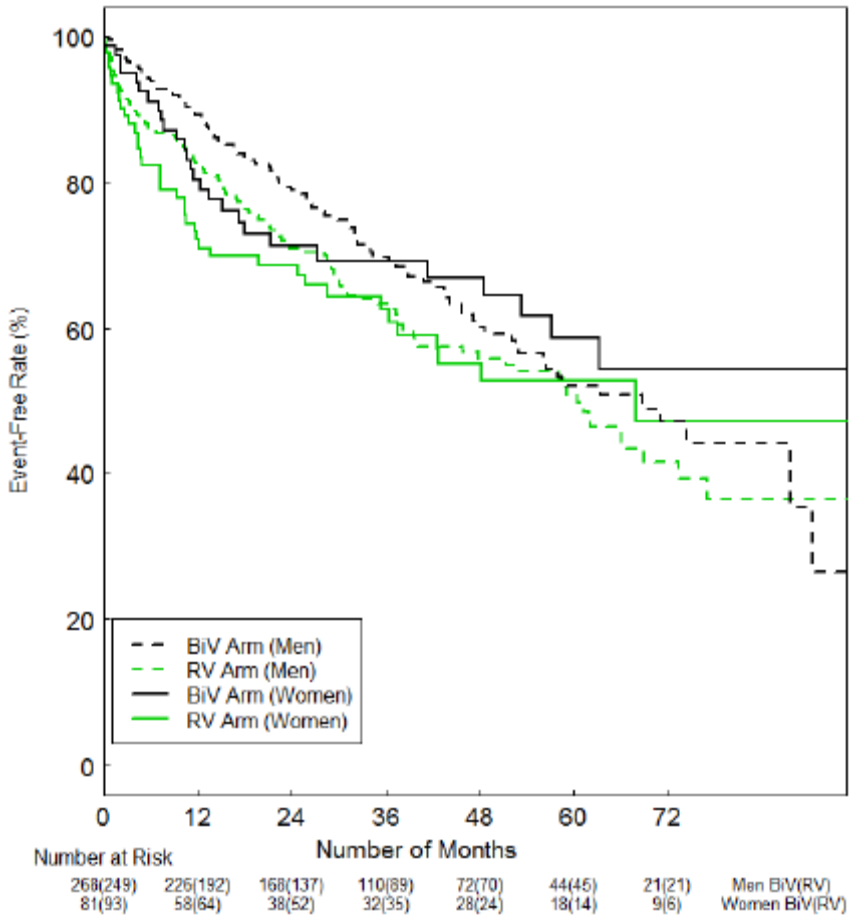
Figure 5. It is important to note that the BLOCK HF study was not designed with a statistically powered sample size for this analysis and that the number of women enrolled in the study was quite low, so interpretation of the results shown in the figure below is limited.

Figure 5: Time to Mortality, HF Urgent Care Visit, or ≥ 15% Increase in LVESVI



An analysis was also done excluding LVESVI. See **Figure 6**. Results still trended toward benefit in both men and women (hazard ratio of 0.80 and 0.76, respectively) when a Frequentist approach is used to analyze the data. A Frequentist approach was used given that no Bayesian analysis was pre-specified for this particular analysis and the priors selected may not have been appropriate for this analysis. It is important to note that the number of women enrolled in the study was quite low, so interpretation of the results shown in the figure below is limited.

Figure 6: Time to Mortality or HF Urgent Care Visit



Baseline demographics are provided by gender in **Table 10**. While the overall sample size for women was low, this analysis provides support that women in BLOCK HF had generally similar demographics as men. Women did, however, have more advanced symptoms than men as evidenced by a higher percentage of Class III enrollments. Women were also less likely to meet the criteria for defibrillation coming in to the trial.

