Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation

DATE: November 22, 2010

TO: File

CC: (b) (6) (Consultant Reviewer, Clinical)
Mitchell Shein (Branch Chief)

FROM: (b) (6) (Lead Reviewer)

SUBJECT: P950037 / S083, P000009 / S040, P050023 / S033, P070008 / S017
180-Day PMA Supplement
Biotronik – Atrial Capture Control and Ventricular Pacing Supression (Evia & Entovis)

OVERALL RECOMMENDATION

Based on my review of the submission text, discussions with supporting reviewers, interactions with the sponsor prior to and during the meeting, as well as my review and approval of the meeting minutes, **I recommend approval of the submission**.

Signature	*Date*	*Signature*	*Date*
(b) (6)		Mitchell Shein	
Scientific Reviewer		Branch Chief	
(Lead Reviewer)		(Management Oversight)	

PURPOSE OF SUBMISSION

The purpose of the submission is to request approval of the Atrial Capture Control (ACC) and Ventricular Pace Suppression (Vp Suppression) features in the Evia and Entovis families of pacemakers.

The Evia and Entovis families of pulse generators were reviewed and approved as part of P950037/S72. As part of that interactive review, FDA determined that the submission lacked the necessary clinical data to support the performance of the ACC and Vp Suppression features. Therefore, the company decided to lock out these features, which allowed FDA to complete the review process. The company locked out these features by eliminating the capability of selecting these features within the software application, thereby removing programmability of these features. The company planned to collect and summarize additional clinical data regarding these features and to submit another PMA supplement to request approval of the features.

This submission was bundled and affected 4 files: P950037 / S083, P000009 / S040. P050023 / S033, and P070008 / S017.

CONSULTANT REVIEWS

This submission included clinical data in order to support the safety and effectiveness of the ACC and Vp Supression features. (b) (6) previously reviewed these features as part of the review of P950037 / S072. Therefore, (b) (6) was consulted to review this submission too. (b) and I met to discuss

the file, discussed our concerns with the submission in teleconference calls with the company, and provided written feedback to the company in order to clarify our concerns. (b) (6) also provided written consult memos, both following his initial review and then at the end of the review process after the sponsor had addressed our concerns.

DEVICE DESCRIPTION

FDA previously reviewed and approved the Evia / Entovis families of pacemakers. The only change to these products is the introduction of the Atrial Capture Control (ACC) and Ventricular Pace Suppression (Vp Suppression) features. These features are described in detail within the submission. The following text was provided by the company and revised to convey the key concepts of the features.

Atrial Capture Control (ACC)

Automatic threshold monitoring in the atrium and pacing output adjustment has been clinically used with other manufacturers' legally marketed devices for several years. Evia family of pulse generators will incorporate the Atrial Capture Control (ACC) feature. BIOTRONIK's ACC feature is similar to our previously approved Automatic Capture Control feature (for the right ventricle) that is available in Philos II and Cylos families of pulse generators (P950037/S36, dated March 31, 2004 and P950037/S41, dated December 21, 2005, respectively). To avoid confusion, Automatic Capture Control is being renamed Ventricular Capture Control (VCC) for the Evia family of pulse generators.

Atrial Capture Control will be available in all dual chamber Evia devices that provide atrial pacing. ACC provides a regular measurement of atrial stimulation threshold and provides the option of adjusting the stimulation amplitude based on the measured capture threshold. Furthermore, the algorithm is based on paced/sensed events, and not evoked response. Atrial Capture Control is performed in four steps when the feature is programmed to the ON setting.

