

# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

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### I. General Information

Device Generic Name: Cardiac Resynchronization Therapy – Pacemaker (CRT-P) System

Device Trade Name: St. Jude Medical Frontier™ Model 5508L and Frontier™ II Model 5586 Cardiac Resynchronization Therapy Pacemakers (CRT-P) supported on the Model 3510 programmer platforms with the Model 3307, v4.8m programmer software

Applicant's Name and Address: St. Jude Medical Cardiac Rhythm Management Division  
15900 Valley View Court  
Sylmar, CA 91342

Date(s) of Panel Recommendation: None

Premarket Approval Application Number: P030035/S3

Date of Notice of Approval to Applicant: **APR 29 2005**

The Frontier Model 5508L was originally approved on May 13, 2004 under PMA P030035. The Frontier II Model 5586 was approved on August 18, 2004 under PMA P030035/S1. This application has been submitted to expand the indications for use statement for both devices, specifically to include the treatment of patients with symptoms of moderate to severe heart failure (NYHA Class III or IV) despite optimal medical therapy (as defined in the clinical trials section), ejection fraction (EF)  $\leq 35\%$  and a prolonged QRS duration. The pre-clinical test results were presented in the original PMA application and subsequent supplement as mentioned above. The summary of P030035 can also be found on the FDA CDRH Internet Home Page located at <http://www.fda.gov/cdrh/pmapage.html>. The clinical data set used to support the expanded indications statement derives from the marketing application for the Epic HF CRT defibrillation (CRT-D) system, approved under P030054.

### II. Indications for Use

Implantation of the Frontier™ Cardiac Resynchronization Therapy System is indicated for:

- Maintaining synchrony of the left and right ventricles in patients who have undergone an AV nodal ablation for chronic atrial fibrillation and have NYHA Class II or III heart failure.

- The reduction of the symptoms of moderate to severe heart failure (NYHA Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy, and have a left ventricular ejection fraction  $\leq 35\%$  and a prolonged QRS duration.

### III. Contraindications

Implantation of the Frontier™ Cardiac Resynchronization Therapy System is contraindicated in patients who have been implanted with an implantable cardioverter-defibrillator (ICD).

### IV. Warnings and Precautions

Please refer to the specific device labeling for a list of warnings and precautions.

### V. System Description

The Frontier™ pulse generators are multi-site, implantable cardiac devices with biventricular sensing and stimulation capabilities including cardiac resynchronization therapy (CRT-P), intended for use with a St. Jude Medical left heart pacing lead. Additionally, the Frontier™ II pulse generator allows independently programmable left and right ventricular outputs.

The Frontier™ devices are equipped with automatic rate-adjusting algorithms, patient safety features, and diagnostic tools and tests. The Frontier devices contain the Omnisense™ accelerometer activity sensor to provide rate-modulated operation.

In addition, with the Frontier devices, the Model 3510/3500 Programming System offers:

- On-screen Reference Manual
- Floppy disk database interface
- Continuous real-time printing of ECG, EGM, and Markers (only available on the Model 3510 Programmer)
- FastPath™ Summary and Measured Data Screens (only available on the Model 3510 Programmer)

A single setscrew for each lead secures the pin within the connector. The device header accepts unipolar or bipolar IS-1 and VS-1, or 3.2 mm leads.

The Frontier II device is supported on Model 3510 programmer platforms while the Frontier device is supported on Model 3500/3510 programmer platforms. Both devices use Model 3307, v4.8m or higher programmer software.

Please refer to the Physician User's Manual specific to the device being implanted.

### VI. Alternative Practices or Procedures

The present established therapies for the treatment of patients with chronic atrial fibrillation include pharmacological therapy or standard right ventricular pacing therapy post AV nodal ablation. The present established treatment of heart failure patients include pharmacological therapy, heart transplantation, other legally marketed CRT pacemakers (CRT-P) or CRT defibrillators (CRT-D) or other surgical procedures.

## VII. Marketing History

The Frontier™ family of pulse generators is currently distributed commercially in and outside the United States. Specifically, the Frontier™ pulse generator is market approved in the US, European Community, Argentina and China. The Frontier™ II is market approved in the US and the European Community.

The Frontier™ devices have not been withdrawn from the market in any country for any reason related to safety and effectiveness.

## VIII. Adverse Events

The safety data presented in this section includes data from two clinical studies using the Frontier Cardiac Resynchronization Therapy System. One study was the Ventricular Resynchronization Therapy Randomized Trial (VecToR) study and the second was the Post AV Node Ablation Evaluation (PAVE) study.

The PAVE study for the Frontier biventricular pacing system (approved under PMA P030035 on May 13, 2004) supports an indication of “maintaining synchrony of the left and right ventricles in patients who have undergone an AV nodal ablation for chronic atrial fibrillation and have NYHA Class II or III heart failure”. The identical system was used in the Ventricular Resynchronization Therapy Randomized Trial (VecToR) (IDE G000229) to obtain additional labeling for a heart failure indication.

The VecToR clinical study began on October 11, 2000. As of September 7, 2004, there were 144 attempted implants of which 120 were successful from centers in the United States and Canada with average implant duration of 22.7 months (range: 0.1 – 45.3 months).

### Potential Adverse Events

Potential adverse events associated with the use of the transvenous leads and pacing systems include:

- ◆ Body rejection phenomena
- ◆ Cardiac/coronary sinus dissection
- ◆ Cardiac/coronary sinus perforation
- ◆ Cardiac tamponade
- ◆ Coronary sinus or cardiac vein thrombosis
- ◆ Death
- ◆ Device migration and pocket erosion
- ◆ Endocarditis
- ◆ Excessive bleeding
- ◆ Hematoma/seroma
- ◆ Induced atrial or ventricular arrhythmias
- ◆ Infection
- ◆ Local tissue reaction; formation of fibrotic tissue
- ◆ Loss of pacing and/or sensing due to dislodgment or mechanical malfunction of the pacing lead
- ◆ Myocardial irritability

- ◆ Myopotential sensing
- ◆ Pectoral/diaphragmatic/phrenic nerve stimulation
- ◆ Pericardial effusion
- ◆ Pericardial rub
- ◆ Pneumothorax/hemothorax
- ◆ Pulmonary edema
- ◆ Rise in threshold and exit block
- ◆ Thrombolytic or air embolism
- ◆ Valve damage

The following in addition to the above, are potential complications associated with the use of rate modulated pacing systems.

