Summary of Safety and Effectiveness

P880086/S83 and P830045/S76

St. Jude Medical, CRMD

Integrity AFx DR Model 5346
Dual Chamber Pulse Generator

Summary of Safety and Effectiveness for a Supplemental PMA Application

I. General Information

Device Generic Name:	Implantable Dual Chamber Pulse Generator
Device Trade Name:	Integrity™ AFx DR Model 5346 Dual Chamber Pulse Generator and Model 3510/350 programmer with software Model 3307
Applicant's name and Address:	St. Jude Medical Cardiac Rhythm Management Division 15900 Valley View Court Sylmar, CA 91342
PMA Number:	P880086/S83 and P830045/S76
Date of Notice of Approval:	

II. Indications and Usage

Implantation of the Integrity pulse generator is indicated in the following permanent conditions, when associated with symptoms including, but not limited to:

- syncope
- presyncope
- fatigue
- disorientation
- or any combination of those symptoms.

- Rate-Modulated Pacing is indicated for patients with chronotropic incompetence, and for those who would benefit from increased stimulation rates concurrent with physical activity.

- Dual-Chamber pacing is indicated for those patients exhibiting:

  - sick sinus syndrome
  - Chronic, symptomatic second- and third degree AV block
  - recurrent Adams-Stokes syndrome
  - symptomatic bilateral bundle branch block when tachyarrhythmia and other causes have been ruled out.

- Atrial pacing is indicated for patients with sinus node dysfunction and normal AV and intraventricular conduction systems.

- Ventricular pacing is indicated for patients with significant bradycardia and:

  - normal sinus rhythm with only rare episodes of A-V block or sinus arrest
  - chronic atrial fibrillation
  - severe physical disability.

- Dynamic Atrial Overdrive is indicated for suppression of atrial tachyarrhythmias including paroxysmal or persistent atrial fibrillation episodes in patients with one or more of the above pacing indications.

III. Contraindications

Implanted cardioverter-defibrillator (ICD). Because Integrity pulse generators will be automatically programmed to a unipolar pulse configuration if the device initiates Backup VVI pacing, the Integrity is contraindicated in patients with an implanted cardioverter defibrillator (ICD).

Rate-Modulated Pacing may be inappropriate for patients who experience angina or other symptoms of myocardial dysfunction at higher sensor-driven rates. An appropriate *Maximum Sensor Rate* should be selected based on assessment of the highest stimulation rate tolerated by the patients.

Dynamic Atrial Overdrive stimulation is not recommended in patients who cannot tolerate high atrial-rate stimulation.

Dual-Chamber Pacing, though not contraindicated for patients with chronic atrial flutter, chronic atrial fibrillation, or silent atria, may provide no benefit beyond that of single-chamber pacing in such patients.

Single-Chamber Ventricular Demand Pacing is relatively contraindicated in patients who have demonstrated pacemaker syndrome, have retrograde VA conduction, or suffer a drop in arterial blood pressure with the onset of ventricular pacing.

Single-Chamber Atrial Pacing is relatively contraindicated in patients who have demonstrated compromise of AV conduction.

IV. Warnings and Precautions

See Professional labeling.

V. Device Description

The Integrity AFx DR Model 5346 dual chamber pulse generator is an implantable, multi-programmable, mode-switching pacing device. These devices are equipped with a number of automatic, rate-adjusting algorithms, patient safety features and other diagnostic tools and tests, including:

- AutoCapture Pacing System, which automatically sets the ventricular pulse amplitude and regularly adjusts the setting according to the patient's measured capture threshold; and

- Dynamic Atrial Overdrive (DAO) which is a unique automatically-adjusting pacing algorithm intended to suppress atrial tachyarrhythmias including paroxysmal or persistent atrial fibrillation. When the DAO algorithm is programmed ON, the device adjusts its pacing rate to increase or decrease with variation in the patient's intrinsic atrial rate in order to maintain a high percentage of atrial pacing.

- The Advanced Hysteresis Response selection augments previously approved Hysteresis options by allowing the user to specify the resultant pacing rate and duration when the Hysteresis feature is triggered. The basic Hysteresis feature and its intended use are unchanged.

Integrity AFx DR Model 5346 pulse generators can be programmed with the Model 3510/3500 programmer equipped with programmer software Model 3307, v2.2a or higher.