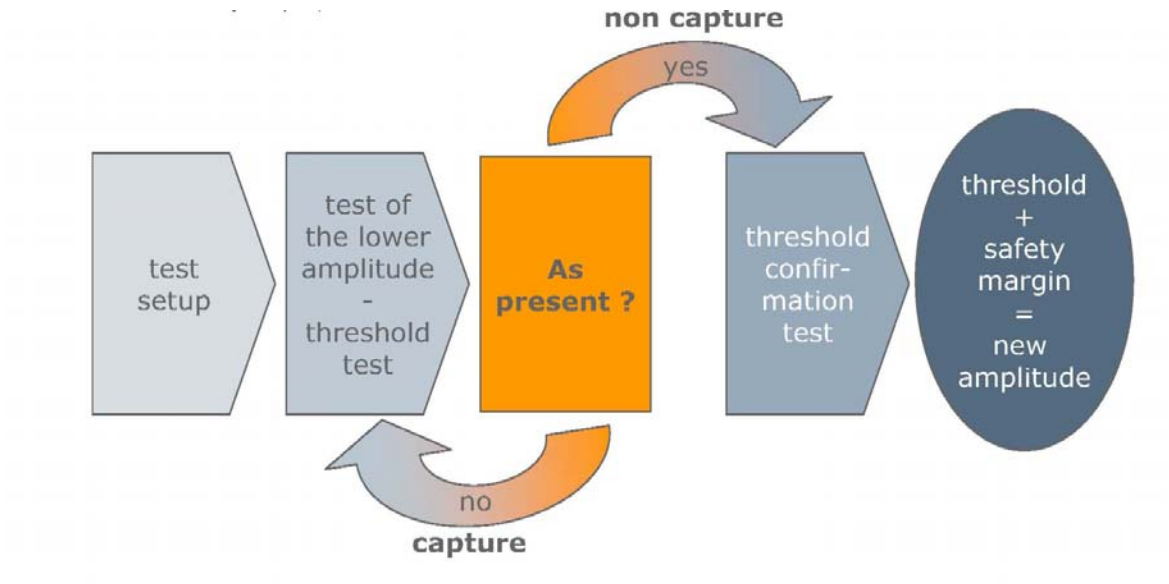
1. **Setup Phase:** The device monitors the rate and rhythm condition and determines the actual rate in the atrium immediately before it starts the threshold search. Automatic measurements are only allowed if the atrial and ventricular rates are below 110 ppm and mode-switching is not currently active. If these conditions are met, the activation of the capture control algorithm causes a mode switch to DDI. The AV delay is set to 50 ms, to avoid retrograde conduction from the ventricle in the atrium during the measurements.
2. **Threshold Search:** The pacing rate is set to 20% + the measured rate. The threshold is determined by decreasing the amplitude stepwise at the programmed pulse duration until loss of capture occurs. No atrial intrinsic events or retrograde conducted events will occur if the pacemaker delivers successful atrial paces. Loss of capture for one test amplitude is declared if in a test window of five cardiac cycles (5 Ap-Vp intervals) two or more intrinsic atrial events are sensed. During the initial search, the pacing amplitude is decreased by 0.6 V steps, starting at the programmed value (e.g. 3.6 V). Below 0.6 V, the search switches to 0.1 V steps. After the first loss of capture, the device will go back to the last captured amplitude and decrease the test amplitude in steps of 0.1 V until it detects the next loss of capture. After this detection, the device declares the end of the threshold search.

   The algorithm is designed using this methodology because a single sensed event during the 5 test-cycle could be a premature atrial contraction (PAC) and therefore would not necessarily indicate loss of atrial capture.
3. **Confirmation Phase:** In the final phase, the initially determined threshold will be confirmed by pacing one test window, consisting of 5 Ap-Vp intervals, at +0.3 V of the measured pacing threshold and one test cycle, consisting of 5 Ap-Vp intervals, at -0.3 V of the measured pacing threshold. The pacing threshold is considered to be confirmed if capture is determined during the first step and loss of capture is confirmed during the second test. Otherwise, the atrial threshold search is considered to be failed, and in this case, the device paces with the amplitude valid at the start of threshold measurement which is user programmable.

4. **Amplitude Adjustment:** With the ACC feature switched on, the pacemaker automatically adjusts the atrial pacing amplitude by adding the programmed safety margin to the measured threshold and returns all other programmed settings back to the previously programmed values.

The figure below provides a visual representation of the feature.

Figure 1: Atrial Capture Control



The table below shows the programmability of the ACC feature.

Table 1: Programmable Parameters of Atrial Capture Control

Parameter	Range	Standard Value
Atrial Capture Control	ON, OFF, ATM (monitoring only)	ON
Minimum Amplitude	0.5…(0.1)…4.8 V	1.0 V
Threshold Start	2.4, 3.0; 3.6; 4.2; 4.8 V	3.0 V
Safety Margin	0.5…(0.1)…1.2 V	1.0 V
Search Scheduling	Interval or Time of Day	Time of Day
Interval	0.1; 0.3; 1; 3; 6; 12; 24 h	24 h
Time of Day	User programmable (10 min increments)	2:00 am

The default mode for the Atrial Capture Control feature is ON. The Active Threshold Monitoring (ATM) mode is a monitoring mode for logging changes in the atrial pacing threshold in the diagnostics. The pacing amplitude remains set to its programmed value and is not adjusted when set to the ATM mode. The ATM mode is used by physicians who want to observe chronic threshold changes without actually programming pulse amplitudes based on the measurements. The atrial threshold trend can provide the clinical user with important information about the status of the interface between the pacing lead and the heart tissue.

