

**Summary of Safety and Effectiveness Data
Diva Platform Implantable Pulse Generators
and ProVit III Application Software (Version 3.3.2)**

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Summary of Safety and Effectiveness Data
Div a Platform Implantable Pulse Generators
and ProV it III Application Software (Version 3.3.2)

Vitatron, Inc.

1. General Information

Device Generic Name: Implantable Pacemaker Pulse Generator

Device Trade Name(s): Div a Platform Implantable Pulse Generators
Diamond II Model 820 Pulse Generator
Ruby II Model 720 Pulse Generator
Topaz II Model 520 Pulse Generator
Jade II Model 220 Pulse Generator
Vita DDDR Model 810 Pulse Generator
Vita DDD Model 710 Pulse Generator
Vita VVIR Model 310 Pulse Generator

ProV it III Application Software Version 3.3.2

Applicant's Name and Address: Vitatron, Inc.
7000 Central Ave N.E.
Minneapolis, MN 55432

PMA Application Number: P990001

Date of Panel Recommendation:..... Not Applicable

Date of Notice of Approval to the Applicant:...

2. Indications and Usage

The Diva Platform Implantable Pulse Generators are indicated for:

- Rate adaptive pacing in patients who may benefit from increased pacing rates concurrent with increases in activity and/or QT interval;
- Accepted patient conditions warranting chronic cardiac pacing which include:
 - Symptomatic paroxysmal or permanent second or third degree AV block;
 - Symptomatic bilateral bundle branch block;
 - Symptomatic paroxysmal or transient sinus node dysfunctions with or without associated AV conduction disorders;

- Bradycardia-tachycardia syndrome to prevent symptomatic bradycardia or some forms of symptomatic tachyarrhythmias; and
- Vasovagal syndromes or hypersensitive carotid sinus syndromes;
- Diva Platform Implantable Pulse Generators are also indicated for dual chamber and atrial tracking modes in patients who may benefit from maintenance of AV synchrony. Dual chamber modes are specifically indicated for treatment of conduction disorders that require restoration of both rate and AV synchrony, which include:
 - Various degrees of AV block to maintain the atrial contribution to cardiac output; and
 - VVI intolerance (e.g., pacemaker syndrome) in the presence of persistent sinus rhythm.

3. Contraindications

The Diva Platform Implantable Pulse Generators are contraindicated for the following applications:

- Chronic refractory supraventricular tachyarrhythmias, including atrial fibrillation or flutter;
- Asynchronous pacing in the presence (or likelihood) of competition between paced and intrinsic rhythms; and
- Co-implant in a patient with an implanted cardioverter-defibrillator (ICD). The interaction may cause pacemaker reset or permanent damage.

4. Warnings and Precautions

See WARNINGS AND PRECAUTIONS in the final draft labeling (Information for Use)

5. Device Description

The Diva Platform Implantable Pulse Generators are bipolar, multiprogrammable, dual and single chamber devices. As outlined below, several devices employ a dual sensor (Activity and QT interval) rate response.

	Dual IS-1 ¹	Single IS-1	Rate Response
Diamond II, Model 820	√		√
Ruby II, Model 720	√		√ (VVIR, AAIR)
Topaz II, Model 520		√	√
Jade II, Model 220		√	
Vita DDDR, Model 810	√		√
Vita DDD, Model 710	√		
Vita VVIR, Model 310		√	√

¹ Connector standard IS-1 according ISO 5841-3; 1992.

The main features of the Diamond II pacemaker are:

- Dual chamber rate responsive pacing modes (DDDR, DDIR and VDDR).
- Adaptive Mode Switching™ (AMS), based on beat to beat analysis of the atrial rate pattern. The pacemaker automatically selects the most appropriate pacing mode and response. A moving “Physiological Band” is used to trigger Adaptive Mode Switching.
- The “Atrial Synchronization Pace” (ASP) feature, which is designed to restore AV synchrony as quickly as possible by means of atrial pacing. This algorithm includes safety measures to prevent short atrial paced intervals and thereby avoid inducing atrial flutter or atrial fibrillation.
- The Flywheel (FLY) mode, which is intended to be used to avoid sudden drops in heart rate, e.g. in case of sudden atrial bradycardia.
- Automatic adaptation of the AV delay (AUTO AVD) in response to changing atrial rates.
- Automatic lowering of the lower rate limit during selected night hours (NIGHT DROP).
- Automatic retrograde conduction analysis (AUTO RCA). Whenever there is continuous atrial sensing and ventricular pacing the pacemaker will automatically test for retrograde conduction in order to discriminate between atrial tracking and retrograde P-wave sensing. Tracking of retrograde P-waves will be discontinued, thus terminating pacemaker mediated tachycardias.

Other models have a subset of these features, as outlined below:

	DIAMOND II	RUBY II	TOPAZ II	JADE II	VITA DDDR	VITA DDD	VITA VVIR
AMS	√	√			√ (Fixed)	√ (Fixed)	
ASP	√	√			√	√	
FLY	√	√	√	√	√	√	
TFR*		√					
SB**	√	√	√		√		√
AUTO AVD	√	√			√	√	
NIGHT DROP	√	√	√	√			
AUTO RCA	√	√			√	√	
PCS***			√	√			
HYS****				√			

*TFR = Tachy Fallback Rate feature in pacemakers, which determines ventricular rate in case of atrial tachyarrhythmias

**SB = Sensor Blending and Sensor Cross-Checking

***PCS = Pacing Chamber Selection programming feature automatically preselects optimal atrial or ventricular parameter values and suppresses irrelevant modes

****HYS = Programmable conditional Hysteresis, which gives preference to spontaneous rhythm with a user selectable minimum rate

Sensor Blending

Sensor blending determines the relative influence of each sensor on the pacing rate. The following settings can be programmed: QT=ACT, QT>ACT, QT<ACT, QT Only and ACT only.