Table 10: Baseline Demographics of All Randomized Subjects

Subject Characteristic	Men (517, 74.8%)	Women (174, 25.2%)	p-value
Ethnic Origin (N, %)			0.05
Subject did not offer ethnicity	15 (3%)	3 (2%)	
African American	16 (3%)	10 (6%)	
Asian	--	--	
Caucasian	479 (93%)	156 (90%)	
Hispanic	4 (1%)	4 (2%)	
Native American	0 (0%)	1 (1%)	
Other	3 (1%)	0 (0%)	
Age (years)			0.946
Mean ± Standard Deviation	73 ±10	73 ±11	
Minimum - Maximum	26 -93	40 -89	
LVEF Measurement (%)			0.374
Mean ± Standard Deviation	40 ± 8	40 ± 9	
Median	40	45	
25^{th} Percentile - 75^{th} Percentile	35 -45	35 -46	
NYHA Classification (N, %)			0.0008
Class I	81 (16%)	28 (16%)	
Class II	312 (60%)	80 (46%)	
Class III	123 (24%)	66 (38%)	
Class IV	--	--	
Not Available	1 (0%)	0 (0%)	
Heart Failure Stage Classification (N, %)			0.958
Stage A	3 (1%)	1 (1%)	
Stage B	72 (14%)	25 (14%)	
Stage C	441 (85%)	148 (85%)	
Stage D	--	--	
Not Available	1 (0%)	0 (0%)	
Device Type (N, %)			0.012
CRT-P	349 (68%)	135 (78%)	
CRT-D	168 (32%)	39 (22%)	

4. Additional Analysis to Understand the Impact of LVESVI

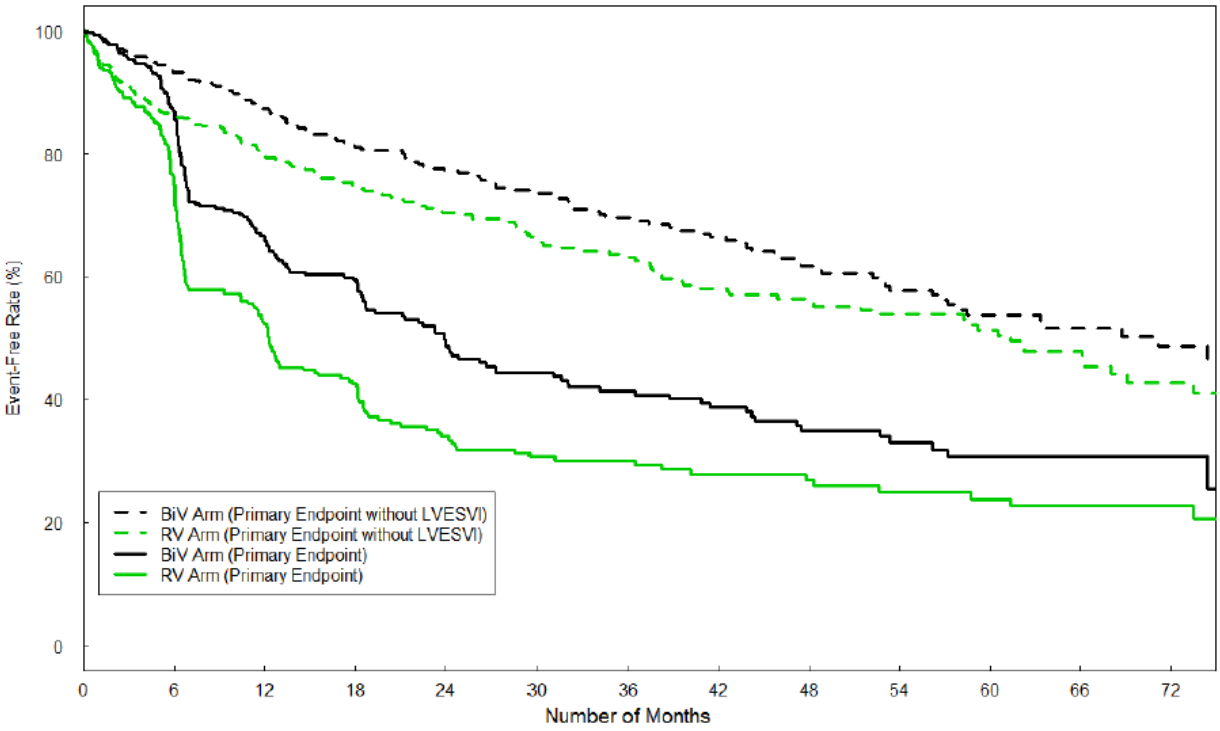
   Given the large contribution of events contributing to the primary objective that were increases in LVESVI (53.1% in the BiV arm and 59.7% in the RV arm), the below analyses were conducted.

   Time to First Event without LVESVI

   The exploratory Kaplan Meier analysis in **Figure 7** shows time to primary endpoint events including mortality or heart failure-related urgent care, but excluding LVESVI events. Superimposed on the graph are the results for the primary objective (when

LVESVI is included). By excluding LVESVI events this analysis has fewer than half the events of the analysis of the primary objective. Results still trend towards benefit (hazard ratio of 0.80) when a Frequentist approach is used to analyze the data. For comparison, the hazard ratio when LVESVI is included is 0.68. A Frequentist approach was used given that no Bayesian analysis was pre-specified and the priors selected may not have been appropriate for this analysis.