BIOTRONIK's ACC feature is comparable to Medtronic's Atrial Capture Management (ACM) which is available in their Adapta pulse generators (P980035, dated July 17, 2006). Both ACC and ACM are based on monitoring the timing of intrinsic events. Similar to Evia, ACM only works in dual-chamber mode when the Mode Switching process is inactive. For ACM to become active the stimulation atrial rate must be below 90 ppm or the sensed rate must be below 87 bpm. Atrial Capture Management (ACM)

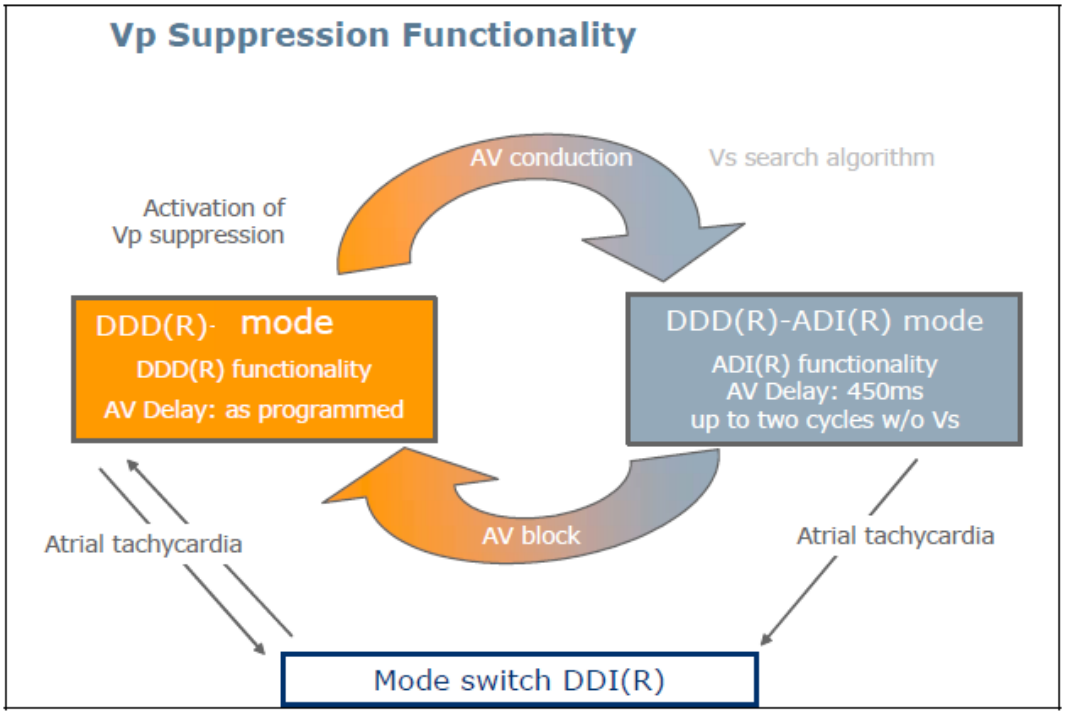
observes the timing of sensed events (not evoked response) to evaluate capture. Both algorithms establish a rate of stimulation for the atrium that is faster than the intrinsic rate, and then gradually decrement the atrial stimulation output. When atrial intrinsic events are observed, this signals that the pacing stimulus is no longer capturing the atrium, and loss of capture is declared. Both algorithms continue testing and adapting the atrial stimulation output to confirm the threshold.

Ventricular Pacing Suppression (Vp Suppression)

Evia will also offer a Ventricular Pace Suppression (Vp Suppression) feature. Dual chamber pacemakers are often implanted in patients with Sick Sinus Syndrome (SSS). Although such patients often have intact AV conduction or 1st degree AV block, the device is often programmed to the DDD(R) mode with factory AV delay setting, which is more suitable to third degree AV block patients. Therefore, many patients are unnecessarily paced in the ventricle. Unnecessary ventricular pacing is avoided by promoting intrinsic conduction through the Vp Suppression feature.

The Vp Suppression feature provides continuous beat-to-beat monitoring of the patient's AV conduction. This feature will provide an automatic switching between ADI(R) mode (i.e., sensing in both chambers, but pacing only in the atrium) and DDD(R) mode depending on the patient's AV conduction condition (as shown below). In the event of disturbed AV conduction, the device will switch to DDD(R) to support pacing in both chambers.