- **QT=ACT:** This is the shipped setting for the Sensor Blending. In this setting, both sensors are designed to have an equal influence on the pacing rate. This setting is intended to provide a fast onset of the rate response at the start of the physical activity (due to the contribution of the Activity sensor), as well as a proportional rate increase to prolonged physical activity and emotional and isometric stress, due to the contribution of the QT interval sensor.
 - **QT>ACT:** This setting is designed to allow a greater influence of the QT interval sensor than that of the activity sensor. This setting is advised if the rate increase at onset of exercise is too fast in the QT=ACT setting, but that of the QT Only setting is too slow.
 - **QT<ACT:** In this setting, the influence of the activity sensor is designed to be greater than the influence of the QT interval sensor. This setting is advised if the initial rate increase upon exercise in the QT=ACT setting is too low, but a desire to use the QT sensor exist.
- **QT Only:** For this setting the pacemaker is designed to respond to signals from QT sensor. This setting is advised if the Activity sensor input is not appropriate. The rate response is intended to result in a gradual heart rate increase in response to physiological changes in the QT interval. Since the QT Only setting responds only to physiologic changes, the response to physical activity is not as immediate as with the mechanical response of the Activity sensor.
- **ACT Only:** In this setting, the pacemaker is designed to only respond to signals from the activity sensor. This setting is advised where QT interval input is not desired. The activity sensor will increase the pacing rate rapidly at the onset of physical activity, but rate response to physical activity will not be as gradual.

Programming System

Programming and telemetry are done using the Medtronic/Vitatron 9790 (c) programmer. Printed copies of the programmed pacemaker status, measurement results, histograms and Holter data can be obtained using the built-in printer of the Medtronic/Vitatron 9790 (c) programmer. The extent of programmability options depends on the specific device type in the Diva series.

Lead Compatibility

For pacing and P-, R- and T-wave sensing a conventional unipolar or bipolar pacing lead is used. Diva Platform Implantable Pulse Generators are compatible with unipolar or bipolar IS-1 leads.

6. Alternative Practices or Procedures

While surgery or drug therapy may be alternatives to cardiac pacing in certain instances, cardiac pacing is the standard treatment for the indications described above. Other commercially available single or dual chamber pacemakers provide alternatives to the Vitatron Diva pulse generators.

7. Marketing History

All of the Diva Platform Implantable Pulse Generators and the ProVit III Application Software are marketed in Austria, Belgium, Canada, Croatia, Denmark, France, Germany, Greece, Hungary, Iran, Ireland, Italy, Japan, Lebanon, Macedonia, Netherlands, Portugal, Serbia, Slovenia, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey, UK. None of the devices have been withdrawn from the market in any country for any reason related to the safety and effectiveness of the device.

8. Adverse Events

The Vitatron Diamond II DDDR model 820 devices were evaluated in a multicenter prospective study [34 investigational centers, 20 centers in the US, and 14 centers outside the US (OUS)] of the features and rate response of the device. Clinical study of the Vitatron Diamond II device began on January 15, 1996. As of May 21, 1999 there were 258 devices implanted in 258 patients worldwide. Mean duration of implant was 15.9 months with a range of 0.03 to 40.1 months.

There were a total of eighteen deaths in the study; all were reviewed and judged to be non-device related. Three were attributed to carcinoma, two to sudden death, two to congestive heart failure, two to respiratory distress, two to arteriosclerotic cardiovascular disease, one to asbestosis, one to cardio-pulmonary arrest, one to cardiac insufficiency, one to coronary disease, one to myocardial infarction, and two to unknown reasons.

A total of four devices were explanted. Two were explanted due to infection of the pacing system. One was explanted for further analysis after an apparent ventricular exit block. Analysis revealed an improperly tightened set screw to be the most likely cause of this event. One patient required the implant of an ICD, which necessitated pacemaker explantation.

In four cases, there was difficulty inserting the ventricular lead. This was subsequently resolved by adapting the connector design within the tolerances of the IS-1 standard.

The Diamond II has all of the possible features of the Diva product line, which also consists of Ruby II, Topaz II, Jade II, and the VITA series (DDDR, DDD and VVIR). Based on the similarities between the Diamond II and the devices listed above, the clinical data collected for the Diamond II was considered representative of all the above models for the safety evaluation.

Observed Adverse Events

Table 8-1 reports the pacing related adverse events on a per patient and a per device-year basis in the descending order of frequency. Of the 297 events reported, 88 were pacing related events.

Table 8-1: Adverse Events Reported in Three or More Patients--

Event	Total Number of Events	Number (%) of Patients with Events			Total Events per Device year (n=342)
		US (n=146)	OUS (n=112)	Total (n=258)	
Any adverse event	297	96 (65.8%)	43 (38.4%)	139 (53.9%)	0.87
Any pacing related events	88	48 (32.9%)	23 (20.5%)	71 (27.5%)	0.26
Atrial lead dislodgment	13	4 (2.7%)	8 (7.1%)	12 (4.7%)	0.04
Palpitations/ rapid pulse	10	10 (6.8%)	-	10 (3.9%)	0.03
Implant site discolored/ swelling/ painful/ ecchymosis	8	7 (4.8%)	-	7 (2.7%)	0.02
Ventricular lead dislodgment	7	3 (2.1%)	4 (3.6%)	7 (2.7%)	0.02
Atrial undersensing	6	5 (3.4%)	1 (0.9%)	6 (2.3%)	0.018
Inappropriate ventricular lead connection	4	-	4 (3.6%)	4 (1.6%)	0.012
Infection of pocket/ system	3	1 (0.7%)	2 (1.8%)	3 (1.2%)	0.009
Diaphragmatic/ extracardiac stimulation	3	3 (2.1%)	-	3 (1.2%)	0.009
Atrial exit block	3	2 (1.4%)	1 (0.9%)	3 (1.2%)	0.009

Table 8-2 reports the pacing related complications (adverse events that required invasive measures to correct) on a per patient and a per device-year basis in the descending order of frequency. Of the 297 adverse events reported, 71 were complications, and 35 of these were pacing related complications.