VI. Alternative Treatments

Other pacemaker systems may meet the needs of patients with diseases and conditions for which the Integrity AFx DR Model 5346 device is indicated.

VII. Marketing History

Integrity AFx DR Model 5346 is currently marketed in the EU and the following countries: Israel, Saudi Arabia, South Africa, Turkey, Greece, New Zealand, Hong Kong and Venezuela. The Integrity AFx DR Model 5346 device has not been withdrawn from any country for safety and/or effectiveness reasons.

VIII. Adverse Events

The clinical study evaluating the Dynamic Atrial Overdrive (DAO) algorithm (called the ADOPT-A study) involved 399 patients. For the total study population, the mean patient implant duration was 399.4 days ± 216.6 days (range of 36 to 901 days). For the DAO ON group, the mean implant duration

was 410.4 ± 226.8 days (range of 47 to 901 days). For the DAO OFF group, the mean implant duration was 388.0 ± 205.5 days (range of 36 to 901 days).

A total of 17 deaths occurred during the study. None of the deaths were device-related. Table 1 summarizes the deaths reported during the study.

Table 1: Patient Deaths

Cause of Death	DAO OFF	DAO ON	TOTAL
Congestive Heart Failure	3	3	6
Cerebral Vascular Accident	1	0	1
Cardiopulmonary Arrest	0	1	1
Chronic Obstructive Pulmonary Disease	0	1	1
Complication of Pericardiocentesis	1	0	1
Coronary Artery Disease	0	1	1
Pancreatic Cancer	0	1	1
Renal Shutdown	0	1	1
Respiratory Failure	0	1	1
Shock with Undetermined Etiology	0	1	1
Unknown	1	1	2
Total	6	11	17

Observed Adverse Events

An Adverse Event was defined as any unfavorable clinical event, which impacted or, had 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 can occur during exposure to the procedure, exposure to the device, and/or, at implant (including, but not limited to, adverse events related or potentially related to any device utilized, including accessories, regardless of manufacturer).

These reported events were reviewed by an internal Adverse Events Committee and were first classified as an Adverse Event or an Other Reported Event. Adverse events were further classified as a complication or an observation. A complication was defined as any adverse event resulting in an injury or an invasive intervention (e.g., lead repositioning after lead dislodgment) which would not have occurred in the absence of the implanted device and/or system components. An observation was defined as any adverse event that is not associated with injury to the patient or an invasive intervention (e.g., intermittent loss of capture) which would not have occurred in the absence of the implanted device and/or system components. An other reported event was defined as any other clinical event that was reported by the investigator, which was not caused by, or associated with the study device.

Table 2 summarizes the adverse events reported and classified as complications during the study.

Table 2: Complications (See page 8 for footnotes)

Type of Complication	Number of Patients* (% of Total)		Number of Events		Events per Device-Year †		Events Per Patient-Month ‡	
	DAO OFF	DAO ON	DAO OFF	DAO ON	DAO OFF	DAO ON	DAO OFF	DAO ON
Lead Dislodgment (Ventricular)	4 (2.04)	4(1.97)	4	4	0.019	0.018	0.0016	0.0015
Lead Dislodgment (Atrial)	3 (1.53)	2(0.98)	3	2	0.014	0.009	0.0012	0.0007
Pneumothorax	2(1.02)	1(0.49)	2	1	0.010	0.004	0.0008	0.0004
Myocardial Perforation	0	2(0.98)	0	2	-	0.009	-	0.0007
Lead Dislodgment (Atrial and Ventricular)	1(0.51)	1(0.49)	1	1	0.005	0.004	0.0004	0.0004
System Infection	0	1(0.49)	0	1	-	0.004	-	0.0004
Cardiac Tamponade	0	1(0.49)	0	1	-	0.004	-	0.0004
System Replacement	0	1(0.49)	0	1	-	0.004	-	0.0004
Total	10 (5.1)	13(6.4)	10	13	0.048	0.057	0.004	0.0048

Table 3 summarizes the adverse events reported and classified as observations during the study.