Figure 2: Functional Description of the Vp Suppression Algorithm

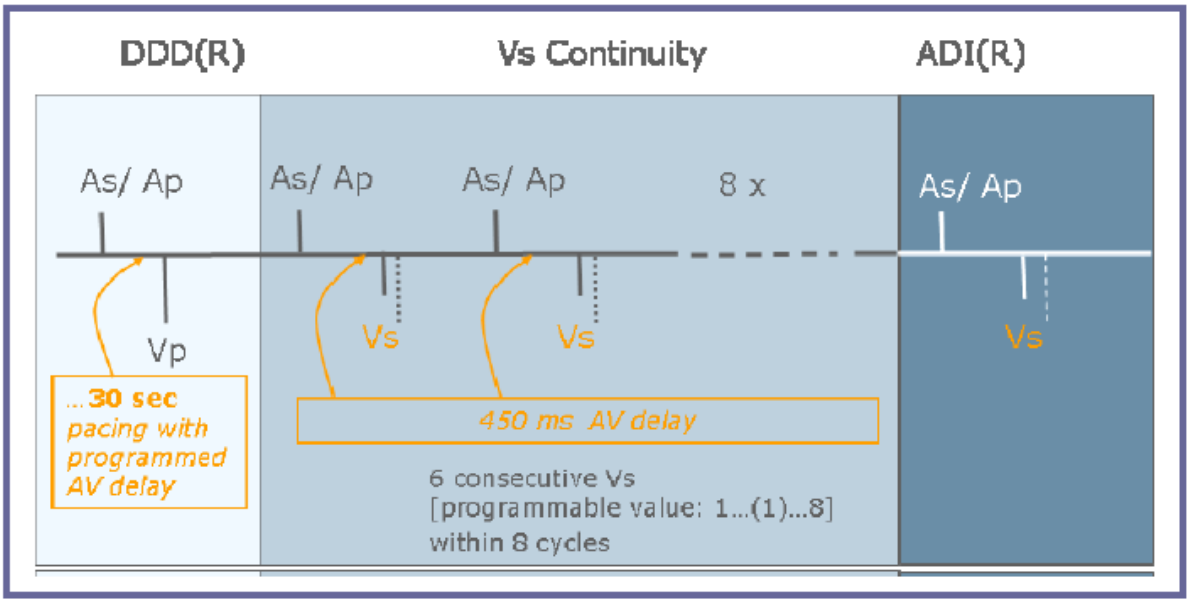


The primary modes while Vp Suppression is activated is DDD(R) mode, providing ventricular pacing at the programmed AV delay, or ADI(R) mode, promoting intrinsic AV conduction. This algorithm promotes AV conduction by limiting pacing in the ventricle to times when intrinsic conduction becomes unstable or disappears. Automatic switching capabilities between those two states promote the intrinsic conduction as much as possible without affecting the patient's pacing/intrinsic heart rate.

The Vp Suppression algorithm utilizes scheduled V_s searching tests (currently used with the FDA approved AV Delay Search Hysteresis feature) to look for intrinsic conduction using an extended AV delay of 450 ms. In order to protect the patient from high ventricular rates, the feature provides Mode Switching independent of the present state of the algorithm. When Vp Suppression is activated, the device starts in the DDD(R) state and looks for intrinsic conduction by starting a Vs-search. Following any suspension (e.g. Mode Switch), the Vp Suppression feature will resume in DDD(R) state. The feature provides user programmability of the switching criteria in order to adjust the response of the algorithm in supporting intrinsic conduction.

1. **DDD (R) Ventricular Pacing State *DDD(R)***: Enabling Vp Suppression will start the algorithm in DDD(R) state which provides ventricular pacing at the end of the AV delay. In the cases where there is no intrinsic ventricular detection for 30 seconds or when triggered by a single intrinsic ventricular detection within the AV delay, the algorithm performs a Vs-searching test (as shown below).

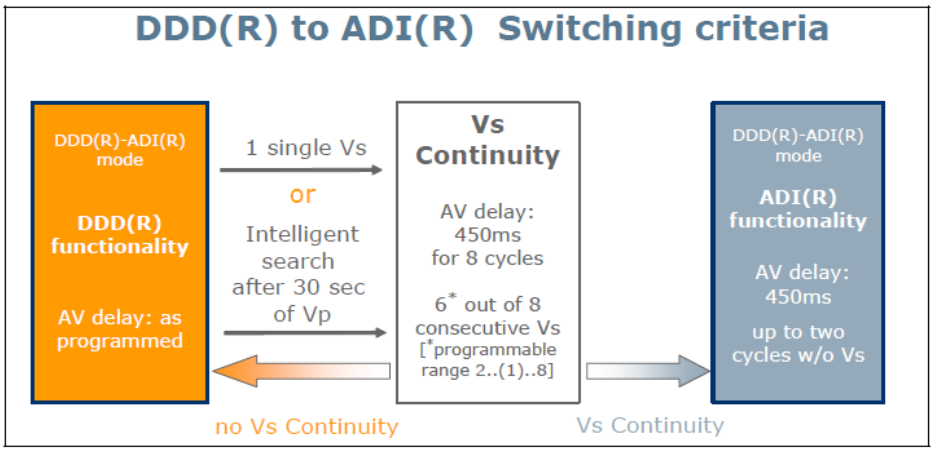
Figure 3: Search Initiated by Time (minimum time of 30 seconds)



2. **Ventricular Pacing Suppression State *ADI(R)*:** In ADI(R) state the intrinsic AV conduction will be promoted, no ventricular pacing will be delivered but the AV conduction is monitored. This reflects the behavior of an ADI(R) mode. The intrinsic conduction is monitored and evaluated on a beat-to-beat basis in the time frame of 450 ms after each atrial event. Monitoring the occurrence of intrinsic detections within these 450 ms provides information about the availability and occurrence of AV conduction. If the AV conduction is not present or unstable, then the algorithms switches to DDD(R) state providing ventricular pacing. One cycle without an intrinsic ventricular event within the 450 ms triggers 8 repetitive cycles during which the following switching criteria are checked:
    - 2 consecutive cycles without Vs or
    - user programmable number X of 8 cycles without Vs, or
    - no Vs for 2 seconds or more.