Table 8-2: Complications*

Event	Total Number of Comps	Number (%) of Patients with Comps			Total Comps per Device year (n=342)
		US (n=146)	OUS (n=112)	Total (n=258)	
Any adverse event	71	33 (22.6%)	24 (21.4%)	57 (22.1%)	0.21
Any pacing related events	35	12 (8.2%)	20 (17.9%)	32 (12.4%)	0.10
Atrial lead dislodgment	12	3 (2.1%)	8 (7.1%)	11 (4.3%)	0.04
Palpitations/ rapid pulse	0	-	-	-	-
Implant site discolored/ swelling/ painful/ ecchymosis	0	-	-	-	-
Ventricular lead dislodgment	7	3 (2.1%)	4 (3.6%)	7 (2.7%)	0.02
Atrial undersensing	0	-	-	-	-
Inappropriate ventricular lead connection	3	-	3 (2.7%)	3 (1.2%)	0.009
Infection of pocket/ system	2	-	2 (1.8%)	2 (0.8%)	0.006
Diaphragmatic/ extracardiac stimulation	0	-	-	-	-
Atrial exit block	2	1 (0.7%)	1 (0.9%)	2 (0.8%)	0.006

* Complications included those adverse events that required invasive measures to correct (e.g. surgical intervention), and were related to the presence of the pacing system or procedure.

The following other pacing related adverse events were reported, but occurred in fewer than three patients: lack of atrial capture, fatigue/ exercise intolerance, thrombosis, angina pectoris, inappropriate atrial lead connection, ventricular exit block (loose set screw), intermittent loss of ventricular capture, elevated atrial threshold, ventricular lead perforation, pneumothorax, twiddler’s syndrome, left subclavian vein approach abandoned, inappropriate programming, far field R-wave sensing, pain in right shoulder, nocturnal palpitations/ slow pulse, atrial fibrillation, apparent battery end of life, increased ventricular thresholds, atrial lead repositioned, superior vena cava syndrome, failure to mode switch, pacemaker reset, chest discomfort, lack of ventricular capture, tiredness/dizziness.

The following adverse events were deemed not pacing related and occurred in at least 2 patients (209 events were reported): atrial flutter/fibrillation, chest pain/angina, dizziness, fatigue, dyspnea, cardiomyopathy, congestive heart failure, sleep problems, unstable angina, syncope, palpitations, diverticulosis, intravascular electrode lengths too short due to rapid growth, high blood pressure, urinary tract infection, colon carcinoma, upper respiratory infection, lymphoma, cold, atrial tachycardia, headache, paroxysmal atrial fibrillation, CABG surgery, shoulder stiffness/soreness/pain, acute myocardial infarction, presyncope, nausea, fast heart rate.

Potential Adverse Events

Adverse events (in alphabetical order), including those reported in Table 8-1, associated with pacing systems include:

- Cardiac perforation
- Cardiac tamponade
- Death
- Erosion through the skin
- Hematoma/seroma
- Infection
- Improper operation caused by theft prevention systems
- Myopotential sensing
- Nerve and/or muscle stimulation
- Pacemaker syndrome
- Rejection phenomena (local tissue reaction, fibrotic tissue formation, pacemaker migration)
- Threshold elevation

9. Summary of Preclinical Studies

Non-clinical testing of the Vitatron Diva devices was conducted to ensure that the components and the finished device perform in accordance with their design specifications.

9.1 Bench Testing

Hazard Analysis

Hazard analyses have been performed on all new features and critical components included in the Diva platform pacing system, including the integrated circuits, firmware, and software. The hazard analyses were incorporated into design and development processes of the pacing system to ensure that critical failure modes, or potential hazard situations have been identified and adequately eliminated or mitigated. This is acceptable.

Integrated Circuits and Hybrid

The L237 Interface IC and the D156 Microprocessor IC were qualified using samples of 76 units. Electrical stability of the ICs was assessed through accelerated life testing. Each Interface IC was stressed at 4.2V and 150 °C for 184 hours minimum. Similarly, each Microprocessor IC was stressed at 3.0V and 150 °C for 184 hours minimum. Results of these tests established appropriate IC performance.

The hybrids, used for all Diva dual chamber and single chamber pulse generator configurations are electrically and mechanically identical. Therefore the qualification testing is applicable to both configurations.

Electrical qualification testing was performed on a sample of 152 electronic modules. Electrical stability of the hybrid module was assessed through accelerated life testing. Each unit was stressed at 3.3V and 125°C for 500 hours minimum. There was one (1) electrical failure during the life test.

The failure was due to an excessive leakage current of a tantalum capacitor. The failure was considered a random component defect and falls within the set reliability limit for non-design related failures. This is acceptable.

Battery Testing and Longevity Assessment

The Diva pulse generators utilize a Zeta 203. The battery types were subjected to application discharge (59 samples) and environmental tests (16 samples). Reliability assessment shows an upper bound for calculated random failure at 0.009 % per month with a confidence limit of 90% (Sample of 487). Normal and expected behavior of lithium-iodine batteries was observed. This is acceptable.

Connector Testing

The Diva dual chamber and single chamber pulse generators are available in IS-1 unipolar/bipolar connector module configurations.

Based on clinical experience, the design of the connector modules was adapted. Compatibility testing on this improved design was conducted on 22 dual chamber, and 22 single chamber Diva devices. Testing included a) IS-1 dimensional testing, b) IS-1 insertion testing, and c) connector electrical leakage testing. Insertion testing included both the go-gage test as required by the standard, and pacing lead insertion testing.

Both connector configurations were found to meet all qualification testing requirements. This is acceptable.

Environmental and Mechanical Testing

Environmental and mechanical qualification testing was performed on twenty-two (22 pulse generators. The test devices were subjected to 1) environmental stress tests including: temperature storage (-15 °C and +55 °C for a minimum of three hours), random mechanical vibration (5 Hz to 150 Hz at an ASD spectrum level of 0.1 g²/Hz), and mechanical shock (500 g, 1 msec half sine wave), and 2) telemetry mapping. Full functionality of each device was verified at the completion of all environmental tests. This is acceptable.

