From: (b)(6) PDLB/DCD
To: Files P980049/S050 and P060027/S015
Subject: Paradym VR and DR ICDs with Smartview Programmer Software Version 2.18UG1, Modifications to the Paradym CRT-D Model 8750 and Labeling and Programmer Software Modifications to the Ovatio VR Model 6250, DR Model 6550 and Ovatio CRT-D Model 6750
Date: March 29, 2010
Office: DCD/ODE

The manufacturer Sorin/ELA Medical is seeking approval for the Paradym VR Model 8250 and the Paradym DR Model 8550. In addition, approval is being sought for minor hardware and manufacturing process changes to the Paradym CRT-D Model 8750 (as they pertain to the VR and DR models) and labeling and programmer software changes to the Ovatio Models. The bundled files, as referenced, also pose the question about whether an inspection of the Saluggia plant for the manufacture of the VR and DR models will be necessary. An overview of the files and our recommendation which takes into account the review from the Lead Reviewer, (b)(6) and consulting reviews ((b)(6) - Software, (b)(6) - Qualification testing (components, battery and capacitors), (b)(6) – Manufacturing, OC and (b)(6) Sterilization are included below.

Overview of the File

Background

The design of the Paradym VR and DR models is similar the Paradym CRT-D Model 8750 approved under P060027/S011. The Paradym ICD family was the subject of a Pre-IDE discussion under (b)(4) ((b)(6) was the Lead Reviewer for the Pre-IDE).

Indications for Use

The Paradym VR and DR devices are indicated for use in patients who are at high risk of sudden cardiac death and who have survived at least one episode of cardiac arrest due to ventricular tachyarrhythmias and have recurrent, poorly tolerated sustained ventricular tachycardia (VT).

Description of the Device

The Paradym VR and DR models are respectively single and dual chamber ICDs. The devices also include an accelerometer for pacing according to the patient's activity. The VR and DR devices are based on the market approved Ovatio VR and DR devices approved under P980049/S020 and the Paradym CRT-D Model 8750 approved under P060027/S011.

The Paradym devices are similar to the Ovatio devices in that the electronics and implant software are identical for all Paradym models (VR/DR, CRT and SonR). The

programming software of the devices is different in that it provides access to device-specific functions.

The manufacturer provided a comparison of the electronic architecture (block diagram) of the Ovatio and Paradym devices. The components in the Ovatio were compared to the corresponding components in the Paradym VR and DR models

The main changes in the electronic circuitry from the Ovatio VR/DR to the Paradym VR/DR are as follows:

Ovatio		Paradym
Low voltage hybrid	to	Low voltage hybrid module
(b)(4) and (b)(4)		(b)(4) circuit
(b)(4) and (b)(4) integrated circuit		(b)(4) integrated circuit
(b)(4) Hybrid module		(b)(4) Hybrid module
Prot 6 Hybrid module		Prot7 Hybrid module
(b)(4) circuits		(b)(4) circuit

Like the Paradym CRT-D, the DR/VR devices have two hybrids, one Prot module and one flex-rigid circuit (Please note that the changes/modifications in the Paradym CRT-D described below are also applicable to the Paradym VR and DR).
The modules can be described with a comparison to the Ovatio VR/DR devices in parentheses as follows:

- Low voltage hybrid includes the active circuits - (b)(4) (b)(4) (b)(4) and all their peripheral components (changed from Ovatio active circuits included on the low voltage hybrid are (b)(4) (b)(4) (b)(4) and the (b)(4) (b)(4))
- (b)(4) includes all components involved in connecting the three shock electrodes to the high voltage capacitors, (b)(4) (b)(4) and (b)(4) (b)(4) (mounted on (b)(4) (b)(4) and were moved to the (b)(4) (b)(4) (b)(4))
- Prot7 hybrid – protection of low voltage channels (Ovatio components for protection of the low voltage channels are on Pro6)
- (b)(4) (b)(4) – these circuits handle all electrical interconnections
- Between hybrids and other components; low voltage and (b)(4) (b)(4) are mounted on a (b)(4) (b)(4), also the components of the high voltage charger are also mounted on the (b)(4) (b)(4) ((b)(4) (b)(4) circuits in Ovatio)