    As soon as one of the above criteria is met, the algorithm switches to the DDD(R) state in order to support the heart with ventricular pacing as shown below.

Figure 4: Switching Criteria for DDD(R) to ADI (R)

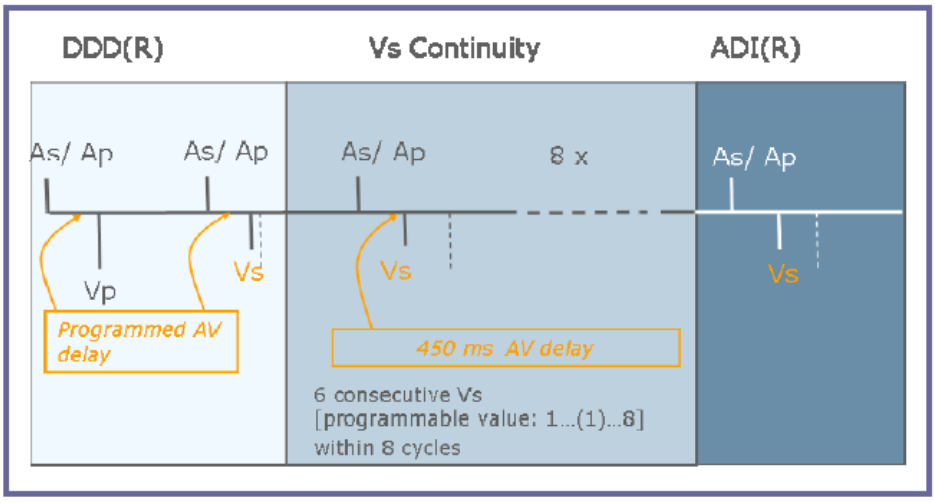


3. **Vs-Searching Test (Vs Continuity):** This test will be performed only in the DDD(R) state. During the Vs-searching test, the AV delay is programmed to 450 ms to unmask any potential intrinsic conduction within this time window. Starting in the DDD(R) state, the 1st Vs-searching test will be performed after 30 seconds (Vp-Vp intervals). The algorithm performs the Vs-searching test for a maximum of 8 beats while searching for ventricular intrinsic events (Vs). As soon as the programmable criterion is met, the device switches from DDD(R) state to ADI(R) state:

    - User programmable X consecutive used Vs events

    Between the Vs searching tests, single used Vs events will trigger a Vs-searching test as well (as shown below). In the case that the criterion is not met, the algorithm stays in the DDD(R) state and goes back to the user programmed AV delay. Each time the Vs-searching test is not successful, the searching interval is increased until a 'Maximum Vs searching interval of 128 minutes' is reached. This happens by doubling the previous interval (0.5, 1, 2, 4, 8…128 minutes, 20h). This process is designed to limit the amount of searches in the absence of intrinsic AV conduction. Anytime a Vs searching test is successful, the Vs-searching interval is reset to 30 seconds. Vs may be detected very quickly again, once the algorithm switches back to DDD(R) state. If the switching criteria are not met until the 'Maximum Vs searching interval' is reached, the Vs-searching interval is increased to 20 hours.

Figure 5: Search Initiated by a Single Ventricular Sensed Event



4. **Unstable AV Conduction:** When the patient has an unstable AV conduction the algorithm might switch between the two states very frequently. This frequent switching is limited to 15 per hour. Whenever this limit is reached, the Vp Suppression feature is suspended until 12:00 am (midnight) the next morning.
5. **Arrhythmia Mode Switching and Vp Suppression:** Enabling the Vp Suppression feature automatically enables the mode switching to DDI(R). Whenever the mode switching criterion is met, the algorithm switches to DDI(R) mode. The algorithm stays in that mode until the resynchronization criteria are met. After resynchronization from mode switch, the algorithm switches to DDD(R) state in order to ensure defined conditions after a tachycardia.

Vp Suppression is comparable to the currently marketed Managed Ventricular Pacing (MVP) feature by Medtronic. The MVP modes, AAIR<=>DDDR and AAI<=>DDD, provide AAIR or AAI mode pacing while monitoring AV conduction. For persistent loss of AV conduction, the pacemaker switches to DDDR or DDD mode. If AV conduction resumes, the pacemaker switches back to AAIR or AAI mode. For transient loss of AV conduction, the pacemaker remains in the AAIR or AAI mode and provides a backup ventricular pace in response to an A-A interval that is missing a ventricular sense.

The following table shows the programmable parameters of the Vp Suppression feature.

Parameter	Range	Default
Pacing suppression after x consecutive Vs events and switch to ADI(R) condition	1, 2, 3, 4, 5, 6, 7, 8	6
Pacing support in the ventricle after x out of 8 cycles without Vs and switch to DDD(R) condition	1, 2, 3, 4	3

INDICATIONS FOR USE

There were no changes to the indications for use, which are provided below.