Table 3: Observations (See page 8 for footnotes)

Type of Observation	Number of Patients* (% of Total)		Number of Events		Events per Device-Year †		Events Per Patient-Month ‡	
	DAO OFF	DAO ON	DAO OFF	DAO ON	DAO OFF	DAO ON	DAO OFF	DAO ON
Chest Pains	0	1(0.49)	0	1	-	0.004	-	0.0004
Hematoma	2(1.02)	1(0.49)	2	1	0.010	0.004	0.0008	0.0004
Infection	1 (0.51)	0	1	0	0.005	-	0.0004	-
Intermittent Loss of Capture (Atrial)	2(1.02)	0	2	0	0.010	-	0.0008	-
Intermittent Loss of Sensing (Atrial)	0	4(1.97)	0	4	-	0.018	-	0.0015
Palpitations with High Rate Pacing**	0	5(2.46)	0	5	-	0.022	-	0.0018
Lead Dislodgment (Ventricular)	0	1(0.49)	0	1	-	0.004	-	0.0004
Lead Fracture	1(0.51)	0	1	0	0.005	-	0.0004	-
Pacemaker Mediated Tachycardia (PMT)	2(1.02)	1(0.49)	2	1	0.010	0.004	0.0008	0.0004
Painful Incision Site	0	1(0.49)	0	1	-	0.004	-	0.0004
Pericardial Effusion	1(0.51)	0	1	0	0.005	-	0.0004	-
Presyncope	1(0.51)	1(0.49)	1	1	0.005	0.004	0.0004	0.0004
Reprogramming	2(1.02)	2 (0.98)	2	2	0.010	0.009	0.0008	0.0007
Telemetry Error	0	1(0.49)	0	1	-	0.004	-	0.0004
Unconfirmed Programmed Parameter Change	0	1(0.49)	0	1	-	0.004	-	0.0004
Total	12 (6.12)	19 (9.33)	12	19	0.058	0.083	0.0048	0.0069

A total of 114 events were classified as Other Reported Events. Other Reported Events of interest in this patient population are listed in Table 4:

Table 4: Other Reported Events

Type of Event	Number of Patients* (% of Total)		Number of Events		Events per Device-Year †		Events Per Patient-Month ‡	
	DAO OFF	DAO ON	DAO OFF	DAO ON	DAO OFF	DAO ON	DAO OFF	DAO ON
Ablation (Atrial Flutter)	2(1.02)	2(0.98)	2	2	0.010	0.009	0.0008	0.0007
Ablation (AV Node)	4(2.04)	6 (2.95)	4	7	0.019	0.031	0.0016	0.0026
Ablation (Maze Procedure)	1(0.51)	0	1	0	0.005	-	0.0004	-
Atrial Fibrillation	1(0.51)	2 (0.98)	1	2	0.005	0.009	0.0004	0.0007
Cardioversion	18(9.18)	13(6.40)	18	13	0.086	0.057	0.0072	0.0048
Cerebral Vascular Accident (CVA)	0	1 (0.49)	0	1	-	0.004	-	0.0004
Chronic Atrial Fibrillation	2(1.02)	4 (1.97)	2	4	0.010	0.018	0.0008	0.0015
Hospitalization (Atrial Fibrillation)	2(1.02)	1 (0.49)	2	1	0.010	0.004	0.0008	0.0004
Total	30(15.3)	29 (14.26)	30	30	0.144	0.131	0.0120	0.0110

* All patients implanted (400 pulse generators in 399 patients). A total of 196 devices in 196 patients were in the DAO OFF group and 204 devices in 203 patients were in the DAO ON group). Cumulative implant duration is 76,047 device days for the DAO OFF group and 83,310 device days for the DAO ON group.

† This rate is obtained by dividing the number of adverse events by the total device cumulative implant duration in years (208.34 years for the DAO OFF group and 228.24 years for the DAO ON group).

‡ This rate is obtained by dividing the number of adverse events by the total patient cumulative implant duration in months (6,337.25 months for the DAO OFF group and 6,943.17 months for the DAO ON group).

** Resolved in two patients with adjustment of the overdrive pacing settings, while three patients had overdrive pacing turned OFF without attempting to adjust the parameter settings.

Potential Adverse Events

The following are potential complications associated with the use of any pacing system (listed in alphabetical order):

- Air embolism
- Body rejection phenomena
- Cardiac tamponade or perforation
- Formation of fibrotic tissue; local tissue reaction
- Inability to interrogate or program a pulse generator because of programmer malfunction
- Infection

- Interruption of desired pulse generator function due to electrical interference
- Loss of desired pacing and/or sensing due to lead displacement, body reaction at electrode interface, or lead malfunction (fracture or damage to insulation)
- Loss of normal pacemaker function due to battery failure or component malfunction
- Pacemaker migration, pocket erosion, or hematoma
- Pectoral muscle stimulation
- Phrenic nerve or diaphragmatic stimulation.