The manufacturer also provided a layout of the components on the hybrid modules of the Ovatio devices and the Paradym devices for our review. The changes (new and/or modified) in the Paradym devices from the approved Ovatio devices and the impact on device (Paradym) operation are further discussed below and include the following:

Low Voltage and Protection Hybrid Circuit

Low voltage circuit - electrical interconnection and mechanical support for low voltage ICs and discrete components, (electrical connection to implement all functions already present in Ovatio VR/DR, impact on device operation - add bipolar LV pacing

(b)(4) – IC for performing analog and digital core functions - modified since Pre-IDE, impact on device operation – new (b)(4) function, not activated in Paradym VR/DR

(b)(4) – interface of core IC with external components, high voltage protection, control of shock capacitor charging, discharging and shock delivery and pacing output voltage management, impact on device operation – add bipolar pacing MV sensor and new electrogram configurations

(b)(4) – store on-board Holter data and software and new wafer fabrication, impact on device operation – more stored events in on-board Holter

(b)(4) - used for coupling an EGM sensing amplifier to the device case, ventricular shock electrode, SVC shock electrode and LV electrode, (same types used on Ovatio), impact on device operation – provides measurements of EGM using device case, shock electrodes and LV electrode which is not available in Ovatio devices

(b)(4) – (b)(4) for holding a test pin at a voltage that prevents activation except during test, impact on device operation – none, test pin operates only during production testing

(b)(4) – (b)(4) for applying start-up current to (b)(4), impact on device operation – none, startup occurs during production testing

(b)(4) and (b)(4) switch used to provide regulated supply voltage) - impact - modification of programmed settings for pacing output voltages in atrium and ventricles

(b)(4) and (b)(4) produces a supply voltage for optocouplers that drive high side switches for shock delivery, impact – none

(b)(4) and (b)(4) used in voltage divider for measuring stored voltage on shock capacitors, impact- higher energy shocks available – modified since Pre-IDE

(b)(4)

(b)(4)

bipolar transistors used to generate a (b)(4) supply to drive low side shock generator switches and the shock capacitor charging transistor, impact – none

Shock Hybrid Circuit

(b)(4) electrical connection and mechanical support for (b)(4) (b)(4) and passive components, has switches to deliver shocks or discharge the shock capacitors internally, impact – none

Protection (low voltage hybrid) – limits current from electrodes to the (b)(4) during internal or external shocks, impact on device operation – electrogram available using shock electrodes and LV electrodes

(b)(4) and (b)(4) used in the driver circuit for the transistor that charges shock capacitors, impact – none

(b)(4)

(b)(4) with (b)(4) and rigid sections used for interconnection of hybrid circuits, discrete components, battery and feedthroughs. The rigid parts consist of (b)(4) (In (b)(4) is included with the (b)(4) the (b)(4) support is removed, and the material of the (b)(4) is changed - improved robustness to temperature during manufacturing). Impact – none

Transformer – charges shock capacitors from the battery (modified construction) impact – none

(b)(4) used to measure primary current in transformer used to charge shock capacitors to determine time at which to terminate charging phase, impact on device operation - none

(b)(4) – removed with the introduction of new (b)(4) impact on device operation - new component (b)(4) on the accelerometer sensor, modified since last Pre-IDE

Mechanical Components

Battery – QHR chemistry rather than LiSVO in Ovatio, new reforming schedule that cannot be modified by the physician, impact – improved longevity

Shock capacitors – (b)(4) used in series to provide adequate shock voltage, increased stored energy, same capacitance as Ovatio VR/DR/CRT-D, impact – high energy shocks

Feedthrough – provides electrical connections through the ICD (b)(4) instead of (b)(4) in Ovatio, impact – added LV bipolar functions

(b)(4) (b)(4) – provides containment and mounting for ICD components, impact – none

(b)(4) (b)(4) provides a means to identify manufacturer, noninvasively and without a programmer, impact- none

The new or modified components of the Paradym models presented little or no impact on device operation. The components in most instances supported improved performance which was verified in the tests as described below.