Figure 7: Time to 1st Event With (solid lines) and Without (dotted lines) LVESVI by Randomization Arm



Predictive Value of LVESVI

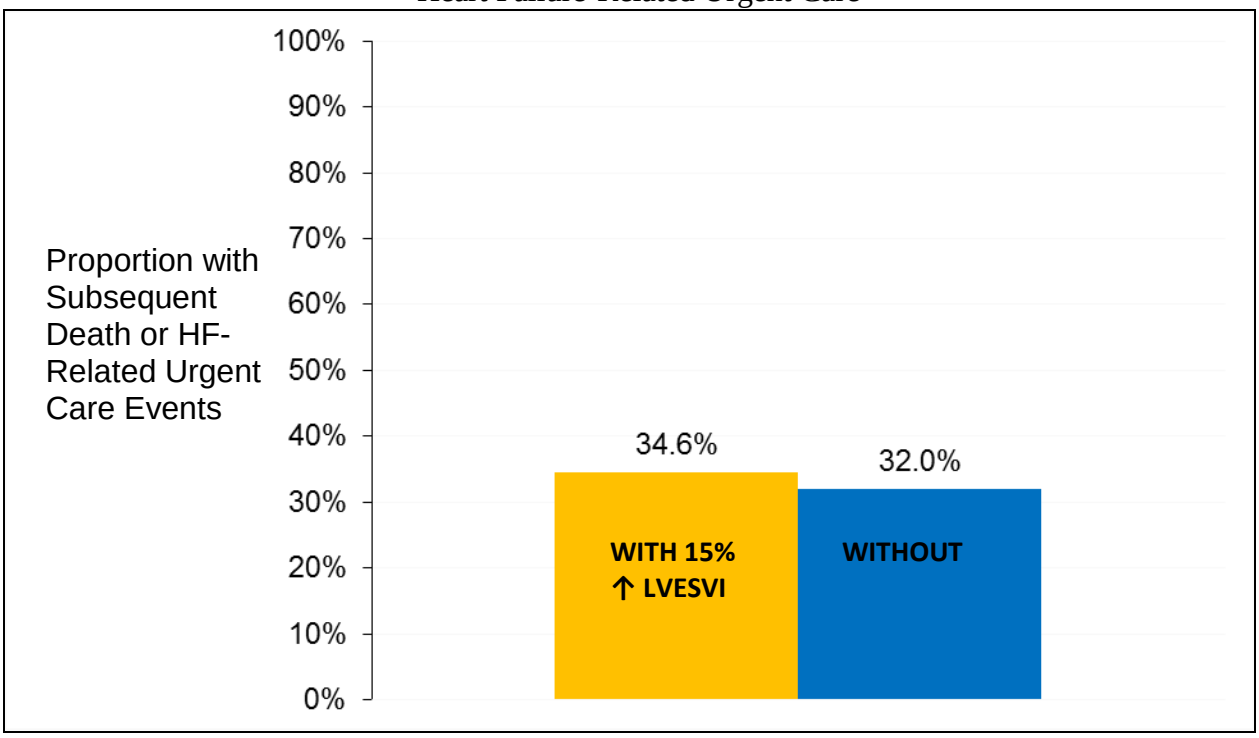
LVESVI events counted equally as death and heart failure events toward the composite primary objective. LVESVI events also occurred more often than death or heart failure events combined. For this reason, the value of LVESVI events was examined further, including whether LVESVI events predicted (i.e. preceded, in this study) future clinically meaningful death or heart failure-related urgent care events. The predictive value of an LVESVI event was examined using two methods.

Proportion of Subjects with Future Death or Heart Failure-Related Urgent Care Events

Subjects whose first primary endpoint event was a significant increase in LVESVI were examined for the occurrence of subsequent death or heart failure-related urgent care to assess whether LVESVI changes predicted future death or HF-related urgent care events. This proportion was compared to the proportion of death or HF-related urgent care events among subjects who did not have a primary endpoint LVESVI event. Increased proportion of death or HF-related urgent care events for those with