- Inappropriate, rapid pacing rates due to sensor failure or to the detection of signals other than patient activity.
- Loss of activity-response due to sensor failure.

A coronary sinus venogram is unique to lead placement in the cardiac venous system, and carries risks, such as renal failure, cardiac or coronary sinus dissection, and cardiac or coronary sinus perforation.

Potential complications reported with direct subclavian venipuncture include hemothorax, laceration of the subclavian artery, arteriovenous fistula, neural damage, thoracic duct injury, cannulation of other vessels, massive hemorrhage, and rarely death.

## Deaths

Death information was gathered and classified by an independent mortality committee of three practicing physicians according to a published classification scheme. Deaths from the PAVE and the VecToR studies are presented below.

### **PAVE Study**

Fifty-one deaths occurred throughout the study. A summary of the death classification is shown in Table 1 below.

**TABLE 1: ALL DEATHS REPORTED IN THE PAVE STUDY**

<b>Primary Cause</b>	<b>RV (N=106)</b>	<b>BV (N=146)</b>	<b>LV (N=53)</b>	<b>Roll-in (N=56)</b>	<b>Total (N=361)</b>
Cardiac: Arrhythmic	1	1	1	0	3
Cardiac: Other	7	3	3	2	15
Cardiac: Unknown	0	1	0	0	1
Non-Cardiac	4	2	5	4	15
Unknown	6	5	3	2	16
<b>Total</b>	<b>18</b>	<b>12</b>	<b>12</b>	<b>8</b>	<b>50<sup>1</sup></b>
<b>% Death</b>	<b>17.0</b>	<b>8.2</b>	<b>22.6</b>	<b>14.3</b>	<b>13.8</b>

<sup>1</sup>One additional patient was consented, but died prior to any study related procedure.

### VecToR Study

A summary of the death classification through the first 6-months post-implant is shown in Table 2 below.

**TABLE 2: DEATHS AS RANDOMIZED THROUGH SIX MONTHS**

Primary Cause	ON (N=59)	OFF (N=47)	Roll-in (N=38)	Total (N=144)
Non Sudden Cardiac	1	0	2	3
Sudden Cardiac	0	1	0	1
Non Cardiac	0	0	1	1
<b>Total</b>	<b>1</b>	<b>1</b>	<b>3</b>	<b>5</b>
<b>% Death</b>	<b>1.7</b>	<b>2.1</b>	<b>7.9</b>	<b>3.5</b>

Table 3 lists the additional 20 total deaths reported that occurred after 6 months post-implant. Since all patients received the identical system and cross-over was allowed after six months, data was not stratified by treatment assignment.

**TABLE 3: ALL DEATHS BEYOND 6 MONTHS POST-IMPLANT**

Primary Cause	Total (N=144)
Non Sudden Cardiac	8 <sup>*</sup>
Sudden Cardiac	3
Non Cardiac	4
Unknown	2
Unknown Presumed Sudden	2
Unknown-Sudden	1
<b>Total</b>	<b>20</b>
<b>% of Patients</b>	<b>13.8%</b>

\* One death was felt to be related to the procedure by the independent external mortality committee, but not attributed to any components of the investigational system.

### Observed Adverse Events

The PAVE and VecToR studies' cumulative implant duration for all enrolled patients (N=505) was 7,948 months with a mean of 15.7 ± 12.2 months (range of 0.1 to 45.3 months). The PAVE and VecToR studies' cumulative implant duration for all enrolled patients (N=505) was 7,948 months with a mean of 15.7 ± 12.2 months (range of 0.1 to 45.3 months). The cumulative duration for patients in the investigational group (n=399) including patients from the left ventricular (LV), biventricular (BV) and roll-in arm of the study (patients receiving the investigational therapy without randomization); i.e. all patients from PAVE and VecToR except the right ventricular (RV) group in the PAVE study was 6,393 months (532.8 years).

During the entire study period for both studies, 230 adverse events were reported for the investigational group (n=399) including 80 complications and 150 observations. Tables 4 and 5 summarize the complications and Table 6 summarizes the observations that occurred during the studies. System-related complications and observations are based on patients with the investigational system only (Note that one patient in the PAVE study died prior to receiving the investigational system: PAVE, N = 254; VecToR, N = 144; Total, N = 398). Procedure-related complications are based on total number of attempted implants (PAVE, N = 255; VecToR, N = 144; Total, N = 399).

An Adverse Event is defined as an unfavorable clinical event, which impacts, or has the potential to impact, the health or safety of a clinical study participant caused by, or associated with, a study device or intervention. An adverse event is classified as a Complication when it results in an injury or an invasive intervention (for example, lead repositioning after lead dislodgement) that would not have occurred in the absence of the implanted device and/or system components. An Observation is defined as an adverse event that is not associated with injury to the patient or an invasive intervention, but which is associated with the system under investigation, or the programming thereof.