IX. Summary of Preclinical Study

Integrity AFx DR Model 5346 Pulse Generator is mechanically and electrically identical to and includes the same device software as in the legally marketed Integrity AFx DR Model 5342 pulse generator (approved by FDA on April 6, 2000 under PMA P880086/S70). In addition to the features available in the commercially released Integrity AFx model 5342 device, the programmer software model 3307,v2.2a makes the Dynamic Atrial Overdrive (DAO) and the Advanced Hysteresis features accessible in the Integrity AFx Model 5346.

Device qualification testing of the Integrity AFx included functional testing and verification that appropriate parameters are available for the individual models, as well as testing to verify the markings/labeling and manufacturing document compliance. In addition, verification and user testing of the programmer software was performed. In all cases, all samples passed all qualification tests performed, confirming compliance with the respective product specifications.

X. Summary of Clinical Study

Patients enrolled in the ADOPT-A study were implanted with either a Trilogy® DR+ /DAO 2360L /2364L or an Integrity™ AFx DR 5346 device. The DAO (Dynamic Atrial Overdrive) algorithm was incorporated in all 3 models. The DAO algorithm is designed to provide atrial pacing (atrial overdrive pacing) a majority of the time and base the pacing rate on the detection of intrinsic atrial activity (or on sensor indicated rate).

A total of 39 clinical centers worldwide participated in the ADOPT-A study. Of these clinical centers, 28 were in the U.S., 8 were in Canada and 3 were in the U.K. A total of 399 patients were studied. Patients were enrolled who had symptomatic paroxysmal or persistent atrial fibrillation and sinus node dysfunction with one or more 1991 ACC/AHA Class 1 bradycardia pacing indications.

The primary objective of this randomized, controlled, single-blinded study was to investigate whether DDDR pacing at 60 ppm with the Dynamic Atrial Overdrive (DAO) pacing algorithm can prevent episodes of symptomatic atrial fibrillation more effectively than DDDR pacing at 60 ppm. Secondary endpoints included Quality of Life assessments and number of symptomatic AF episodes, as well as freedom from cardioversions and hospitalizations.

Patient Population

Individuals enrolled in the study satisfied all of the following inclusion criteria as specified in the ADOPT-A protocol:

a) Had symptomatic paroxysmal or persistent AF;

b) Had sinus node dysfunction with a 1991 ACC/AHA Class I bradycardia indication for a dual-chamber pacemaker;

c) Had two atrial fibrillation episodes in the last month prior to implant, with at least one episode occurring within the past 12 weeks documented by an ECG or rhythm strip; and

d) Had the two qualifying episodes of atrial fibrillation while maintained on a stable (5 half-lives) antiarrhythmic drug and/or AV nodal blocking agent regimen (or no such therapy, if applicable). Amiodarone therapy must have been stable for 30 days prior to implant.

The protocol required that the patient's antiarrhythmic drug regimen be maintained through the 6-month follow-up visit.

Of the 399 patients, 196 patients were randomized to the DAO OFF group and 203 patients were randomized to the DAO ON group. Of these patients, 201 (50.4%) were males and 198 (49.6%) were females. The mean age at implant for the total population was 71.3 ± 9.9 years. Additional patient demographics are given in Table 5 below. There were no statistically significant differences in gender, age, ejection fraction, NYHA class, antiarrhythmic drug use or pre-implant symptomatic AF episode frequency between the DAO On and DAO Off groups.

Of the 399 patients, a total of 288 (158 in the DAO OFF group and 130 in the DAO ON group) were included in the efficacy analysis. Patients were prospectively excluded for the following reasons: lack of follow-duration (n=55), DAO parameter misprogramming at implant (n=22), missing baseline ECG/data (n=8) and unsuccessful atrial lead implant (n=1). In addition, the first 25 enrolled patients were excluded as investigator requested changes were made to the protocol precluding pooling of the data.