Electromagnetic Compatibility (EMC) Testing

Electromagnetic Compatibility (EMC) testing was performed for radiated electric fields, low frequency conducted currents, transthoracic and ICD defibrillation pulses, electrosurgical cautery, and cellular phone susceptibility.

Incident inhibition was observed for radiated fields only at 3.5 MHz modulated fields above 400 V/mrms, and 28.5 MHz modulated fields above 600 V/mrms. Diva pulse generators were found to meet performance specifications for exposure to radiated electric fields. This is acceptable.

No devices were observed to exhibit rates above or below the specified test tolerances, and the pulse amplitude and duration of all devices were observed to remain within acceptable tolerances when subjected to sinusoidal currents. This is acceptable.

Diva devices were found to meet the performance specifications for devices exposed to in-vitro transthoracic defibrillation currents. No anomalies were observed during testing. All devices were fully functional and survived with no damage following defibrillation exposure. ICD testing had similar and acceptable results.

Electrosurgical cautery currents testing on Diva pulse generators did not reveal parameter shifts, nor reset of devices. Pacing always resumed within the required 2 basic pacing intervals. All devices performed according specification. This is acceptable.

Div a pulse generators exhibited no susceptibility upon exposure cellular phone signals. This is acceptable.

Parameter Stability

Testing was performed on the Div a single and dual chamber pulse generators to determine the stability of the device pacing parameters, when exposed to varying environmental conditions. Pacing rate, pulse amplitude, pulse width, AV delay, refractory, magnet interval, high rate and A, V and T sensitivity were evaluated under varying load impedance, supply (battery) voltage, and temperature conditions.

The test results demonstrate that the device parameters met specifications and remained stable under varying temperature, pacing load and supply voltage conditions. This is acceptable.

Packaging Qualification

Qualification testing was conducted on dual chamber device package inner and outer trays. The testing consisted of Shelf life stability testing, including accelerated life testing, and Package design qualification testing. All tray packages tested met the package design test requirements. This is acceptable.

Pulse Generator (Firmware) Testing

The firmware for the Div a platform was developed in accordance with the applicable Vitatron development processes. Qualification was formally planned and test details were documented in test scripts. Test scripts were generated for the test groups Pacing Modes, Pacing Options, AV delay, Decision Rates, Sense Interpretation, Rate Responsive requirements, Diagnostic functions, Analysis functions, and Communication. Test observations were described in test reports. This is acceptable.

During the qualification of the Div a firmware functionality 1228 test scripts were executed. As a result of the executed tests, 33 test reports were generated. A total of 21 test reports were corrected and 11 test reports were accepted upon evaluation. One test report was canceled as it was written due to a misinterpretation. This is acceptable.

All firmware corrections were validated by regression testing. The qualification activities have shown that the Div a firmware operates as intended. Therefore the Div a firmware has passed the qualification tests. This is acceptable.

Programmer Software Testing

The Vitatron 9790(C) Application Software (version 3.3.2) was developed and tested in accordance with formal procedures for software development and testing. These procedures include development of a Software Requirements Specification, a Hazard Analysis, Detailed Design specification, Qualification Test Plan and Qualification Test Specifications. The software was tested per the Qualification Test Plan and Specification. Errors, anomalies, and inconsistencies were noted in test reports. This is acceptable.

During the qualification test of the software, more than 4000 test cases were executed. A total of 24 test reports were generated. Of these, 16 test reports were corrected. The remaining 8 test reports were accepted upon evaluation. This is acceptable.

All software corrections were validated by regression testing. The software qualification activities have shown that the software operates as intended. It therefore has passed the qualification tests. Final configuration status was verified and documented in a Version Description Document. This is acceptable.

System Testing

System testing of the Diva pacing system evaluated the interaction of the pulse generators with the programmers, software, and pacing system analyzers to assure their operation is within the limits of their respective specifications. Issues associated with the technical literature and/or software were identified and resolved during testing. This is acceptable.

Conclusion Concerning Non-clinical Bench Tests

Vitatron conducted a hazard analysis on all new features and critical components and then conducted testing to evaluate these and other device features. All test results were found to be acceptable.

9.2 Biocompatibility

The materials used in the Diva pulse generators that are directly exposed to body tissue and/or fluids are titanium, silicone rubber, epoxy and parylene C. These materials have all been used for several years in Vitatron pulse generators marketed outside the United States. Standard biocompatibility testing (except for carcinogenicity testing) has been performed for these materials after being subjected to all aspects of the manufacturing process. All of the materials passed these tests.

Although carcinogenicity testing in an animal model was not conducted, the sponsor conducted a risk assessment of the materials used to fabricate this pacemaker and identified all of the potential breakdown products. The device materials were also subjected to an exhaustive chemical extraction test to determine the amount of the potential carcinogens available in the final device, and this study showed that the potentially releasable amounts are low. In addition, a literature review was conducted to determine which breakdown products have a potential for carcinogenicity. The only material with potential carcinogenic breakdown products is Bisphenol A epoxy.

This chemical testing and literature information, in addition to full genotoxicity testing and a warning (see below) regarding the potential for carcinogenic breakdown products, provide a reasonable measure of assurance that the risk for carcinogenicity has been appropriately addressed.

The sponsor agreed to include the following warning in the labeling:

Bisphenol A epoxies like the one used to fabricate the header component of this pacemaker may break down into compounds that could be carcinogenic. Long-term carcinogenicity testing in an animal model has not been conducted on this device. However, pacemakers using this type of material have a long history of use in the US, and this particular type of device has been used for over 10 years outside the US.

9.3 Animal Testing

No animal testing was required.

10. Summary of Clinical Studies

10.1 Objectives

Clinical studies were performed on the Diamond I and Diamond II pacemakers. The Diamond I pacemaker is an earlier version of the Diamond II with the same rate response functionality. However, the Diamond I is not being market-released in the US.