Rate-adaptive pacing with the Evia pulse generators is indicated for patients exhibiting chronotropic incompetence and who would benefit from increased pacing rates concurrent with physical activity.

Generally accepted indications for long-term cardiac pacing include, but are not limited to: sick sinus syndrome (i.e. bradycardia-tachycardia syndrome, sinus arrest, sinus bradycardia), sino-atrial (SA) block, second- and third- degree AV block, and carotid sinus syndrome.

Patients who demonstrate hemodynamic benefit through maintenance of AV synchrony should be considered for one of the dual chamber or atrial pacing modes. Dual chamber modes are specifically indicated for treatment of conduction disorders that require both restoration of rate and AV synchrony such as AV nodal disease, diminished cardiac output or congestive heart failure associated with conduction disturbances, and tachyarrhythmias that are suppressed by chronic pacing.

CLINICAL STUDIES

FDA previously indicated that clinical data would be required in order to support the safety and effectiveness of the ACC and Vp Suppression features. The company conducted a clinical study in Europe to collect the data necessary. The company provided a complete clinical report, which contained all of the relevant information about the study.

FDA's initial review of the clinical data identified some remaining deficiencies, which Brian provided in his review memo. Those deficiencies are also outlined below.

DEFICIENCY #1 -- ACC

Regarding the clinical data submitted and necessary to support FDA finding a reasonable assurance of safety and effectiveness of the ACC algorithm, FDA was largely able to determine that disagreement of a clinically relevant degree did not occur comparing the ACC feature pacing capture thresholds and manual. FDA also requests that you provide a description and justification to assure that the data provided was not selected from any larger available data on ACC performance in your study. Reasonable approaches to address this include assuring that the data was either all that was collected or all in a sequence. Please also address whether deviations could have biased the data by excluding notably poor performing instances of ACC function.

DEFICIENCY #2 – Vp Suppression

Regarding the clinical data submitted and necessary to support FDA finding a reasonable assurance of safety and effectiveness of the Vp algorithm, FDA cannot determine whether the feature reduces the percent ventricular pacing and to what degree and whether pauses occurred, which FDA considers necessary assurances that the feature is safe and effective. In that you have Holter data on file and expect to collect between 18 and 30 total Holters, FDA requests that you submit the full Holter data and analyses to show

- Assurance of capture, i.e. that Holter showed that VERY, VERY few subjects had any pauses or dysfunction of the algorithm and

- a demonstration/confirmation by Holter that the percent ventricular pacing was reduced by the algorithm, with an estimate of the reduction.

We also shared these concerns in a teleconference call with the company. The company agreed to address these concerns and to submit the necessary documentation to FDA, in order to continue our interactive review. The company subsequently submitted additional information.

Regarding the ACC feature, the company clarified that there were 93 patients with both automatic and manual atrial pacing threshold measurements at the same follow-up. The company also agreed to address FDA's concern regarding the difference in the number of enrolled patients versus the number of paired measurements. The company also agreed to provide the 6 month master study report, in addition to the preliminary report included in the submission. The company also agreed to include a clinical summary in the labeling. Again, there was no reference to the supporting clinical study used to support the feature in the labeling that was included in the submission.

Regarding the Vp Suppression feature, the company analyzed the performance of the Vp Suppression feature as part of the master study. The analysis focused on the one and three month follow-up data. The report includes the analysis of seventeen (17) 24-hour Holter recordings. The company also agreed to include a clinical summary in the labeling. Again, there was no reference to the supporting clinical study used to support the feature in the labeling that was included in the submission.

(b) (6) and I quickly reviewed the information and agreed that a major deficiency letter was not necessary. (b) (6) also provided information about products with similar features from other companies. The company confirmed that they would address our remaining issues during an interactive review.

The company sent some additional draft information, based on our previous requests, and then the company sent a complete update to address FDA's previous requests.

The updated master study report included 175 patients enrolled at 34 clinical sites outside of the United States. The following bullets summarize the results:

- 175 Evia pacemakers have been implanted: 121 Evia DR-T, 20 Evia DR, 27 Evia SR-T, 7 Evia SR.
- Evia DR-T and DR only: The difference between the automatic and manual atrial capture threshold at one month follow-up (primary endpoint) was -0.01 V ± 0.14 V, n = 93 pairs of measurements, range = -0.7 V to +0.6 V, 95% confidence interval [-0.03 V, 0.02 V].
- At the beginning of the one and three month follow-up visits atrial stimulation with activated atrial capture control feature was successful in 99.4%, 95% confidence interval [96.5%, 100.0%], n = 156.
- The core laboratory analyzed 21 Holter ECG recordings with a duration of 24 hours, and revealed short episodes of atrial non-capture in 3 Holter ECGs: In one patient 3 consecutive beats, in another patient 9 beats within 1 minute, and in one patient atrial non-capture was recorded, but not linked to the atrial capture control feature.
- In total 98 adverse events were reported, whereof two were classified as pacemaker-related complications. Hence the per-patient complication-free rate is 173/175 = 98.9%, 95% confidence interval [95.9%, 99.9%].