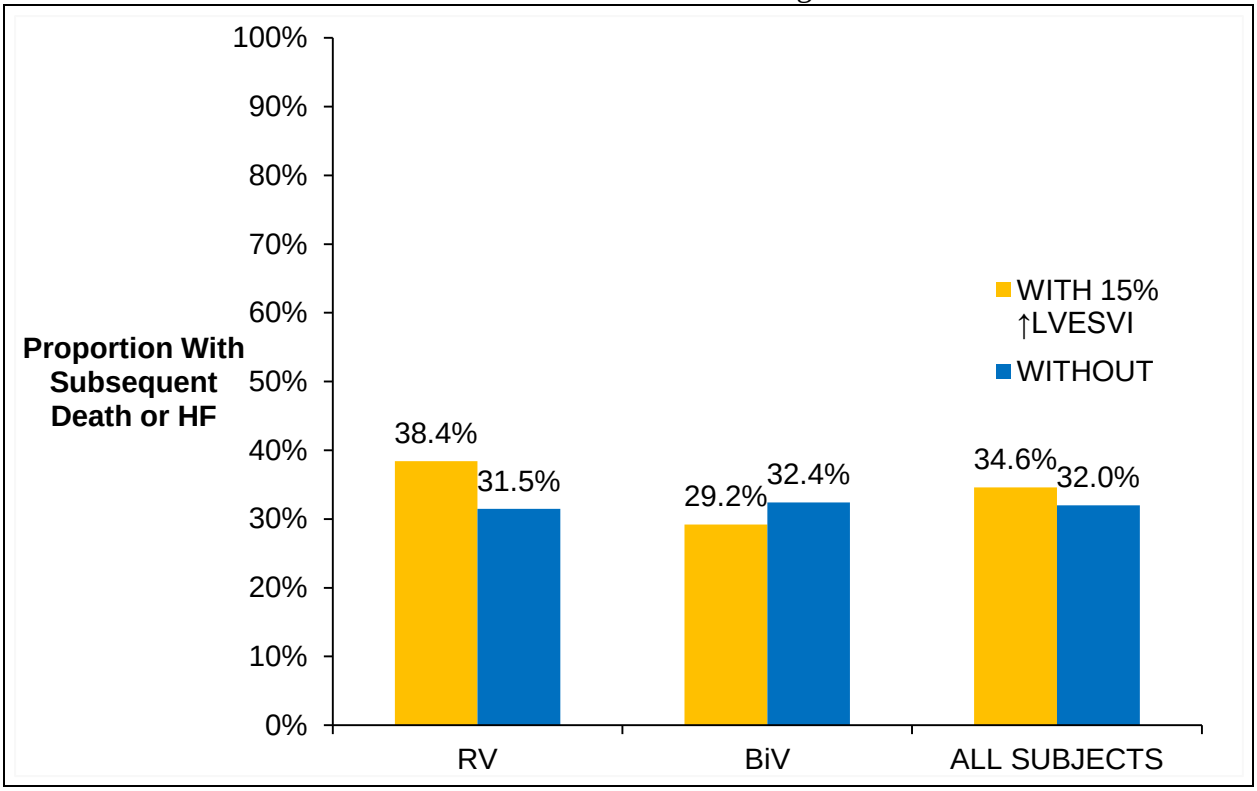
LVESVI events first versus those without LVESVI events was considered evidence that LVESVI changes predicted clinically meaningful outcomes. See **Figure 8.**

Figure 8: Proportion of Subjects with 1st Event of LVESVI Increase and Future Event of Death or Heart Failure-Related Urgent Care



This same analysis was conducted for BiV vs. RV arms and for the entire randomized cohort. See **Figure 9.**

Figure 9: Proportion of Subjects with 1st Event of Increase in LVESVI that have Later Event of Death or Heart Failure-Related Urgent Care



The results indicated that LVESVI is of limited value in predicting future death or heart failure-related urgent care.

Cox Regression Analysis

The question of predictive value was also examined through a Cox Regression Analysis (**Table 11**). In this analysis, values greater than one suggests that having a 15% or more increase in LVESVI predicts future death or heart failure-related urgent care. A hazard ratio of one suggests no predictive value.

Table 11: Cox Regression Analysis for Predictive Value of 1st Event being LVESVI for Future Death or Heart Failure-Related Urgent Care

Category	Hazard Ratio	95% Confidence Interval
All Subjects	1.35	(1.00, 1.82)
RV Arm	1.74	(1.15, 2.65)
BiV Arm	1.00	(0.63, 1.59)

The results indicated that there is no consistent predictive value of LVESVI events for future death or heart failure-related urgent care. However, the trial was not

prospectively designed nor powered to determine the predictive nature of LVESVI events with regard to mortality/morbidity; this represented a post-post analysis, and so the results should be considered with caution.