The Diamond II DDDR model 820 pacemaker study was a prospective evaluation of the major device features as well as the dual sensor (i.e. QT=ACT, QT<ACT, QT>ACT) and single QT sensor (metabolic QT interval sensor) rate response of the device. Rate response of the single Activity sensor was evaluated with data from the Diamond I study. The following five rate response sensor blending settings are available in the Diva pacemakers: QT=ACT, QT<ACT, QT>ACT, QT-only (metabolic QT interval sensor), and ACT-only (activity sensor).

Rate response of the QT=ACT, QT<ACT, and QT only sensor settings were evaluated using data from the Diamond II study. These rate response features were evaluated at a chronic follow-up visit (at least 3 months post-implant) during which a modified CAEP treadmill test was performed. In addition, the Sensor Cross Checking feature was evaluated at the chronic follow-up visit.

Data from prior studies of the Diamond I pacemaker was used to evaluate the performance of the ACT-only and the QT>ACT rate response, as well as to supplement the Diamond II data on the QT=ACT, QT<ACT, and QT-only sensor blending settings. Because the Diamond I is the predecessor of the Diamond II device with rate responsive behavior identical to the Diamond II device, this data can be used to evaluate the rate response features of the Diamond II. Patients in the Diamond I studies performed a treadmill exercise test.

The Diamond II contains all of the possible features in the Diva Platform Implantable Pulse Generator product line, which also consists of Ruby II, Topaz II, Jade II, and the VITA series (DDDR, DDD and VVIR). Based on the similarities between the Diamond II and the devices listed above, the clinical data collected for the Diamond II is in support of the safe and effective operation of said devices.

10.2 Study Design

Rate Response Objective. In both the Diamond I and Diamond II studies, dual sensor rate response operation was evaluated during a graded treadmill exercise test. Maximum heart rates were analyzed and compared to the programmed Maximum Sensor Rate. In addition, the slope of heart rates to workload was evaluated using the Metabolic Chronotropic Response model described by Wilkoff as applied by Kay². Patients that performed the treadmill test for at least six minutes with periods of pacing were included in the analysis.

In the Diamond II study, patients were also randomized to two different procedures designed to set the rate response slope during pacemaker follow-up: Daily Learn (gradual slope optimization over a 6 week period) and Fast Learn (a quick method to approximately set the rate response slope during a pacemaker follow up).

Sensor Cross Checking Objective. The effectiveness of Sensor Cross Checking was evaluated by analyzing the rate response (Activity only versus dual sensor QT=ACT) by the evoking of false positive activity sensing by tapping of the implanted pacemaker.

Secondary Objectives.

Secondary objectives evaluated the performance of the following programmable features: Auto Polarity Check, Night Rate Drop, Adaptive Mode Switching and Atrial Synchronization Pacing, Rate Adaptive AV Delay, AV Delay Hysteresis and AV Delay Scanning, PVC Synchronous Atrial Stimulation, Atrial Hysteresis, Flywheel, PMT Termination, automatic Atrial Blanking.

Appropriate operation of the software for the 9790 Programmer was also evaluated. Additionally, rate response for the single sensor settings of QT and Activity were evaluated.

² Kay, Neal G., "Quantitation of Chronotropic Response: Comparison of Methods for Rate-Modulating Permanent Pacemakers", JACC 20(7):1533-41, Dec 1992.

10.3 Description of Patients and Gender Bias

Diamond II Study. In the Diamond II study, a total of 258 patients were enrolled and implanted: median age was 72 years (range: 0.6 to 91 years); 96 patients were female, 162 were male. Patients met the indications for dual chamber pacing: sick sinus syndrome in 161, atrial fibrillation/flutter in 42, and normal AV conduction in 85 patients (patients could have more than one indication). Mean duration of implant was 15.9 months with a range of 0.03 to 40.1 months and a total experience of 4102 patient months.

Inclusion and exclusion criteria were chosen to avoid gender bias. "The preponderance of male patients reflected both the gender referral pattern for cardiac disease and the severity of the disease in the centers involved. In addition, the comparability of the gender distribution is supported by U.S. epidemiological data obtained nationwide in a 1988 survey of 122,310 individuals where the age-adjusted pacemaker prevalence in males was 1.5 times that in females (60% male: 40% female)".

No important differences in success rate or adverse event rate were detected between males and females in this patient population so the results presented are representative of both genders.

European Diamond I Study. In the European Diamond I study, a total of 96 patients were enrolled and implanted: mean age was 63.5 years (range: 35 to 82 years); 39 patients were female, 57 were male. Patients met the indications for dual chamber pacing: sick sinus syndrome in 20, atrial fibrillation/flutter in 7, and normal AV conduction in 16 patients (patients could have more than one indication.) Mean duration of implant was 12 months with a range of 2.8 to 34.0 months and total experience of 1152 patient months.

U.S. Diamond I Study. In the Observational Diamond I study in the U.S., a total of 50 patients were enrolled and implanted: mean age was 64.7 years (range: 33 to 85 years); 13 patients were female, 37 were male. Patients met the indications for dual chamber pacing. Mean duration of implant was 22.8 months with a range of 18 to 27.6 months and a total experience of 1140 patient months.

10.4 Results

Table 10-1 provides an accountability of the patients from the Diamond II, European Diamond I and U.S. Diamond I studies.

Table 10-1: Patient Accountability – Rate Response Slope Analysis

	Diamond II	Diamond I (Europe)	Diamond I (U.S.)
Total patients	258	96	50
Included in rate response analysis	38	30	24 (56 tests) *
QT=ACT	28	-	18
QT<ACT	2	-	13
QT>ACT	-	-	13
QT only	8	-	12
ACT only	-	30	-

* Patients in the U.S. Diamond I study were required to perform the treadmill test in more than one sensor blending setting; only those meeting the analysis inclusion criteria are reflected in the table.

³ Chorus RM/Opus RM SS&E - P950029 March 3, 1997

The results of the analysis of the rate response slope for the five available sensor blending settings are provided in Table 10-2. Note that QT=ACT (bolded) represents the sensor blending setting at delivery.