**TABLE 4: System-Related Complications for BV Group<sup>2,3,4</sup>**

Events	# of Events	# of Patients	% of Patients	Events/Device Months <sup>5</sup>
<b>LV Lead Related:</b>	<b>36</b>	<b>34</b>	<b>8.5</b>	<b>0.0056</b>
Acute LV Lead Dislodgement	11	11	2.8	0.0017
High Implant Thresholds (LV Lead)	8	8	2	0.0013
Diaphragmatic Stimulation	7	7	1.8	0.0011
LV Lead Loss of Capture	5	5	1.3	0.0008
High Pacing Thresholds (LV Lead)	2	2	0.5	0.0003
Chronic LV Lead Dislodgement	1	1	0.3	0.0002
LV Lead Fracture	1	1	0.3	0.0002
Pectoral Stimulation	1	1	0.3	0.0002
<b>RA/RV Lead Related:</b>	<b>8</b>	<b>7</b>	<b>1.8</b>	<b>0.0013</b>
Acute RA/RV Lead Dislodgement	4	3	0.8	0.0006
Chronic RA Lead Dislodgement	1	1	0.3	0.0002
RV Perforation	1	1	0.3	0.0002
RV Insulation Failure	1	1	0.3	0.0002
Lead Fracture (RA Lead)	1	1	0.3	0.0002
<b>System – Other:</b>	<b>4</b>	<b>4</b>	<b>1</b>	<b>0.0006</b>
Inadequate Lead Connection	2	2	0.5	0.0003
Ventricular Tachycardia	1	1	0.3	0.0002
Erosion (Pocket Erosion)	1	1	0.3	0.0002
<b>Total System-Related</b>	<b>48</b>	<b>41</b>	<b>10.3</b>	<b>0.0075</b>

<sup>2</sup> Each patient may have more than one complication in more than one category.

<sup>3</sup> System-related complications based on total number of attempted implants (N = 398).

<sup>4</sup> The BV Group consists of all patients from the PAVE and VecToR studies except the RV group from the PAVE study.

<sup>5</sup> Events per Device-Month calculated as number of events divided by the total device cumulative duration in months in BV, LV and Roll-in groups for PAVE and the ON, OFF and Roll-in groups for VecToR. The cumulative duration in months in these groups was 6,393 months.

**TABLE 5: Procedure-Related Complications for BV Group<sup>6, 7, 8</sup>**

<b>Events</b>	<b># of Events</b>	<b># of Patients</b>	<b>% of Patients</b>	<b>Events/Device Months<sup>9</sup></b>
<b>Procedure Related:</b>	<b>32</b>	<b>30</b>	<b>7.5</b>	<b>0.005</b>
Coronary Sinus Dissection During Implant	13	13	3.3	0.002
Pneumothorax	4	4	1	0.0006
CS Perforation at Implant	3	3	0.8	0.0005
Pericardial Effusion	2	2	0.5	0.0003
Ventricular Tachycardia at Implant	2	2	0.5	0.0003
Tamponade	2	2	0.5	0.0003
Complete Heart Block at Implant	1	1	0.3	0.0002
Cardiopulmonary Arrest at Implant	1	1	0.3	0.0002
Non-Sudden Cardiac Death	1	1	0.3	0.0002
Pulmonary Edema Post Ablation	1	1	0.3	0.0002
LV Lead Dislodgment During Ablation	1	1	0.3	0.0002
Hemothorax	1	1	0.3	0.0002
<b>Total System-Related and Procedure-Related Complications</b>	<b>80</b>	<b>70</b>	<b>17.5</b>	<b>0.0125</b>

<sup>6</sup> Each patient may have more than one complication in more than one category.

<sup>7</sup> Procedure-related complications based on total number of attempted implants (N = 399).

<sup>8</sup> The BV Group consists of all patients from the PAVE and VecToR studies except the RV group from the PAVE study.

<sup>9</sup> Events per Device-Month calculated as number of events divided by the total device cumulative duration in months in BV, LV and Roll-in groups for PAVE and the ON, OFF and Roll-in groups fro VecToR. The cumulative duration in months in these groups was 6,393 months.

**TABLE 6: Observations for BV group<sup>10, 11, 12</sup>**

Events	# of Events	# of Patients	% of Patients	Events/Device Months <sup>13</sup>
Diaphragmatic Stimulation	35	29	7.3	0.0055
Pectoral Stimulation	19	17	4.3	0.003
High Pacing Threshold (LV Lead)	18	18	4.5	0.0028
High Implant Thresholds (LV Lead)	10	10	2.5	0.0016
Loss of Capture (LV Lead)	9	9	2.3	0.0014
Hematoma at Implant	8	8	2	0.0013
CS Dissection	6	6	1.5	0.0009
Fatigue	6	6	1.5	0.0009
Infection	6	6	1.5	0.0009
Heart Failure- Worsening	3	3	0.8	0.0005
Telemetry Error	3	2	0.5	0.0005
Oversensing	3	3	0.8	0.0005
Discomfort- Device Site	2	2	0.5	0.0003
Thrombosis	2	2	0.5	0.0003
VVI Back-Up	2	2	0.5	0.0003
Stuck Stylet	2	2	0.5	0.0003
Undersensing (RA Lead)	1	1	0.3	0.0002
Loss of Capture- Intermittent (LV Lead)	1	1	0.3	0.0002
Hypotension	1	1	0.3	0.0002
Palpitation	1	1	0.3	0.0002
Arrhythmia- Torsades	1	1	0.3	0.0002
Noise on IEGM	1	1	0.3	0.0002
Dyspnea on Exertion	1	1	0.3	0.0002
RV Back-up Pacing Due to PVCs	1	1	0.3	0.0002
Acute LV Lead Dislodgment (minor)	1	1	0.3	0.0002
RV Loss of Capture	1	1	0.3	0.0002
LV Lead Undersensing	1	1	0.3	0.0002
Medication Reaction	1	1	0.3	0.0002
Pneumothorax	1	1	0.3	0.0002
CS Perforation	1	1	0.3	0.0002
Pre-Syncope	1	1	0.3	0.0002
Syncope	1	1	0.3	0.0002
<b>Total Events</b>	<b>150</b>	<b>112</b>	<b>28.1</b>	<b>0.0235</b>

<sup>10</sup> Each patient may have more than one observation in more than one category.

<sup>11</sup> Observations based on total number of attempted implants (N = 398).

<sup>12</sup> The BV Group consists of all patients from the PAVE and VecToR studies except the RV group from the PAVE study.

<sup>13</sup> Events per Device-Month calculated as number of events divided by the total device cumulative duration in months in BV, LV and Roll-in groups for PAVE and the ON, OFF and Roll-in groups fro VecToR. The cumulative duration in months in these groups was 6,393 months.