Annualized Rates for Death and Heart Failure-Related Urgent Care

To further understand the results of the study without LVESVI, the absolute benefit seen in annualized rate for mortality (**Figure 10**) and heart failure-related urgent care (**Figure 11**) was examined.

Figure 10: Annualized Mortality Rate by Randomization Arm

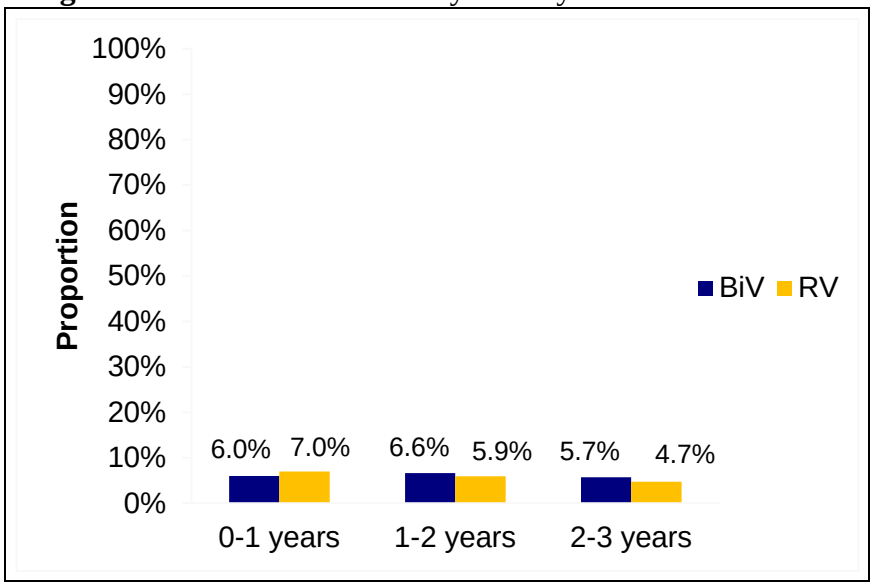
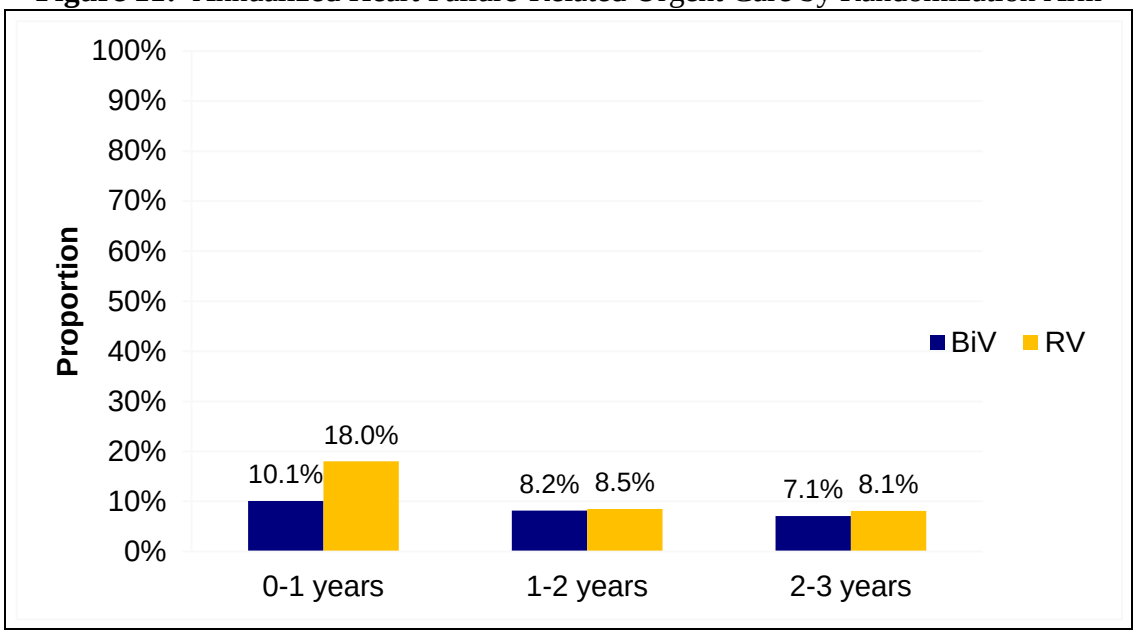