The company conducted a separate, additional analysis of the Holter recordings in order to support the Vp Suppression feature. Holter data from 17 patients and stored follow-up diagnostic data were included in the analyses. The company included relevant data about the percentage of pacing with Vp Suppression as compared to devices programmed with Hysteresis on and Hysteresis off. At the 3-month follow-up, the mean percentages of ventricular pacing were 17%, 37%, and 91% in devices with Vp Suppression, Hysteresis, and no Hysteresis, respectively. This data was useful but not entirely clear. As a result, FDA asked the company to clarify the results, specifically to focus on those patients without AV block, who would most likely benefit from the Vp Suppression feature.

(b) (6) completed his review of the additional information and requested some additional clarification. His requests are outlined below. These requests were forwarded to the company.

- Biotronik should modify the clinical results labeling to call out the VpS analysis and results as a stand alone section in something of the same way ACC is called out -- even if the VpS aspects of the study were, in their view, a minor component of the study not prespecified with statistical power. FDA views the feature as new and itself requiring modest clinical supportive data that users can look up.
- Biotronik should modify the VpS results to show the reduction in pacing among patients without AV block. This could be done either by showing what is currently shown and adding a table showing results only for those with and without AV block, or the firm can add a histogram showing the frequency of patients with various degrees of Vpacing when the feature is ON. The histogram should be annotated with a comment at the bottom indicating that those patients with AV block are those in whom Vpacing persists despite the feature being ON, since that is the way the feature is intended to function. Conversely, the patients with substantial reduction in Vpacing are those without AV block, i.e. the group indicated for the feature in the first place!

The company submitted additional information to address our requests for clarification. Excluding those patients with AV block, there were 12 patients data at the 1-month follow-up and 13 patients with data at the 3-month follow-up. The mean percentage of ventricular pacing was 12% and 13%, respectively.

(b) (6) reviewed the labeling and updated his review memo to outline his remaining concerns. I then discussed the labeling with (b) provided feedback to the company regarding the proposed labeling. The following text outlines our requested modifications.

- Section 1.1.1.2 - Please revise the text as suggested below:

  Primary Endpoint

  The purpose of primary endpoint 1 (ACC efficacy) was to compare the <insert:> mean automatic atrial pacing threshold measurements of the ACC algorithm to the <insert:> mean manual right atrial pacing threshold measurement at one-month follow-up. The associated hypothesis is evaluated based on the difference in the <insert:> mean ACC and manual thresholds as smaller than 0.2 V and greater than -0.2V.

- Section 1.1.1.3 - Please insert a flowchart similar to the one provided titled Figure 1: ACC Flowchart of Paired Measurements. FDA would like you to present a flowchart that shows which patients were included and excluded in the analyses for ACC and VpS. In addition, FDA recommends the addition of two sentences indicating that review of the reasons for missing data showed the following most common reasons: 1) xx subjects had xx reason for missing data 2) xx subjects had xx reason for missing data, etc. The second sentence, if possible and appropriate should state that review of the missing data did not reveal that they would have likely altered the main study results and that they did not indicate new concerns about ACC feature effectiveness.

- Section 1.1.1.4 - FDA recommends the addition of a conclusion sentence such as "The low rate of pacing threshold estimates that differed between ACC and manual methods was consistent with good ACC performance."

- Section 1.1.1.5 - FDA recommends the addition of a conclusion sentence such as "The low rate of complications was consistent with acceptable, high overall device performance."

- Section 1.1.1.6 - FDA recommends the addition of a conclusion sentence such as "The high rate of ACC feature pacing capture was consistent with acceptable, high overall performance of the algorithm."

- Section 1.1.1.9 - FDA recommends the addition of a conclusion sentence such as "Analysis of the reduction in percentage of ventricular pacing in patients without AV block showed that most had marked reductions as intended for this algorithm."

The company submitted updated labeling to address our concerns. I reviewed the labeling and believe that the sponsor addressed our remaining concerns. I also asked (b) (6) to review the labeling in order to ensure that the issues were addressed from his perspective. (b) (6) confirmed that the labeling changes were sufficient to address our remaining concerns and updated his consult review memo.

Supporting Clinical Data

The following text summarizes the final supporting clinical data used to support the performance of the ACC and Vp Suppression features.