Design Verification/Qualification Tests

Component verification tests were performed to verify the modifications as mentioned above. The SonR version which has the full set of device functions was used during the qualification tests. The manufacturer used international standards to guide the design and testing of the Paradym models. The bench tests (design verification/qualification) consisted of component, subassembly and finished device tests. The tests consisted of electrical, mechanical, environmental, burn-in/life testing, labeling verification, microbiological, biocompatibility and/or functional testing. In addition, software validation was used when measurements involved implant/programmer software.

The design verification tests encompassed a series of tests which can be described as follows:

Defibrillator protection (EMI, and induced currents)
Measurement of brady arrhythmia characteristics (tests in DDD and VVI modes)
Measurement of pulse amplitude and duration AA and VV pulse interval, atrial and ventricular basic rate, sensitivity thresholds, input impedance, Escape interval, refractory periods, A-V intervals after pacing and sensing, VV delay after ventricular pacing and anti-tachyarrhythmia pacing pulse amplitude.
Sensing with automatic sensitivity control
Measurement of biventricular pacing in DDD mode (unavailable in Paradym VR/DR)
Verification during pacing into short circuit and shock on low impedance, internal defibrillation, AC/DC leakage current, post pace and post shock recovery, life testing and temperature increase
Measurement of shock characteristics and charging time
Battery qualification, including measurement of current consumption (b)(4) (b)(4)
Evaluation of inductive telemetry performance (performed on finished devices with loaded implant software)
Electrical and mechanical integrity testing on the connectors/header/feedthroughs (qualification of wiring, VR/DR, CRT, SonR)
Validation/qualification of the (b)(4) (b)(4) (environmental, electrical and mechanical stress testing)
Qualification of transformers, antenna, (b)(4) (b)(4) and high voltage capacitors

Tests (environmental, mechanical and biocompatibility) on unpackaged and/or packaged device before implantation, biocompatibility tests are referenced below

A description of the test protocol and the results of testing were provided for our review. The results for the above reported tests demonstrated compliance to specifications; in all cases, the acceptance criteria were met. All tests were passed.

Software Qualification/Verification

The software version, (b)(4) named in the referenced files is embedded software in RAM for the Paradym devices. (b)(4) is the same version as in the Paradym CRT-D.

The software (implant and programmer) or feature changes in Paradym VR as compared to Ovatio VR device include the following:

Maximum shock energy- in Paradym max stored energy = 42 J and in Ovatio 34 J
Brady lead impedance measurement – in Paradym available in automatic and manual measurements; in Ovatio only manual measurement
Coil impedance measurement – in Paradym automatic and manual measurements; in Ovatio manual only
Threshold test – in Paradym max programmable pacing rate for the test is (b)(4) bpm; in Ovatio (b)(4) bpm
Third EGM channel added in Paradym, not available in Ovatio
Mixed telemetry during EPS - increased telemetry robustness during high voltage charge, not available in Ovatio
Memories: EGM V and markers storage on technical and clinical events - not available in Ovatio
Battery consumption measurement – in Paradym the current consumption measurement is performed permanently between follow-ups, an over-consumption measurement is also performed every 6 hours; in Ovatio the measurement can be activated once using the programmer
Magnet test – in Paradym test performed at (b)(4), in Ovatio (b)(4)
Battery reforming – in Paradym, battery reforming periods set to a fixed value of 6 months; in Ovatio depends on the measurement results
Automatic capacitor discharge – in Paradym after a shock capacitor charging, after a programmable delay, the device automatically launches a capacitor discharge if the patient rhythm has returned to a slow rate; in Ovatio automatic discharge launched only after a battery reforming
Software stored in a protected (b)(4)- not available in Ovatio