Figure 11: Annualized Heart Failure-Related Urgent Care by Randomization Arm



The suggested clinical benefit is a reduction in the occurrence of heart failure related urgent care of 7.9% in year one. No consistent mortality benefit was observed.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 127 investigators of which none were full-time or part-time employees of the sponsor and 37 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 (none)
- Significant payment of other sorts: 36
- Proprietary interest in the product tested held by the investigator: 0 (none)
- Significant equity interest held by investigator in sponsor of covered study: 1

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were not conducted by FDA as they were not deemed necessary to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The percent of investigators receiving any significant payment was relatively small and, in addition, the study design included the following measures that minimized bias and were determined to be sufficient to address the above financial incentives.

- Randomized, double-blind trial design.
- Trial oversight and monitoring by an independent Data Monitoring Committee (DMC).
- Patients were screened for eligibility for enrollment into the Block HF study with defined inclusion/exclusion criteria prior to enrollment.
- A documented protocol and standardized case report forms were used by all centers.
- Each study site was also monitored for adherence to the protocol and accurate data collection.
- Patient data were monitored for potential under reporting of adverse events.
- Rigorous classification of all reported adverse events and heart failure hospitalizations were adjudicated by an Adverse Event Advisory Committee.

There are no concerns about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on October 8, 2013, the Circulatory System Devices Panel, Panel voted 6-1 that there is reasonable assurance the device is safe, 7-0 that there is reasonable assurance that the device is effective, and 4-3-1 (yes, no, abstain) that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indications.

Summarized below are the primary discussion points by the panel members.

1) Clinical Meaning of LVESVI Events: Regarding the clinical meaning of LVESVI and how best to interpret the results of BLOCK HF given the contribution of LVESVI, the Panel confirmed FDA's concerns and overall conclusions. In favor of LVESVI having clinical meaning the Panelists acknowledged existing literature that LV dysfunction tracks with clinical outcomes to varying degrees in some patient populations (predominantly among patients with progressive heart failure). The Panel also noted that results with and without LVESVI in this trial were concordant using either Bayesian or Frequentist methods. However, the Panel noted that LVESVI did not appear to predict future clinically meaningful events in this study and that examining the results with LVESVI excluded suggested a much reduced clinically meaningful benefit of BiV pacing.

2) Treatment Effect Across Subgroups: The Panel confirmed FDA's interpretation of the forest plot results - the treatment effect is consistent across subgroups though some subgroups were less represented than others. The sponsor was asked to provide a forest plot including only death and heart failure urgent care events; this plot was consistent with that including LVESVI.

3) Indications Statement: The Panel requested FDA and Medtronic continue to refine the indications statement to better specify patients expected to need frequent RV pacing. The Panelists, particularly those with electrophysiology background, presented concerns that many patients have good clinical outcomes when treated with currently indicated RV pacing. The Panel recommended that additional labeling language was needed to capture a population for whom the benefit risk assessment would be more in favor of receiving BiV instead of just RV pacing on the basis of existing knowledge on the potential detrimental effects of RV pacing from the DAVID[2] and MOST[3] trials.

4) Overall Benefit Risk Assessment: The Panel confirmed FDA's assessment of the modest degree of benefit as seen in a reduction in heart failure-related urgent care events in year one. The Panel also mentioned the potential benefit of saving a patient from a future surgery to implant a BiV system should the patient end up developing an indication that is already approved for CRT. That being said, Panelists acknowledged the relatively low number of subjects in BLOCK HF who

went on to become indicated for a CRT as currently approved and that the results of the BLOCK HF study did not provide a means of easily identifying those subjects a priori. The Panel also confirmed FDA's assessment of the risks of the devices including LV lead related complications. The Panel noted that earlier battery replacement (an additional surgery) should be considered as a risk as well.

5) Post Approval Study: The Panel indicated that value would be gained from a post approval study both larger and more specific than that proposed by the sponsor. The question to be addressed by such a study would be to confirm that the treatment effect observed in larger cohorts in the premarket study is also seen in women and minorities (less represented subgroups).

The materials for the meeting and summary for the panel meeting are available at the following link:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM370947.pdf

B. FDA's Post-Panel Action

Based on Panel feedback, FDA worked with Medtronic interactively after the panel meeting to refine the indications for use statement to make the benefit-risk profile of the proposed expansion of indications more favorable. The Panel recommended that only those patients who require a high percentage of RV pacing due to their AV block be eligible to receive BiV pacing instead of RV pacing.