- 175 patients were enrolled at 34 investigational sites outside of the US.
- Mean follow-up time was 5.7 months, median follow-up time was 6.0 months.
- In 93 pairs of measurements at the one month follow-up, the mean difference in the measured atrial pacing threshold was 0.01 V with a minimum of -0.7 V and a maximum of 0.6 V. In 384 pairs of measurements at all follow-ups (pre-discharge, one month, three months, and six months), the mean difference in the measured atrial pacing threshold was 0.01 V. In 19 out of 384 tests (4.9%), the difference was greater than +/- 0.2 V.
- The complication free rate was 98.9%, with the lower 95% confidence interval of 95.9%.
- Atrial capture control performance was evaluated in 156 cases in 92 patients. In 155 cases, atrial stimulation was successful. In the one case without appropriate stimulation, atrial fibrillation was the cause.
- There were 17 Holter recordings for patients who had completed the 1 and 3 month follow-ups. These Holter recordings were analyzed for the presence of pauses ≥ 2 seconds. The analysis did not identify a problem.
- Follow-up data from the one month follow-up was analyzed for 132 patients to evaluate the percentage of ventricular pacing. At the one month follow-up, the percentages of ventricular pacing were 16%, 33%, and 95% for the Vp Suppression, Hysteresis, and No Hysteresis groups, respectively. The data from the three month follow-up was very similar.
- In the 11 patients without AV block, the mean ventricular pacing percentage was 11.3%.

Final Analysis

The clinical data and analyses provided by the company are sufficient to support safety and effectiveness of the ACC and Vp Suppression features. Furthermore, the quantity of clinical data collected is consistent with was used to support similar features in devices from other companies. The final labeling is sufficient to summarize the supporting clinical data with the clinician.

LABELING

The initial submission did not include revised labeling. During our interactive review with the company, we recommended that they revise the labeling to include summaries of the clinical data gathered and analyzed in order to support the approval of the new features. FDA believes that the labeling is also an important part of the submission, as the clinicians might need to review the clinical studies section of the labeling in order to evaluate the performance of the features. The company revised the labeling to include clinical summaries for the ACC and Vp Suppression features. The company then revised the labeling again to address FDA's concerns and feedback. The final labeling now includes the necessary information. Specific details regarding the labeling and the review process are provided in the Clinical Studies section above.

SOFTWARE VERIFICATION AND VALIDATION

FDA previously reviewed and approved programmer software version, ICS 3000 SW 1002.U, as part of P950037 / S072. The software has been modified to create software version 1002.U/1, for use with the ICS 3000 programming system (P950037/S35). With this PMA Supplement, BIOTRONIK is proposing to unlock the ACC and Vp Suppression features, which were described above, with the updated programmer software version 1002.U/1. Apart from unlocking these two features, there are no other changes to the programmer software. None of these changes necessitated changes to the device itself.

The sponsor submitted the appropriate documentation and conducted appropriate testing relevant to the change. I have no concerns regarding the testing completed or the results of the tests.

HARDWARE / FIRMWARE TESTING

There were no changes relevant to this issue. This section is not applicable to this submission.

EMC / EMI TESTING

There were no changes relevant to this issue. This section is not applicable to this submission.

BIOCOMPATIBILITY

There were no changes relevant to this issue. This section is not applicable to this submission.

STATISTICAL

There were no changes relevant to this issue. This section is not applicable to this submission.

ANIMAL TESTING

There were no changes relevant to this issue. This section is not applicable to this submission.

PACKAGING, STERILIZATION, AND SHELF-LIFE

There were no changes relevant to this issue. This section is not applicable to this submission.

POST-MARKET REQUIREMENTS

There were no changes relevant to this issue. This section is not applicable to this submission.

INTERACTIONS WITH OTHER FDA PERSONNEL AND SPONSOR

The primary contact for the sponsor is Jon Brumbaugh (888-345-0374, Jon.Brumbaugh@biotronik.com).

September 9, 2010

(b) (6) provided his review memo, which outlined some remaining concerns. (b) (6) and I subsequently met to review these concerns and to prepare for an interactive discussion with the company.

September 22, 2010

(b) (6) and I discussed our concerns with the company. Meeting minutes were prepared in order to document the discussion.

September 23, 2010

The company submitted additional information in order to address our questions.

(b) (6) and I quickly reviewed the information and agreed that a major deficiency letter was not necessary. (b) also provided information about products with similar features from other companies.

September 24, 2010

The company confirmed that they would submit the additional information necessary for FDA to complete the review of the file.

September 28, 2010 and September 29, 2010

The company sent some additional draft information, based on our previous requests.

September 30, 2010

The company sent a complete update to address FDA's previous requests.

October 8, 2010

(b) (6) completed his review of the additional information and requested some additional clarifications. These requests were forwarded to the company.

October 14, 2010

The company submitted additional information to address our requests for clarification.

October 20, 2010

(b) (6) reviewed the labeling and updated his review memo to outline his remaining concerns.

October 28, 2010

I then discussed the labeling with (b) provided feedback to the company regarding the proposed labeling.

October 29, 2010

The company submitted updated labeling to address our concerns.

November 2, 2010

(b) (6) confirmed that the labeling changes were sufficient to address our remaining concerns and updated his consult review memo.