Table 10-2: Effectiveness Analysis – Rate Response Slope

Sensor Mode	Number of Patients in Analysis	Diamond II	Diamond I (Europe)	Diamond I (U.S.)	Mean Slope	95% Confidence interval	Patients with Slope > 0.65
Blended Sensors							
QT=ACT blending	46	28	-	18	0.82	[0.77, 0.87]	39/46 (85%)
QT<ACT blending	15	2	-	13	0.77	[0.56, 0.97]	11/15 (73%)
QT>ACT blending	13	-	-	13	0.86	[0.78, 0.95]	12/13 (92%)
QT only	20	8	-	12	0.81	[0.66, 0.96]	16/20 (80%)
ACT only	30	-	30	-	0.75	[0.67, 0.82]	20/30 (67%)

Figure 10-1 shows the observed heart rate vs. the Wilkoff predicted heart rate achieved using during the modified CAEP tests performed at the chronic stage follow-up for the Diamond II patients in the analysis of the rate response objective.

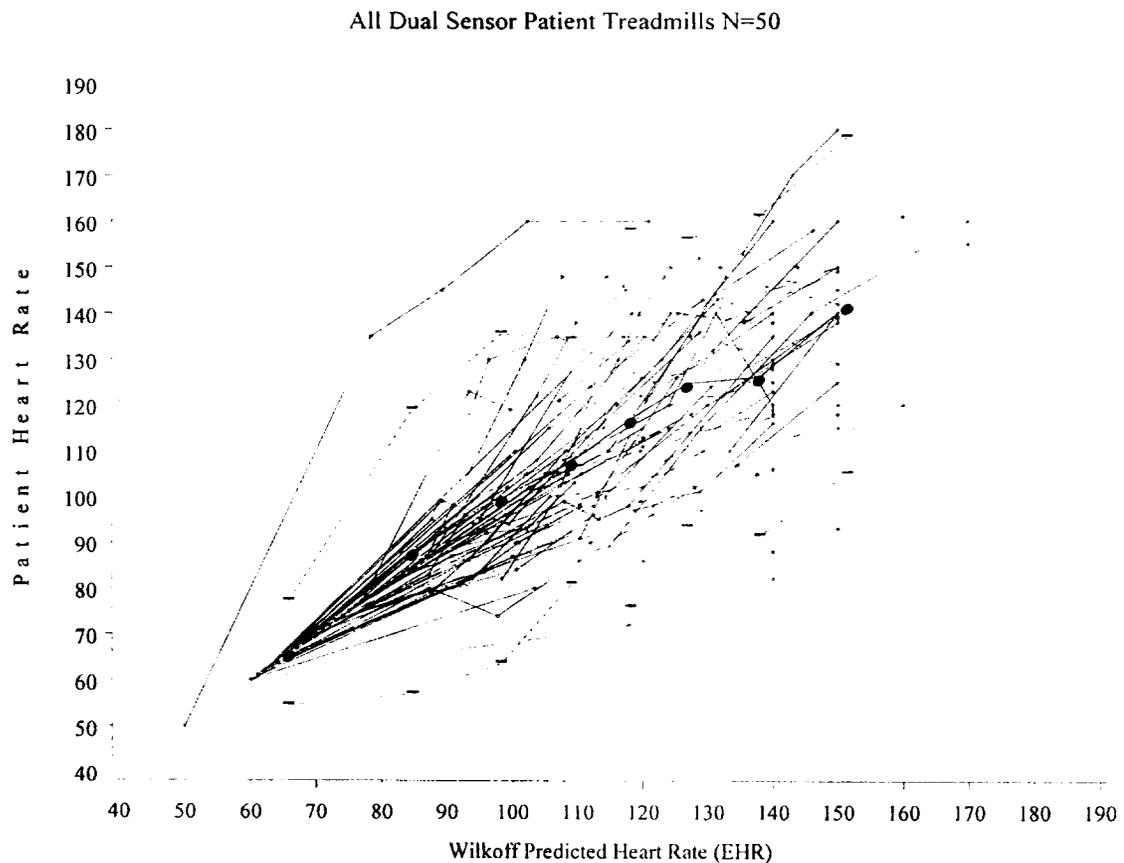


Figure 10-1: Heart Rate (HR) vs. Expected Heart Rate (Diamond II) – Individual Patient Results

Figure 10-2 through Figure 10-6 below, each show the rate response exercise data for one of the five available sensor blending settings: QT=ACT, QT<ACT, QT>ACT, QT Only, and Activity Only. Theoretically, those settings which have a larger contribution from the activity sensor (i.e., ACT only and QT<ACT) should show a more rapid increase in heart rate at the onset of exercise than those settings which have a larger contribution from the QT Sensor (i.e., QT Only and QT>ACT). However, this was not observed in the clinical study, where the clinical results for these settings are both qualitatively and statistically indistinguishable from each other (see Figure 10-2 through Figure 10-6). This may be due in part to the limited sample size available for the QT<ACT and QT>ACT settings.

However, when compared to the expected heart rate predicted by the Wilkoff model, the exercise data do demonstrate that all five settings provide an appropriate and proportional response to exercise.

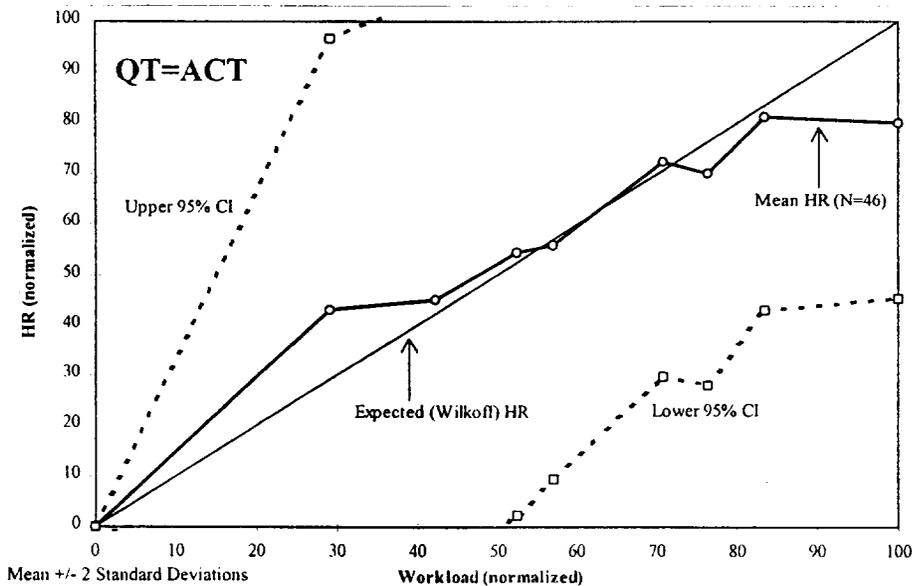


Figure 10-2: QT=ACT HR (Normalized) vs. Expected HR (Normalized)