FDA also worked with Medtronic to discuss the need and content of a post approval study. Although Panelists were in favor of a post approval study, after further internal discussion, FDA determined that a post approval study should not be required given the following concerns and challenges regarding the ability of a post approval study to answer the potential post market question raised by the Panel in their deliberations (namely, whether the benefits observed in the premarket study extended to less represented subgroups):

- Regarding the feasibility of completing a post approval study adequately powered to address the questions of treatment effect in less well represented subgroups, the review team noted concern that a post market study would entail the same or more challenges recruiting and completing follow-up as the premarket study. BLOCK HF was a large, well conducted, randomized, and double blinded trial that took 10 years to complete. As typically under represented patient groups, there were a total of 174 women (25.2%), 26 (3.8%) African Americans, and 8 (1.2%) Hispanics randomized. Once approval is granted for the requested expansion in indications, it would most likely be equally (or even more) difficult to enroll less well represented groups in a post market setting compared to the premarket setting, decreasing the practicality of a post approval study. Similarly, the sample sizes needed to thoroughly evaluate the treatment effect in less well represented

groups would be quite large, again decreasing the feasibility of completing such a study.

- Regarding the ability of a post market study to address the questions raised by the Panel of treatment effect in less well represented groups, the review team noted concern that a control arm could no longer be expected for studies done after approval and that analysis of any post approval studies to prior data may not support meaningful comparisons and conclusions. Any post market study would be likely unable to capture the same level of detail for heart failure urgent care events (perhaps only heart failure hospitalizations). In the end, data collected post market would likely be unable to truly answer the post market questions posed by the Panel whether the treatment effect observed in the larger BLOCK HF cohort would be seen in women and minorities.

- The FDA review team reviewed the literature and professional experience among clinicians and found concerns with future women and minority post approval studies given that FDA did not find a biologically plausible reason to expect substantial treatment effect differences between men and women or Caucasians and minorities. This was supported in the limited BLOCK HF subgroup analysis data.

When the above challenges and concerns were all considered, FDA concluded:

- A post approval study is not indicated given the lack of biological plausibility of significant treatment effect differences for subgroups underrepresented in BLOCK HF;

- A post approval study is unlikely to be able to capture critical data to adequately support a characterization of treatment effect differences, if present; and

- A post approval study does not seem possible or practical to complete given the difficulties in recruiting sufficient subjects, especially those in subgroups that were underrepresented in the premarket study.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary objective of the BLOCK HF study examined the effectiveness of BiV pacing over RV pacing at reducing risk of occurrence of death, heart failure-related urgent care, or a ≥15% increase in LVESVI. The study met is its primary objective, demonstrating a 27% relative reduction in the risk of developing one (1) of the three (3) primary endpoint events. However, given the lack of clarity regarding the clinical meaning of an increase in LVESVI, the annualized rates were examined individually for death and heart failure-related urgent care to understand the results when LVESVI is excluded. The absolute benefit seen in clinically meaningful events is a reduction in heart failure-related urgent

care of 7.9%; no consistent reduction in mortality was seen. Time to event analyses were also conducted, which indicated treatment effect still trends towards benefit when LVESVI is removed. These analyses in total suggested a modest benefit from BiV vs. RV pacing predominantly in reduced heart failure events within the first year after implant.

It should be noted that the potential for pharmacological therapy in combination with BiV or RV pacing to impact the occurrence of primary objective events was not thoroughly evaluated since the cardiovascular medication doses prescribed (particularly those for beta blockers) were lower than those recommended by the study protocol and the AHA/ACC Guidelines for Heart Failure.

B. Safety Conclusions

The risks of the Medtronic CRT-P and CRT-D devices are based on data collected in a clinical study to support PMA approval as described above. Safety was examined through documentation of the risks of the additional LV lead required for BiV pacing compared to the system already indicated for required RV pacing. In 51 subjects (6.3%), implantation of an LV lead was not possible. In those subjects in whom an LV lead was implanted and BiV pacing was used, 20 (5.7%) had an LV lead related complication. The definition of a complication in the BLOCK HF study is an adverse event that resulted in death, involved any termination of significant device function, or required invasive intervention. The LV lead complications most commonly did not result in death, but required a second surgery to revise the lead or involved loss of LV lead function. During deliberations, the Panel also indicated that the need for an additional surgery due to more frequent battery usage, and therefore, quicker battery depletion, when BiV pacing is used instead of RV pacing should be considered as a potential risk. The Panel and FDA acknowledged that the infrequent risks associated with LV lead use were different in kind and severity than the infrequent occurrence of heart failure and death attributable to RV pacing instead of BiV pacing.