## IX. Summary of Pre-Clinical Studies

The St. Jude Medical biventricular pacing system used in the VecToR study is legally marketed. This includes the Frontier Models 5508/5508L and the Aescula LV lead Model 1055K (approved under PMA P030035 on May 13, 2004). In addition, Frontier™ II Model 5586 (approved under PMA P030035/S1 on August 16, 2004), which is legally marketed, is also the subject of this PMA supplement. All pacing systems were previously tested via nonclinical laboratory testing including bench testing, biocompatibility evaluation, electromagnetic compatibility, sterilization, packaging, shelf life testing and animal study. Device design and system compatibility involved verification and validation of each system. The test results were previously found acceptable.

## X. Summary of Clinical Investigations

Three clinical data sets contribute to this marketing application: The VecToR study, the PAVE study and the RHYTHM study. Two of the studies, VecToR and PAVE, were conducted on the Frontier CRT-P system, which is the subject of this marketing application. The third, RHYTHM, was conducted on a device that delivers the same biventricular pacing therapy but from a device that also offers defibrillation (CRT-D).

The VecToR CRT-P study was designed to pursue approval for cardiac resynchronization therapy for a Heart Failure (HF) patient population not requiring back up defibrillation, but did not enroll sufficient numbers of randomized patients to meet its effectiveness objectives. Although the VecToR (CRT-P) study and the RHYTHM (CRT-D) study used different pulse generators (Frontier and Epic HF, respectively), both used the same biventricular pacing function which is delivered through the legally marketed SJM Aescula lead to provide cardiac resynchronization therapy.

### ***VecToR Study***

The VecToR study was a prospective, double-blind, randomized, controlled, multi-center clinical trial of patients with New York Heart Association Class III/IV congestive heart failure, and was conducted at 41 participating sites (39 in the US, 2 in Canada). The study compared the safety and effectiveness of cardiac resynchronization pacing therapy (CRT-P), using the Frontier Model 5508 pulse generator and the Aescula 1055K Left Heart Lead to no CRT-P therapy.

Study Inclusion and Exclusion criteria are listed below:

#### ***Inclusion Criteria***

1. Symptomatic ischemic or nonischemic dilated cardiomyopathy, which is not due to reversible causes.
2. Left ventricular end-diastolic diameter >54mm as measured by echocardiography.
3. Left ventricular ejection fraction ≤ 35% as measured by echocardiography.
4. QRS duration of ≥ 140 ms.
5. Stable but advanced heart failure due to left ventricular dysfunction (diagnosed for at least 6 months) despite stable conventional medical therapy.
6. Completed the 6-minute walk test as outlined in the protocol with the only limiting factor(s) being fatigue and/or shortness of breath.

7. Adequate cardiographic acoustic windows.
8. Provided informed consent for study participation and, are willing and able to comply with the prescribed follow-up tests and schedule of evaluations.

### **Exclusion Criteria**

1. Can walk >450 meters during the 6-minute walk test.
2. Have standard bradycardia indications or likely to need pacing within the next 6-months.
3. Are classified as NYHA Class I or II.
4. Have a history of persistent or chronic atrial fibrillation or a history of atrial fibrillation which required intervention to revert to normal sinus rhythm.
5. Have an implanted cardioverter defibrillator (ICD) or, are being considered for implantation of an ICD.
6. Are contraindicated for an emergency thoracotomy.
7. Are considered status 1 for cardiac transplantation and are likely to receive transplantation within 1 year
8. Are being treated with parenteral inotropic agents (e.g., dobutamine) or have been treated with such agents within the past 30 days.
9. Have prosthetic valve replacement(s).
10. Have severe musculoskeletal disorder(s).
11. Are under the age of 18 years.
12. Are pregnant or plan a pregnancy in the next 6 months.
13. Are currently participating or participated within the past 30 days in any clinical investigation.
14. Have a life expectancy of less than 6 months.
15. Cannot independently comprehend and complete the Minnesota Living With Heart Failure questionnaire.
16. Are allergic to dexamethasone sodium phosphate (DSP).

Patients who met the inclusion/exclusion requirements were randomized 2:1 to CRT ON or CRT OFF. All patients were then implanted with the CRT-P system and followed with the endpoint data collection completed at the 6-month visit. Crossover in CRT treatment was then allowed at physician discretion.