Diamond II and Diamond I QT=ACT patients completing at least 6 minutes, N=46, HR at end of each stage (2 min), Expected (Wilkoff) rate, mean and 95% CI.

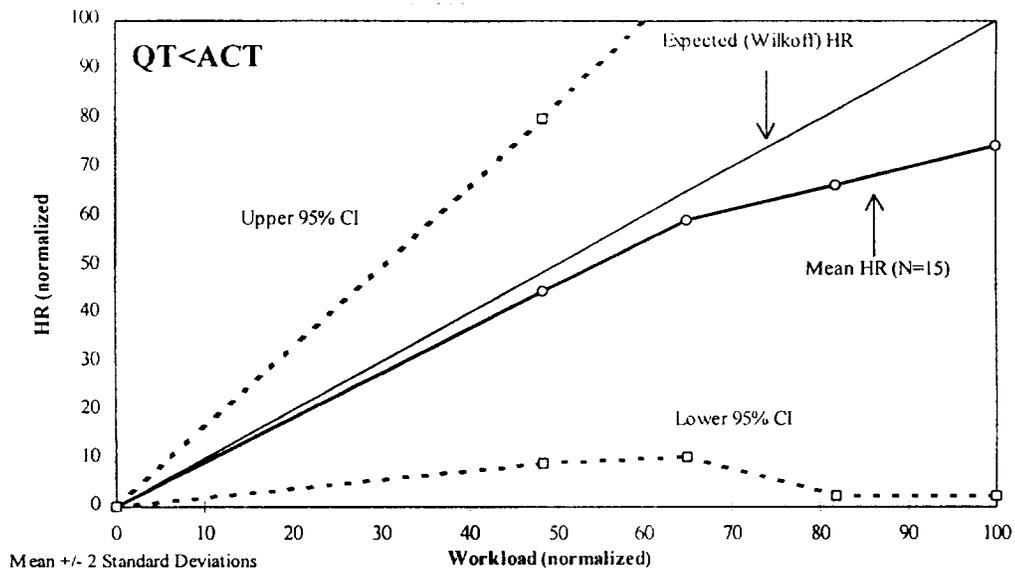


Figure 10-3: QT<ACT HR (Normalized) vs. Expected HR (Normalized)

Diamond II and Diamond I QT<ACT patients completing at least 6 minutes, N=15, HR at end of each stage (2 min), Expected (Wilkoﬀ) rate, mean and 95% CI.

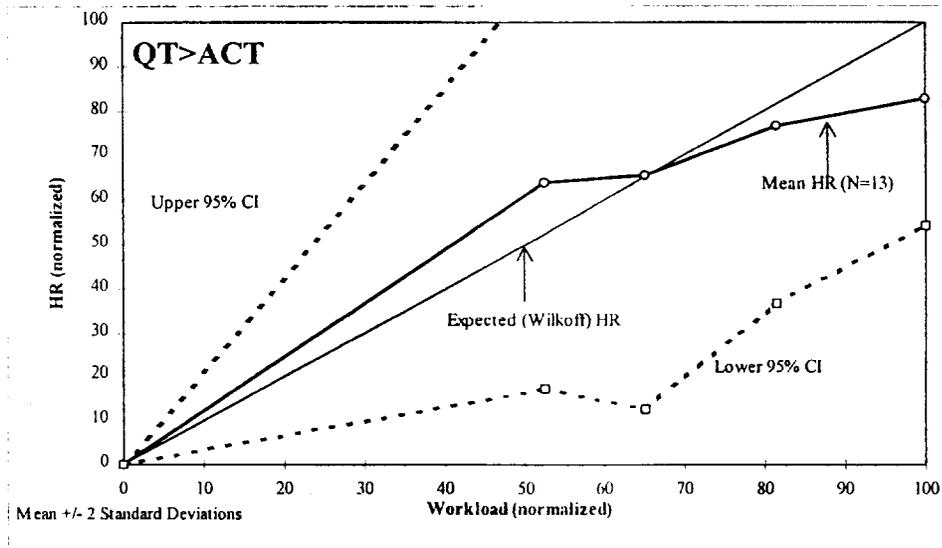


Figure 10-4: QT>ACT HR (Normalized) vs. Expected HR (Normalized)

Diamond I QT>ACT patients completing at least 6 minutes, N=13, HR at end of each stage (2 min), Expected (Wilkoﬀ) rate, mean and 95% CI.