C. Benefit Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. While the primary endpoint included three (3) event types, FDA considered death and heart failure related urgent care visits most clinically meaningful and, therefore, weighed them more when evaluating the risks and benefits of BiV pacing compared to RV pacing in the BLOCK HF population. Annualized rates were calculated for death and heart failure related urgent care visits to understand the benefit of CRT as shown in the BLOCK HF study. This evaluation indicated little if any benefit with respect to death, but modest benefit with respect to heart failure related urgent care visits. Within the first year, a 7.9% reduction in the occurrence of heart failure related urgent care visits was seen, with 18.0% of RV subjects and 10.1% of BiV subjects receiving urgent care for heart failure. Little to no difference in the number of subjects requiring heart failure related urgent care visits was seen after the first year.

Additional factors to be considered in determining probable risks and benefits for the Medtronic CRT-P and CRT-D devices included the following. At the Panel meeting, the potential to prevent second surgeries needed should an approved indication for CRT arise was discussed. Of the 691 randomized subjects in the BLOCK HF study, 65 (9.4%) were observed to have an already approved indication for CRT at randomization; and for an additional 91 (13.2%) it could be determined that the subject met an approved indication based on available data collected during follow-up. The study did not, however, provide any evidence to prospectively identify the subjects who would develop an approved CRT indication during follow up.

The primary incremental risk of BiV pacing compared to RV pacing alone is the implantation of an LV lead to provide the therapy. In 51 (6.3%) of the 809 subjects in which implants were attempted, an LV lead implant was not possible. Out of the 349 subjects who received BiV pacing (and for whom the LV lead was required to function), 20 subjects (5.7%) experienced an adverse event that resulted in an invasive intervention or the termination of significant device function. As highlighted in Panel discussions, the interventions associated with LV lead complications are typically better tolerated by patients and, while not insignificant, should not be considered equivalent to any benefit of a reduction in heart failure related urgent care visits.

In addition to the risks associated with an LV lead, the potential need for earlier, more frequent pulse generator replacements due to added battery usage in a CRT-P or CRT-D device compared to a traditional RV pacemaker was discussed at the Panel meeting. While more CRT-D subjects assigned to BiV pacing required pulse generator replacements during this study than those assigned to RV pacing, numbers were comparable between the two (2) arms who received a CRT-P.

D. Overall Conclusions

The data in this application provide a reasonable assurance of safety and effectiveness of the Medtronic CRT-P and CRT-D devices when used in accordance with the indications for use.

Medtronic conducted a large, randomized, double blinded study enrolling over 900 subjects in multiple centers in order to evaluate the benefits of BiV pacing over RV pacing in the expanded population of patients. The study met its primary objective and, although the meaning of an LVESVI event is still unclear, the study trends towards benefit even when LVESVI is removed from the analysis.

At the October 8, 2013 advisory meeting, Panel members voted that the benefits (as evidenced by a small reduction in occurrence of heart failure-related urgent care) outweigh the risks (LV lead-related complications as well as potentially more often pulse generator replacements due to more battery requirements) in a population that is restricted to those who require a significant amount of RV pacing. FDA worked with Medtronic to further refine the indications for use statement based on feedback from this Panel.

Based on the above, Medtronic has provided valid scientific data to demonstrate a reasonable assurance of safety and effectiveness for the expansion of indications for Medtronic CRT-P and CRT-D devices to NYHA Functional Class I, II, or III patients who have a LVEF ≤ 50%, are on stable, optimal heart failure medical therapy if indicated and have atrioventricular block (AV block) that are expected to require a high percentage of ventricular pacing that cannot be managed with algorithms to minimize right ventricular pacing.

XIII. CDRH DECISION

CDRH issued an approval order on April 10, 2014.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: None (see discussion in Section XI.B. "FDA's Post Panel Actions")

XV. REFERENCES

1 Hsich, E. and Pina, I. (2009). Heart failure in women: a need for prospective data. *JACC*, 491-498.

2 The David Trial Investigators. (2002). Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator. *JAMA*, 3115-3123.

3 Sweeney, M., et. al. (2002). Effect of pacing mode and cumulative percent time ventricular paced on heart failure in patients with sick sinus syndrome and baseline QRS duration less than 120 millisecond in MOST. *Pacing Clin Electrophysiol*, 690.