Table 5: Patient Characteristics

	DAO OFF	DAO ON
Mean Age	71.22 ± 9.81	71.31 ± 9.97
Male **Female**	50% (98) 50% (98)	51% (103) 49% (100)
Mean LVEF	57% ± 12	56% ± 13
Mean Symptomatic AF Episodes Prior to Implant (6 Months)	7.89 ± 4.24	8.14 ± 4.19

In addition to the required sinus node dysfunction indication, other indications for pacemaker were also reported. Table 6 lists the additional reported indications for implant.

Table 6: Indications for Pacemaker Implant

INDICATION	No. of Patients: DAO OFF (%)	No. of Patients: DAO ON (%)
Second Degree AV Block	7 (3.6%)	10 (4.9%)
Third Degree AV Block (Complete)	3 (1.5%)	8 (3.9%)
Bifascicular or Trifascicular	2 (1.0%)	2 (0.9%)
Hypersensitive Carotid Sinus Syndrome or Neurovascular Syndrome	3 (1.5%)	0 (0.0%)

Gender Bias

There was no gender bias demonstrated, as the study comprised 50% male subjects vs. 50% female subjects in the DAO OFF group and 51% male vs. 49% female subjects in the DAO ON group. This indicates that both sexes are appropriately represented in the study population. Adverse events observed during the study and the effectiveness of the system similar between males and females.

Methods

Prior to discharge, all patients were provided with a cardiac event recorder and instructed to use it whenever they felt symptomatic. Patients were asked to carry this recorder with them until the 6-month follow-up evaluation at which time it was returned to the investigational center. Patients were instructed to transmit all ECG episodes recorded by the device by telephone to a central receiving center. All transmitted ECGs were analyzed by two electrophysiologists on an ECG Review Committee to classify the rhythm and assess the existence of Atrial Fibrillation (AF) according to a specific ECG classification system. In case of disagreement, the ECG Review Committee was convened with a third physician to determine a final classification.

An AF day was defined as a day on which a patient transmitted a recording documenting AF, as classified by the ECG Review Committee. AF burden was assessed by measuring the number of symptomatic AF episodes over a given period of time. For this study, AF burden is defined as the total number of AF days divided by the cumulative follow-up days of the population over the study period.

Results

The percentage of atrial pacing in the DAO ON group was 92.9% compared to 67.9% in the DAO OFF group ($p<0.0001$). Antiarrhythmic drug use during the follow-up period for the large majority of patients did not change. There was no statistically significant difference between the DAO OFF and DAO ON groups in the number of patients reporting a change in the antiarrhythmic drug regimen. In addition, of all of the symptomatic atrial tachyarrhythmias observed during the study, 90.4% were classified as Atrial Fibrillation episodes, 4.6% were classified as Atrial Flutter episodes and 5% were classified as Other Atrial Arrhythmia (e.g. Atrial Tachycardia).

As indicated in Table 7 below, the DAO ON group had 22,526 days of total cumulative follow-up time with a total of 421 AF days, while the DAO OFF group has 27,359 days of cumulative follow-up time with a total of 682 AF days. The AF burden for DAO ON and DAO OFF groups were 1.87% and 2.49% respectively ($p<0.05$). The AF burden observed over time is shown in Figure 1.

Table 7: AF Burden

	DAO OFF	DAO ON
TOTAL PATIENTS	158	130
PATIENTS WITH AF DAYS	81	73
TOTAL AF DAYS	682	421
TOTAL FOLLOW-UP DURATION	27,359 days	22,526 days
AF BURDEN	2.49%	1.87%