Features, e.g., atrial arrhythmia prevention, ventricular tachyarrhythmias prevention locked out in the Paradym CRT-D are also locked out in the Paradym VR/DR models

Feature changes in the Paradym DR as compared to the Ovatio DR are as follows:

Atrial pacing on (b)(4)- in Paradym atrial pacing on (b)(4) only; in Ovatio pacing on (b)(4) and (b)(4)

PhD feature based on (b)(4) and (b)(4) sensors and Automatic adjustment of ATP between follow-ups locked out by programmer in Paradym DR; not available in Ovatio
Other features, e.g., max shock energy, brady lead and coil impedance measurements, threshold tests, 3rd EGM channel mixed telemetry during EPS, Memories, battery consumption measurement, magnet test, battery reforming, are identical in the Paradym DR to those mentioned above for the Paradym VR versus the Ovatio VR

Features locked out in the Paradym CRT-D are also unavailable in the VR/DR models.

Software qualification/validation will be addressed below as per the software consultant's review.

Manufacturing

According to the manufacturer, the Paradym hybrid modules are manufactured in the same way for each Paradym model (VR, DR, CRT-D, Son-R). The final assembly, packaging and sterilization are performed at the Sorin plant in Saluggia, Italy instead of in the ELA plant in France. The manufacturer described the changes to the manufacturing processes which affected the ParadymVR/DR models and the Paradym Model 8750. These changes were reviewed by the OC consulting reviewer and will be discussed below.

Biocompatibility and Sterilization and Packaging

All materials used in the Paradym models are identical to those in the ELA marketed devices. The sterilization cycle of the Paradym devices was changed from ETO at (b)(4) (b)(4) during (b)(4) min to ETO at (b)(4) during (b)(4) min. The manufacturer provided adequate qualification of the change and stated that the only risk associated with the sterilization changes (which do not alter the chemistry of the polymers) is a potential contamination of the device with chemical substances introduced because of the different manufacturing processes. To mitigate the risk, cytotoxicity, irritation, sensitization, acute systemic toxicity, Ames test and pyrogenicity according to applicable ISO10993 and 21 CFR Standards were performed. The results of testing demonstrated compliance with ISO 10993-7 requirements. The Lead Reviewer spoke to (b)(6) (b)(6) about the sterilization change. (b)(6) emphasized that we should ask about the version of ISO 10993-7 used and note upcoming requirements.

Packaging of the Paradym VR/DR devices is identical to those of the marketed Ovatio VR and DR. The inside shape of the packaging was modified to take into account the slightly different shape of the Paradym VR/DR as compared to the Ovatio VR/DR.

Clinical Study

The manufacturer provided a copy of the investigational plan, case report forms and guidelines for monitoring and reporting adverse events which were used in their OUS study (b)(4). This CE study gathered data on the performance of the Paradym models (CRT 8750 and DR 8550) to provide support for the proper functioning of the devices (Paradym 8750 is approved for marketing in the U.S. and the (b)(4) is currently under IDE). The study results can be summarized as follows:

- Primary safety objective – report the number patients free from unanticipated adverse device effects at one month post implantation

- Secondary objectives: safety - report the incidence of other types of adverse events and effectiveness - document the global performance of the device, report the defibrillation therapy efficacy; report electrical and sensing performances; describe the performances of the pacing lead monitoring function; and document the quality of the new programming system.

- The clinical evaluation of the devices was based on the analysis of 24-hour Holter recordings during hospitalization and data collected during pre-discharge and one month.

- (b)(4) patients were implanted with the Paradym (CRT - 108 and DR - 33).

- Mean follow-up was (b)(4) days (b)(4)

The manufacturer concluded the following:

- No unexpected serious adverse events were observed during the clinical evaluation.