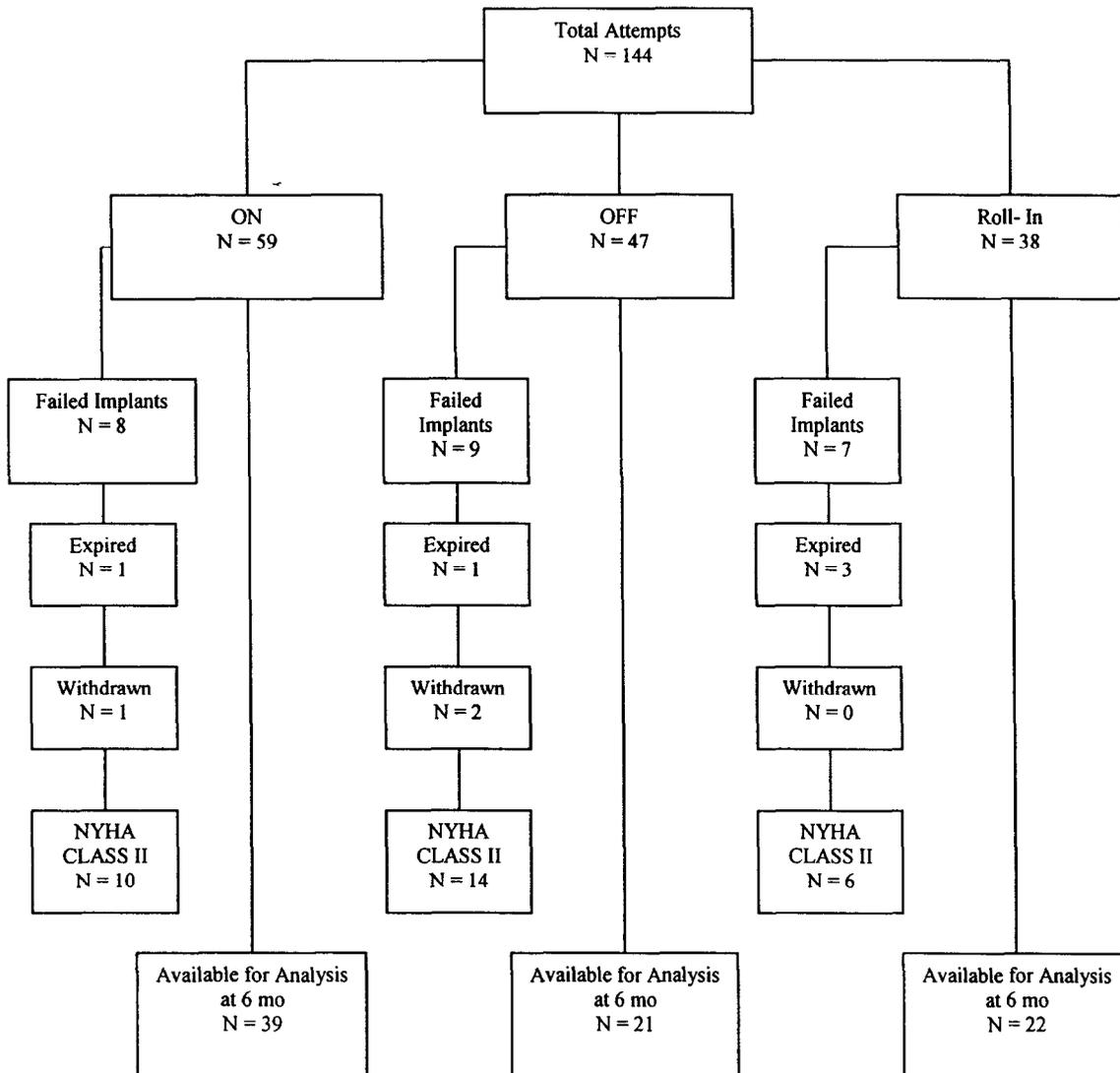
As of September 7, 2004, the total time of follow-up from the time of successful implant in 120 patients was 2383 patient months. The average time of follow-up was  $19.9 \pm 8.9$  (range 0.8 to 35.4) patient months.

### **Patient Population**

The overall VecToR study population included 144 patients. Fifty-nine (59) patients were randomized to ON, and 47 patients were randomized to OFF. Revision C of the VecToR protocol excluded NYHA Class II patients. Thirty-eight (38) were “roll-in” patients (non-randomized) and received the cardiac resynchronization pacing therapy system (Frontier pulse generator and Aescula lead system). Safety analyses include all patients with the Frontier pulse generator and the Aescula left heart lead, including ON, OFF, and roll-in. The mean age was  $67.1 \pm 9.7$  years and there were 62.5% male and 37.5% female. Twenty-nine

percent (29%) of the patients were NYHA Class II, 65% were NYHA Class III, and 6% were NYHA Class IV prior to implant. Figure 1 outlines the patients analyzable at 6 months.

**FIGURE 1: VecToR PATIENT ACCOUNTABILITY**



## Primary Safety Objectives and Results

The primary safety objectives for the VecToR study are presented below.

### 1. FREEDOM FROM SYSTEM-RELATED COMPLICATIONS THROUGH SIX MONTHS

*Objective:* The lower bound of the one-sided 95% confidence interval of the freedom from system-related complications will not be less than 70%. A system-related complication was defined as a complication that is caused by a failed pacing system. A pacing system refers to all implanted components, including the pulse generator, leads, and the interaction of these components.

*Results:* There were 12 system-related complications in 11 patients within six-months follow-up. The freedom from system-related complications is 90.7% with a lower bound of 86.4%. Objective met.

### 2. FREEDOM FROM PULSE GENERATOR-RELATED COMPLICATIONS THROUGH SIX MONTHS

*Objective:* The lower bound of the one-sided 95% confidence interval of the freedom from pulse generator-related complications for the combined group through six months will not be less than 90%.

*Results:* There were no pulse generator-related complications through six months. The survival rate is 100% with a lower bound of 97.1%. Objective met.

### 3. FREEDOM FROM AESCULA™ LEAD-RELATED COMPLICATIONS THROUGH SIX MONTHS

*Objective:* The lower bound of the one-sided 95% confidence interval of the freedom from Aescula™ lead-related complication through six months will not be less than 75%.

*Results:* There were 8 Aescula lead-related complications in 8 patients through six-months follow-up. All patients from the VecToR study who were successfully implanted are included in this analysis. The freedom from Aescula lead-related complications is 93.3% with a lower bound of 89.5%. Objective met.

### 4. RATE OF SUCCESSFUL IMPLANTATION OF THE AESCULA™ LEAD

*Objective:* The lower bound of the one-sided 95% confidence interval of the successful implantation rate of the Aescula lead will not be less than 80%. The success rate was defined as the proportion of patients who received the complete pacing system.

*Results:* A total of 144 patients who were roll-in or randomized to CRT ON or OFF in the VecToR study and underwent attempted BV implants. One hundred and twenty (120) were successfully implanted. The rate of successful implant of the Aescula lead is 84% with a lower bound of 78% which does not meet the protocol defined objective for this endpoint (lower 95% confidence bound of 80%).

## 5. AESCULA™ LEAD PACING THRESHOLD AT SIX MONTHS

*Objective:* The upper bound of the one-sided 95% confidence interval of mean capture threshold will not be greater than 3.0 V for the combined group at six months.

*Results:* The electrical performance data of the LV lead were available on a total of 110 patients at six months. The pacing threshold at six months for the LV lead is 2.10 V with an upper bound 95% confidence interval of 2.34 V. Objective met.