Figure 1: Distribution of AF Burden

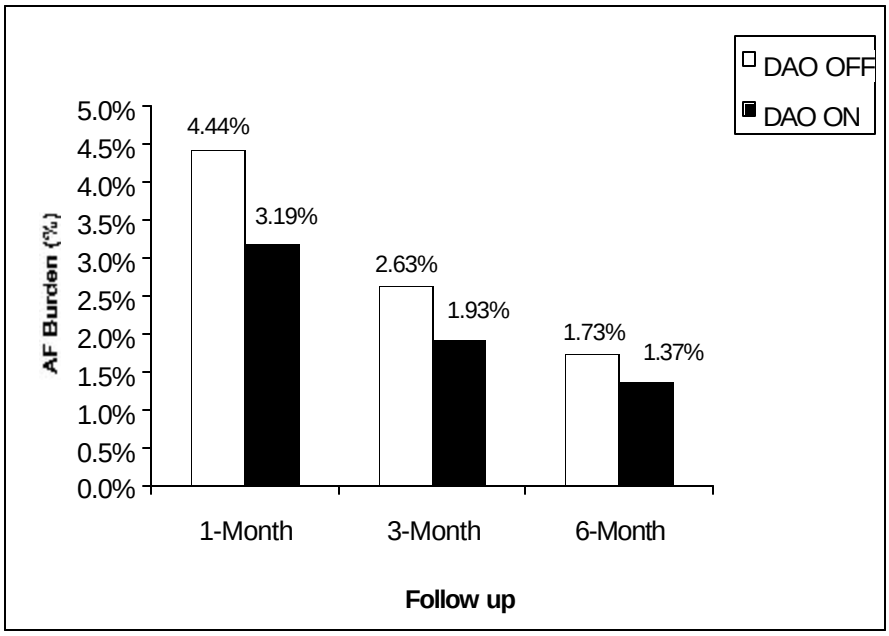


Table 8 below shows the mean number of symptomatic AF episodes reported 6 months prior to implant and during the 6 months of follow-up post implant. Both reductions were statistically significant ($p<0.0001$).

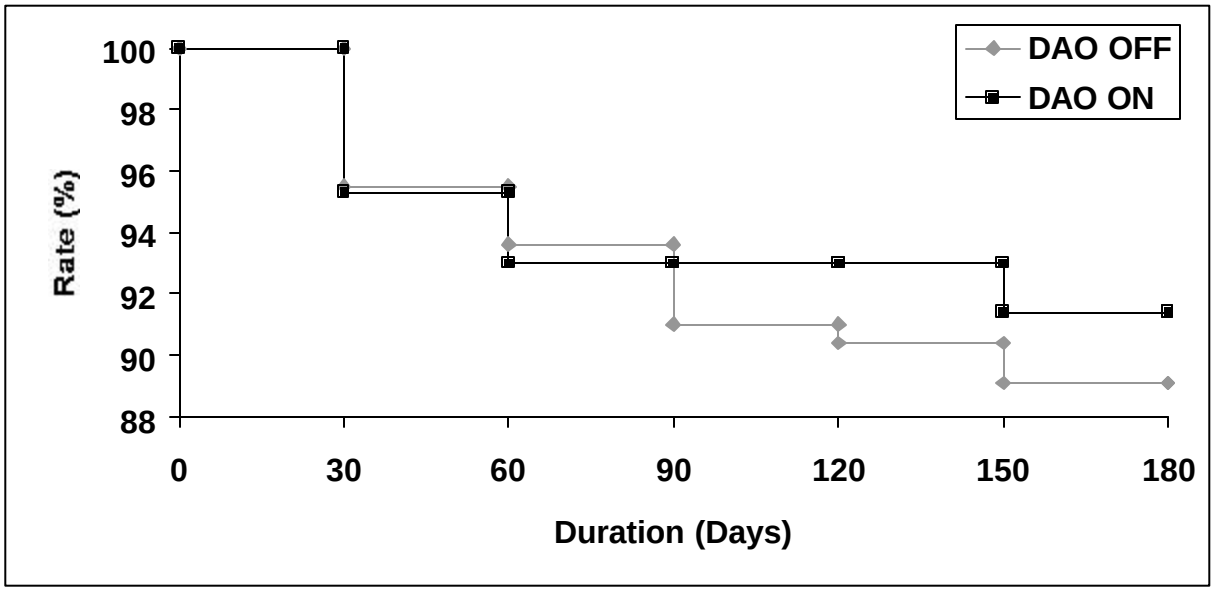
Table 8: Number of Symptomatic AF Episodes

	AF Episodes: 6 Months Prior to Implant		**AF Episodes: Implant to 6 Months**	
	DAO OFF	**DAO ON**	**DAO OFF**	**DAO ON**
Mean AF Episodes	8.139	8.354	4.316	3.238
Standard Deviation	4.218	4.156	11.512	8.593

Quality of Life: The SF-36 Quality of Life questionnaire was utilized in the study as a qualitative measure of the patients' well being. Overall, there was no statistically significant difference between the two groups. There is a statistically significant improvement in the standardized physical component (PCS) scores within the DAO ON group ($p=0.013$). In the standardized mental component (MCS) scores, there is a statistically significant improvement within both the DAO OFF and the DAO ON groups ($p<0.001$). Additionally, in the Self-Functioning (SF) sub-scale, there is a statistically higher improvement in the DAO ON group when comparing between groups ($p=0.003$).