- No software anomalies were observed; the device functioned according to specifications.

- The sensing/pacing and defibrillation features operated appropriately.

Overall, the study results reported that the devices operated according to specifications. There are no concerns regarding the clinical data that were presented. Since the Paradym CRT-D model approved under P060027/S011 had a clinical consult, no clinical consult was necessary for the Paradym VR/DR models (Changes were primarily software and hardware). There were no significant clinical concerns regarding the VR/DR models which could impact device performance/patient safety.

Consulting Reviews

Software

The consulting reviewer concluded that the sponsor "…provided appropriate documentation of the software changes made in support of the application." The Lead Reviewer concurs with the conclusion. The consultant noted that an English translation was needed for data provided in Attachment SW-53. The Lead Reviewer requested the translation and it was provided for the consultant's review. The consultant reviewed the translated data and had no additional questions. No concerns about the consultant's review.

Qualification Testing/ Battery and Capacitors

The consulting reviewer reviewed the qualification testing on the battery and components. The results of testing demonstrated conformance to standards and all tests were passed. The reviewer had clarifications/questions about the battery and energy delivered. In a conversation with the reviewer, he acknowledged that there were no concerns about the component/subassembly qualification testing and stated that he could not locate the qualification testing on the high voltage capacitors. Therefore, we requested that the manufacturer specifically identify where these test data are located in the file. The Lead Reviewer had no additional concerns about the component/subassembly testing.

Manufacturing

The consulting reviewer inquired about the design and manufacturing changes reported in the referenced file and the manufacturer responded. Based on the review of these data and previous reviews of P060027/S011, the consulting reviewer concluded that the manufacturing changes were basically minor changes to the procedures and flowcharts. The reviewer also concluded that since these changes were not significant and do not affect a site change, then no further review of the procedures would be necessary. The Lead Reviewer has no concerns regarding the consultant's conclusions.

Paradym CRT-D Labeling

The manufacturer made the requested modifications to the labeling in P060027/S011. The requests addressed primarily the remaining software anomalies and the plan regarding when the anomalies would be fixed.

Labeling Changes to the Ovatio Devices

The manufacturer is requesting to include the approved change in the automatic sensitivity control algorithm in the device labeling. The implant and online manuals have been updated to include the description of the algorithm. The change was somehow inadvertently omitted from the labeling post approval. No concerns about the lableing.

Device Labeling (Paradym VR/DR)

Copies of the device labeling for the Paradym CRT-D, VR and DR models were provided for our review. The labeling appears to be in order with no immediate concerns.

Recommendation

There are no significant concerns about the device testing/qualification for the Paradym VR/DR devices. The qualification testing consultant had questions about battery longevity, energy delivery and location of the capacitor qualification testing. In addition, clarification regarding the IS0 10993-7 version used for the verification of the sterilization change was requested by the consultant reviewer. Due to Office of Compliance unsettled concerns, we issued an approvable letter pending GMP issues.

The responses to the deficiencies noted in the AGMP letter were reviewed by the Lead Reviewer and the consulting reviewer and were deemed acceptable.

In response to our AGMP letter dated March 16, 2010, the manufacturer, Sorin/ELA Medical Inc., referenced information provided to the Office of Compliance dated February 23, 2010. This information requested that the Paradym VR and DR models as submitted in the referenced files, should not be withheld based on warning letters issued to the manufacturer following inspections of the facilities in Italy and France. The manufacturer especially noted that the Italian facility where the Paradym VR/DR will be manufactured received inspectional observations which were characterized by the Agency "…as not warranting regulatory followup at the time the warning letter was issued." The Office of Compliance reviewed the justification for not withholding the Paradym VR/DR models as submitted in the referenced PMA supplements. OC had no concerns and stated (in an e-mail) that the supplements can be approved and do not require a GMP hold.

There are no pending concerns regarding the referenced files.

Approval is recommended for the referenced supplements.