### ***RHYTHM Study***

The RHYTHM ICD Study demonstrated that the SJM CRT-D system (Epic HF and Aescula lead) was safe and effective in NYHA Class III and IV heart failure patients with prolonged QRS duration and served as the basis for approval for PMA # P030054. The RHYTHM ICD study enrolled patients who also had a current ICD indication, which at the time the study was initiated included patients who were indicated for an ICD solely for primary prevention or prophylaxis (i.e., the patients were at risk of ventricular tachyarrhythmias and sudden death due to other clinical characteristics, but had not experienced a spontaneous or induced tachycardia).

The RHYTHM ICD study was a prospective, multicenter, randomized, double-blind, controlled clinical investigation designed to assess the safety and effectiveness of the Epic HF ICD system in patients who were indicated for implantable cardioverter defibrillation therapy with New York Heart Association Classification of III or IV and a prolonged QRS duration. The objective of this clinical study was to verify the safety and effectiveness of the Epic HF ICD (Model V-338) system in an ICD indicated patient population with advanced heart failure (NYHA Classification III or IV) and prolonged QRS duration.

Study Inclusion and Exclusion criteria are listed below:

#### ***Inclusion Criteria***

1. Approved indication for implantation of an ICD for treatment of a life-threatening ventricular tachyarrhythmia(s).
2. Symptomatic, advanced heart failure (ischemic or non-ischemic) not due to reversible causes, diagnosed for at least 6-months.
3. New York Heart Association (NYHA) Classification of III or IV, despite receiving a minimum of 90 days of appropriate pharmacological therapy.
4. Receive optimal pharmacological therapy for CHF (including angiotensin converting enzyme inhibitor and beta blocker, as tolerated) which has been stable during the 30 days prior to enrollment.
5. Left ventricular ejection fraction (LVEF)  $\leq$  35%.
6. Ventricular conduction delay manifested as a QRS duration  $\geq$ 150 msec.
7. Ability to complete cardiopulmonary exercise stress testing and 6-Minute hall walk test, with the only limiting factor(s) being fatigue and/or shortness of breath.
8. Ability to independently comprehend and complete a quality of life questionnaire (Minnesota Living with Heart Failure).
9. Ability to provide informed consent for study participation and be willing and able to comply with the prescribed follow-up tests and schedule of evaluations.

### **Exclusion Criteria**

1. Standard bradycardic indication for pacing.
2. History of chronic atrial fibrillation (continuous AF lasting > 1 Month) within 1 year prior to enrollment or have undergone cardioversion for AF in the past month.
3. Ability to walk > 450 meters during the 6-Minute walk test.
4. NYHA Classification of I or II.
5. Contraindication for an emergency thoracotomy.
6. Classification of Status 1 for cardiac transplantation or consideration for transplantation over the next 6-months.
7. Recent myocardial infarction, unstable angina or cardiac revascularization (PTCA or CABG) within 1 month of enrollment.
8. Recent CVA or TIA - within 3 months of enrollment.
9. Severe musculoskeletal disorder(s).
10. Pregnant or a planning for pregnancy in next 6-months.
11. Currently participating in, or has participated in any clinical investigation within the last 30 days. (the only exception being that of a registry trial)
12. Life expectancy of less than 6-months.
13. Less than 18 years of age.

All patients who met enrollment criteria underwent implantation of the Epic HF ICD system and a St. Jude Medical left ventricular pacing lead. ICD therapy was activated at the time of implant for all patients. Patients underwent Baseline evaluation between two weeks and 30 days following successful device implantation. Baseline was considered time zero for the purposes of evaluation of resynchronization study endpoints.

Patients were randomized following completion of Baseline testing and were assigned to either the treatment group (CRT ON) or the control group (CRT OFF) at a 2:1 ratio. Patients who underwent unsuccessful implantation of the Epic HF ICD system were followed for a period of 30 days prior to withdrawal from the study. All patients who were successfully implanted were followed at 1, 3, 6 and every 3 months thereafter until the study was completed. Cross-over from the control group was allowed after completing the 6-month visit.

As of March 17, 2004, the total time of follow-up from the time of successful implant was 2205 patient months. The average time of follow-up was  $12.1 \pm 3.4$  (range 0.3 to 20.3) patient months.