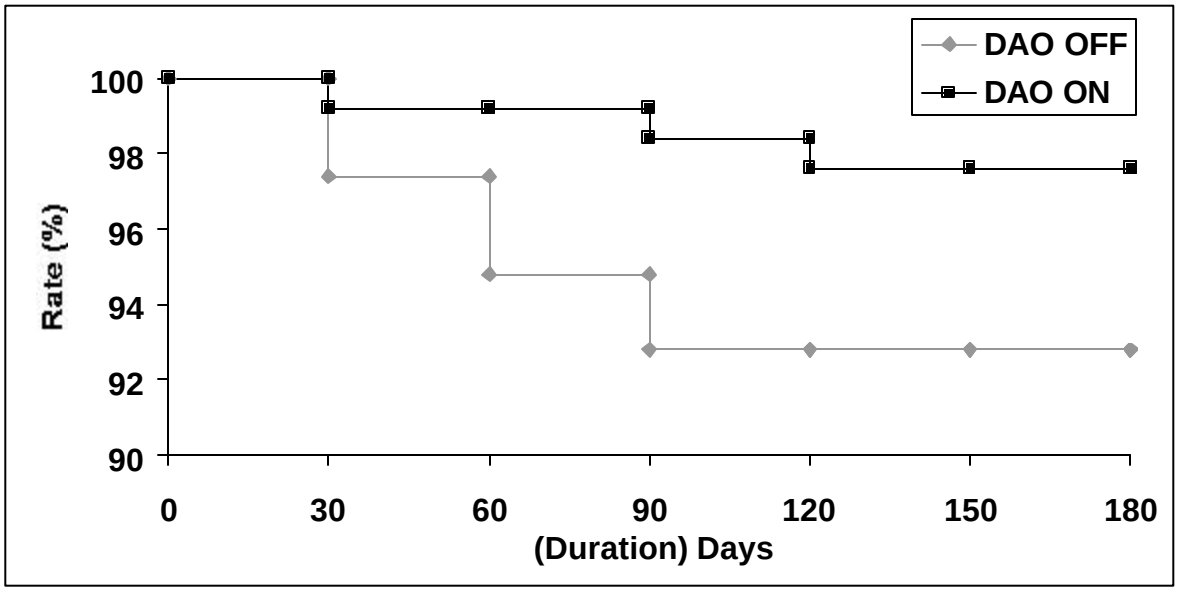
Hospitalization: Freedom from first hospitalization was also calculated. The observed freedom from first hospitalization was not statistically significantly different between groups.

Figure 2: Freedom From First Hospitalization



Cardioversions: Freedom from first cardioversion was also calculated. The observed freedom from first cardioversion did not reach statistical significance, however a trend toward significant improvement in the DAO ON group was observed (p= 0.0925).

Figure 3: Freedom From First Cardioversion



XI Conclusions Drawn from the Study

The results of analyses demonstrate that the AF burden was reduced significantly when the Dynamic Atrial Overdrive (DAO) algorithm was programmed ON when compared to the DAO OFF group. There were no device related patient deaths or complications observed and no unanticipated adverse events reported during the study. Thus, the results provide reasonable assurance of safety and effectiveness of the Integrity AFx DR Model 5346 with Dynamic Atrial Overdrive when used as indicated in accordance with the directions for use.

XII. Panel Recommendations

Pursuant to section 515(c)(2) of the Food, Drug and Cosmetic Act (the Act) as amended by the Safe Medical Devices Act of 1990, this PMA supplement was not referred to the Circulatory System Devices Advisory Panel for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. FDA Decision

Based on the data provided in the PMA supplemental application and its amendments, FDA determined that the device provides reasonable assurance of safety and effectiveness when used as indicated in the labeling. FDA found St. Jude Medical, Inc.'s manufacturing facility to be in compliance with the Device Quality System Regulation (21 CFR part 820).

XIV. Approval Specifications

Directions for use: See the labeling.

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

Post-approval Requirements and Restrictions: See approval order.

The Approval Order, Summary of Safety and Effectiveness Data, and labeling can be found on the Internet at http://www.fda.gov/cdrh/pmapage.html.