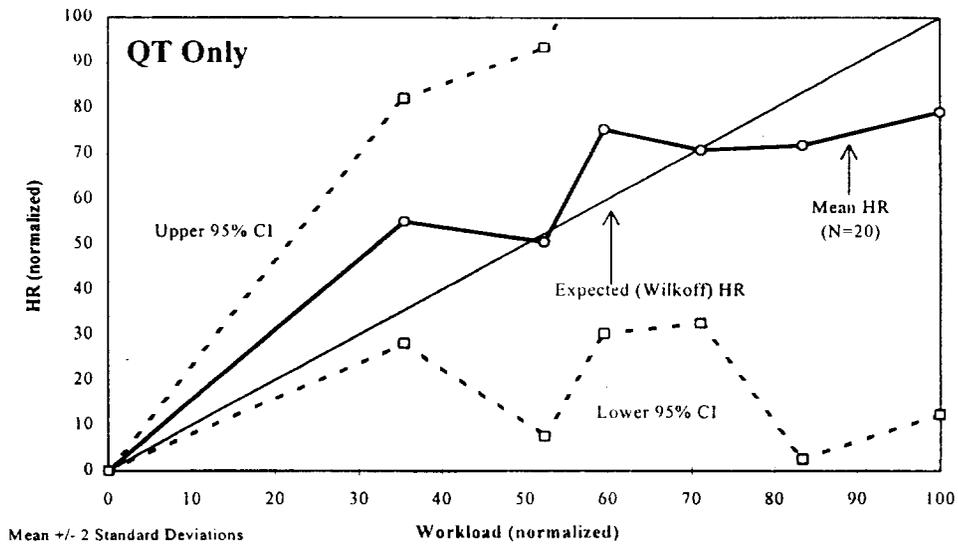


Figure 10-5: QT Only HR (Normalized) vs. Expected HR (Normalized)

Diamond II and Diamond I QT Only patients completing at least 6 minutes, N=20, HR at end of each stage (2 min), Expected (Wilkoff) rate, mean and 95% CI.

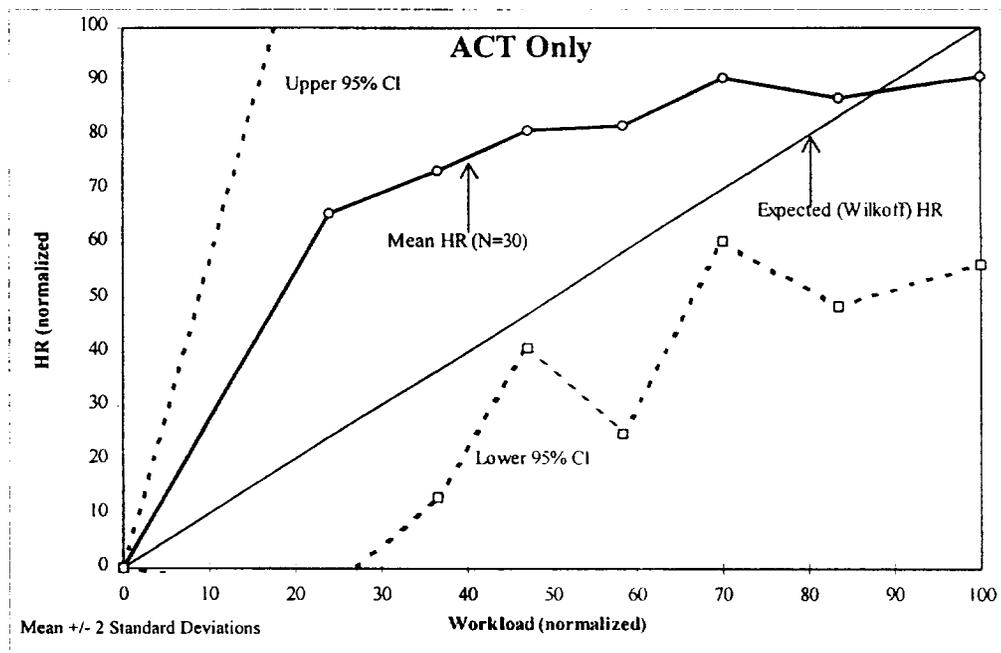


Figure 10-6: ACT Only HR (Normalized) vs. Expected HR (Normalized)

Diamond I ACT Only patients completing at least 6 minutes, N=30, HR at end of each stage (2 min), Expected (Wilkoff) rate, mean and 95% CI.

The ability of the rate response features of the Diamond II device to reach the maximum sensor rate met study objectives. The criteria for maximum observed heart rate required at least 75% of patients must reach within 20 bpm of the programmed MSR, with a lower 95% confidence bound of at least 55%. During the exercise test 38 of 51 (75%) achieved a rate within 20 bpm of the programmed MSR.

The performance of the Sensor Cross Checking feature was found to meet study objectives. The criteria stated that the mean difference in observed rates with dual sensor vs. ACT only must be positive. During the provocative test the mean normalized difference was found to be 0.70.

Table 10-3 provides the results from the maximal exercise testing and sensor cross checking primary objectives of the study.

**Table 10-3: Effectiveness Analysis –
Maximum Rate Response and Sensor Cross Checking**

Primary Objectives	Analysis Result	95% Confidence interval
Rate Response: Maximal Exercise Testing (N=51 patients)		
Percent of patients achieving a max. rate within 20 bpm of MSR	74.5% (38/51)	[60.4%, 85.7%]
Sensor Cross Checking dual sensor rate - rate in ACT normalized (N=103 patients)		
Mean Difference	0.70	[0.65, 0.75]

11. Conclusions Drawn from the Studies

The bench testing and clinical testing provide a reasonable assurance that the Diva Implantable Pulse Generators are safe and effective when used in accordance with their labeling.

12. Panel Recommendation

Pursuant to section 515(f) 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 panel for review and recommendation because the information in the PMA substantially duplicated information previously reviewed by this panel.

13. FDA Decision

The sponsor agreed in writing to the general “Conditions of Approval for Cardiac Pacemakers and Programmers.” There are no specific conditions of approval for this device.

FDA performed an inspection on November 6, 1998, and found the applicant in compliance with the Quality System Regulation (21 CFR Part 820).

CDRH issued an approval order for the stated indication for the applicant’s PMA, P990001, on SEP 27 1999.

14. Approval Specifications

Directions for Use: See Final Draft Labeling (Information for Use)

Hazards to Health from Use of the Device: See INDICATIONS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE EVENTS in the Final Draft Labeling (Information for Use).

Conditions of Approval: See Approval Order

P990001
Diva Platform Implantable Pulse Generators
and ProVit Application Software (Version 3.3.2)

- ◆ Diamond II Model 820 Pulse Generator