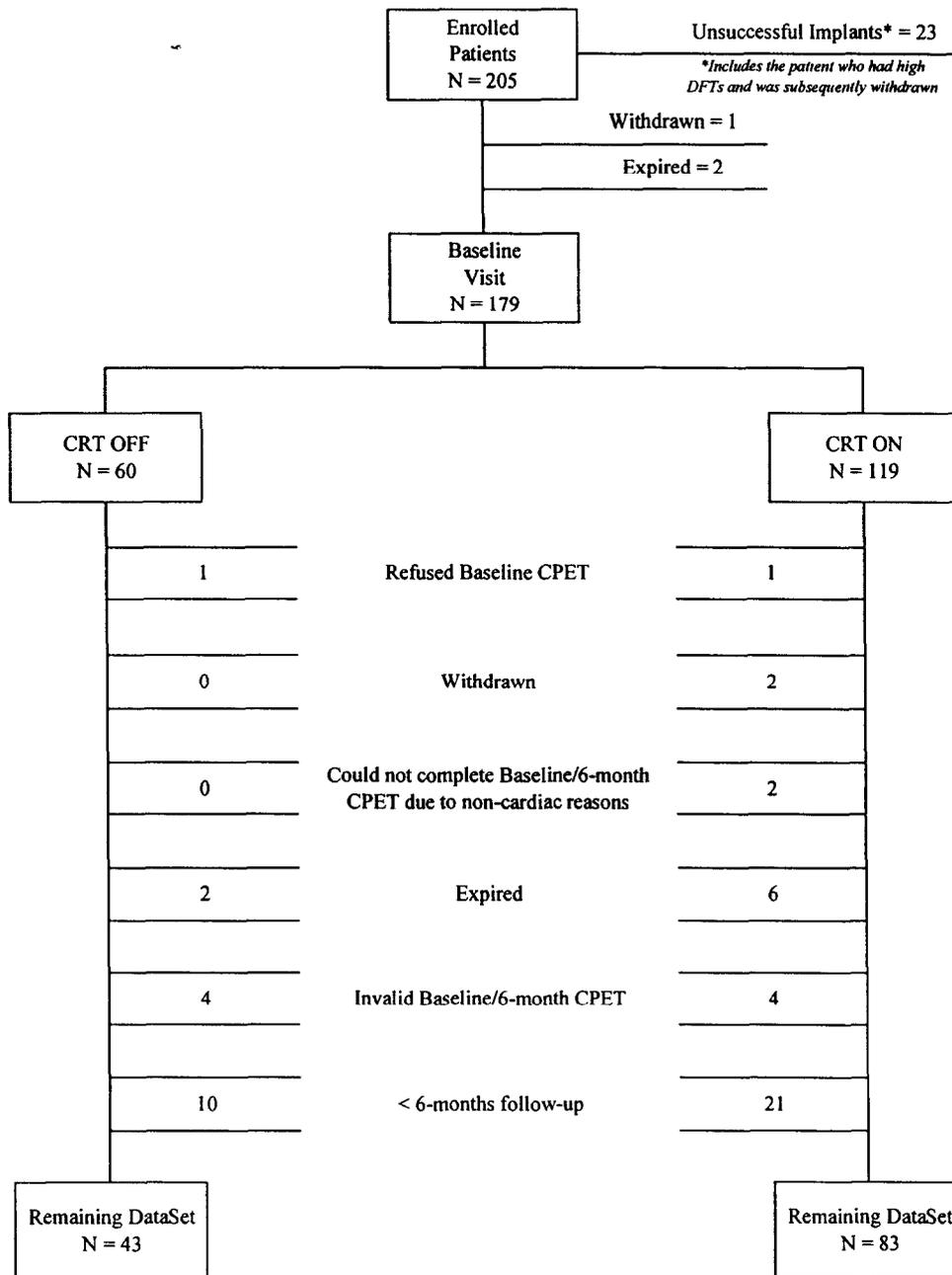
### **Patient Population**

Of the 205 patients enrolled in the RHYTHM ICD study, one hundred and eighty-three (183) lead implant attempts were successful (180 successful on the first attempt and 3 successful on the second attempt). One additional patient had a successful left ventricular lead implant, but had high defibrillation thresholds. This patient was withdrawn from the study and received a heart transplant, leaving a total of 182 successful system implants.

Patients who were successfully implanted with the Epic HF ICD system had a Baseline visit approximately two weeks after implant, during which the following tests/assessments were performed: Electrical measurements on RA, RV and LV leads, cardiopulmonary exercise (CPET) test, echocardiogram, NYHA class assessment, 6 minute walk test, and Minnesota Living with Heart Failure questionnaire. Of the 182 patients with successful implants, two

patients expired and one patient withdrew from the study before the Baseline visit and therefore, 179 patients had a Baseline visit. One additional patient who had a Baseline follow-up visit refused randomization and all the Baseline evaluations except device interrogation and electrical measurements, but remained in the study. Therefore, a total of 178 patients completed the requirements of the Baseline visit. Figure 2 outlines the patient population for the effectiveness analysis.

**FIGURE 2: ANALYZABLE PATIENT GROUP FOR PRIMARY RESYNCHRONIZATION EFFECTIVENESS ANALYSIS**



## Primary Effectiveness Objective and Results

### *RHYTHM Study*

#### CARDIAC RESYNCHRONIZATION THERAPY EFFECTIVENESS (PEAK VO<sub>2</sub>)

*Objective:* To determine if the treatment group (CRT ON) shows a statistically significant improvement over the control group (CRT OFF) at six months.

*Results:* In the intention-to-treat analysis, patients who crossed over from the CRT OFF group to the CRT ON group during the study were analyzed according to the original treatment group they belonged to. Table 7 contains a summary of the improvement in peak VO<sub>2</sub> values in the two treatment groups for this analysis. The average improvement in the CRT ON group over the CRT OFF group was approximately 1.9 ml/kg/min. The p-value was 0.001. Objective met.

**TABLE 7: IMPROVEMENT IN PEAK VO<sub>2</sub> VALUES (ML/KG/MIN)  
INTENTION-TO-TREAT ANALYSIS (N = 126)**

	<b>CRT OFF Mean ± SD (N = 43)</b>	<b>CRT ON Mean ± SD (N = 83)</b>
<b>Baseline</b>	12.8 ± 3.7	11.2 ± 3.0
<b>6-months</b>	11.4 ± 5.6	11.7 ± 3.2
<b>Change</b>	-1.41 ± 4.6	0.52 ± 2.5
Overall improvement in CRT ON vs. CRT OFF = 1.9 ml/Kg/min		

## SECONDARY OBJECTIVES AND RESULTS

### *RHYTHM Study*

#### 1. IMPROVEMENT IN NYHA CLASS AT 6-MONTHS OVER BASELINE

*Objective:* To determine if the treatment group (CRT ON) shows an improvement over the control group (CRT OFF) at six months.

*Results:* Table 8 shows the average change in NYHA Class from Baseline to 6-months for each group. Objective met.

**TABLE 8: BASELINE AND 6-MONTH NYHA CLASS (N = 126)**

	<b>CRT OFF Mean ± SD (N = 43)</b>	<b>CRT ON Mean ± SD (N = 83)</b>
<b>Baseline</b>	2.86 ± 0.52	3.01 ± 0.33
<b>6-months</b>	2.58 ± 0.73	2.53 ± 0.69
<b>Change</b>	-0.28 ± 0.63	-0.48 ± 0.65

**2. IMPROVEMENT IN QUALITY OF LIFE AT 6-MONTHS OVER BASELINE**

*Objective:* To determine if the treatment group (CRT ON) shows an improvement over the control group (CRT OFF) at six months.

*Results:* Patient quality of life (QOL) was assessed with the Minnesota Living with Heart Failure questionnaire. A lower score indicates an improvement in quality of life. Table 9 contains a summary of the improvement in Quality of Life in the two groups from baseline to 6 months.

**TABLE 9: IMPROVEMENT IN QUALITY OF LIFE SCORE (N = 126)**

	<b>CRT OFF Mean ± SD (N = 43)</b>	<b>CRT ON Mean ± SD (N = 83)</b>
<b>Baseline</b>	42.0 ± 23	48.3 ± 24
<b>6-months</b>	45.4 ± 31	40.4 ± 22
<b>Change</b>	3.4 ± 31	-7.8 ± 22

The average improvement in the CRT ON group over the CRT OFF group was approximately 11 points. Objective met.

**3. IMPROVEMENT IN SIX-MINUTE HALL WALK AT 6-MONTHS OVER BASELINE**

*Objective:* To determine if the treatment group (CRT ON) shows an improvement over the control group (CRT OFF) at six months.

*Results:* Table 10 contains a summary of the improvement in 6-minute walk distance between baseline and 6 months.

**TABLE 10: IMPROVEMENT IN 6-MINUTE WALK DISTANCE (METERS)  
(N = 126)**

	<b>CRT OFF Mean ± SD (N = 43)</b>	<b>CRT ON Mean ± SD (N = 83)</b>
<b>Baseline</b>	298 ± 94	284 ± 105
<b>6-months</b>	283 ± 150	297 ± 122
<b>Change</b>	-15 ± 142	13 ± 74

The average improvement in the CRT ON group over the CRT OFF group was approximately 28 meters.

### Additional Data

#### 1. BIVENTRICULAR PACING AT 6-MONTHS

The average percentage of biventricular pacing at the 6-month visit in the 83 patients who were in the CRT ON group among the 126 patients in the primary resynchronization cohort was 95% ± 6%, with a range of 70% to 100%.

#### 2. ECHO DATA

Echocardiographic analysis was performed at the baseline and 6-month follow-up visits. The following parameters were evaluated from the echocardiographic analysis: LVEDD, LVESD, LVEDV, LVEF, MR, E/A Wave Point Ratio, and Sphericity Index. Cardiac dyssynchrony (including Pre-Ejection Delay Time and Intraventricular Mechanical Delay) was also evaluated at baseline and 6-Months. Table 11 displays summaries of the improvement in these parameters between baseline and 6-months.

**TABLE 11: IMPROVEMENT IN ECHOCARDIOGRAPHY PARAMETERS**

<b>Parameter</b>	<b>CRT OFF (N = 40) Mean ± SD</b>	<b>CRT ON (N = 82) Mean ± SD</b>
<b>LVEDD (mm)</b>	-2.4 ± 6.5	-4.3 ± 5.4
<b>LVESD (mm)</b>	-3.0 ± 6.4	-4.6 ± 7.0
<b>LVEDV (ml)</b>	-37 ± 53	-43 ± 69
<b>LVESV (ml)</b>	-36 ± 47	-43 ± 58
<b>LVEF (%)</b>	2.9 ± 6.2	4.3 ± 9.9
<b>MR (grade)</b>	0.10 ± 0.50	-0.06 ± 0.74
<b>E/A Wave Point Ratio</b>	-0.02 ± 1.2	-0.08 ± 0.8
<b>Sphericity Index</b>	0.02 ± 0.1	-0.02 ± 0.1
<b>Pre-Ejection time (ms)</b>	7.3 ± 33	-1.5 ± 52
<b>IVMD (ms)</b>	-6.4 ± 48	-14.5 ± 52
<b>Tei Index</b>	-0.05 ± 0.5	-0.4 ± 0.8
<b>Contraction Interval (ms)</b>	-55 ± 103	-94 ± 124

## **XI. Conclusions Drawn from the Clinical Study**

The results of the VecToR, PAVE and RHYTHM Studies provide reasonable assurance of safety and effectiveness of the legally marketed St. Jude Medical Frontier™ Model 5508L or Frontier™ II Model 5586 CRT-P system to treat patients with symptomatic heart failure when used as indicated in accordance with the directions for use.

## **XII. Panel Recommendation**

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

## **XIII. CDRH Decision**

The VecToR Study and the PAVE Study, which both used the Frontier Biventricular Cardiac Pacing System, demonstrate the safety of the system in a heart failure patient population, as the primary safety endpoints were successfully met at the pre-specified sample sizes. However, the VecToR study did not enroll sufficient numbers of randomized patients to meet its effectiveness objectives.

The RHYTHM ICD Study (P030054) demonstrated that the Epic HF and Aescula lead was safe and effective in reducing the symptoms of moderate to severe heart failure (NYHA Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy, and have a left ventricular ejection fraction  $\leq 35\%$  and a prolonged QRS duration and having a primary indication for an ICD. With the exception of the ICD indication, these are the same criteria used for the VecToR study.

The VecToR (CRT-P) study and the RHYTHM (CRT-D) study utilized different pulse generators (Frontier and Epic HF, respectively), however, both pulse generators use the same biventricular pacing function which is delivered through the legally marketed SJM Aescula lead to provide cardiac resynchronization therapy. This statement also applies to the Frontier II pulse generator and, although it was not used in the clinical trials, the data presented is considered applicable to it.

Data from the VecToR, PAVE and RHYTHM ICD studies together provide a reasonable assurance of the safety and effectiveness of the SJM CRT-P system (Frontier and Aescula lead) in the specified heart failure population. In addition, the same device system is currently legally marketed to provide biventricular pacing in post-AV node ablation patients. Therefore, these data provide reasonable assurance of safety and effectiveness of the St. Jude Medical Frontier Model 5508L or Frontier II Model 5586 CRT-P system to treat patients with symptomatic heart failure.

Based on the above FDA issued an approval order for P030035/S3 on APR 29 2005

## **XIV. Approval Specifications**

<b>Directions for Use:</b>	See labeling
<b>Hazards to Health from Use of the Device:</b>	See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.
<b>Post-approval Requirements, Restrictions:</b>	See approval order.