

SUMMARY OF: PMA # P050023/S076 AND P980023/S057

ILESTO/IFORIA DF4 ICD-CRT-Ds AND PROTEGO DF4 LEADS

Executive Summary

BIOTRONIK has submitted this PMA Supplement to request approval for the DF4 variants of the currently approved Ilest/Iforia ICDs and Linx^{smart} ICD leads. The following changes to the market approved devices are provided below:

- The header of the Ilest ICDs has been modified with a modular DF4 connector port.
- The proximal connector of the currently marketed Linx^{smart} ICD leads has been changed from separate DF-1 and IS-1 connectors to a single DF4 connector. In addition, the connector transition area has been modified. BIOTRONIK DF4 leads will be marketed under the trade name **Protego**.
- The system components conform to the ISO 27186 (DF4) standard.
- Accessories have been modified for compatibility with the Protego lead.
- An adapter, PA 10, is proposed for acute testing of DF4 leads during the implant procedure.
- Labeling has been updated to reflect the design modifications.

There are no changes to the following:

- The components of the Protego leads distal to the lead body to connector transition area remain unchanged compared to Linxsmart leads.
- The Protego lead steroid collar itself; there are also no changes to processes, residues, vapors, or other manufacturing or packaging factors to which the steroid collar is exposed.
- Therefore, there is no expected effect on the drug component of the Protego leads.
- Programmer software; the currently approved PSW 1301.U (P050023/S069) supports the Ilest DF4 ICD family. BIOTRONIK Home Monitoring Service Center software; the plug-in to support the Ilest device family is the same for DF4 and DF-1 variants, and was included in P950037/S121.

The testing listed below support the safety and effectiveness of the DF4 devices and leads. All testing was completed according to plans previously submitted to FDA in Q130538 and Q130538/S001.

- Animal testing demonstrated that the ICDs and leads function as intended with no adverse effects.
- Validation testing of the Ilest/Iforia DF4 devices demonstrated that the ICDs/CRT-Ds meet established specifications. These test reports are identical to the testing that was submitted to support the currently approved Ilest/Iforia devices in P050023/S058.
- Verification testing demonstrated that the DF4 cavity conforms to the ISO 27186 standard.
- Validation testing demonstrated that the Protego leads conform to established specifications, including ISO 27186.

- With one new material and one material previously used in another legally marketed device, biological testing according to ISO 10993-1 demonstrated that these materials pose no biological risk.

In anticipation of a requirement for a post-approval registry as a condition of approval of the Protego lead, the firm has provided a proposed post-approval study protocol.

The initial review identified concerns with the manufacturing information provided in the submission, as well as minor concerns noted with the proposed PAS. Since much of the testing for the proposed devices appears appropriate and adequate, I recommended proceeding interactively to address the noted concerns. The concerns were sent to the firm April 08, 2014.

The firm provided responses to the concerns identified above in an email dated April 17, 2014. The PAS reviewer indicated that all deficiencies had been adequately addressed except for one issue related to the enrollment in 59 months. Normally complete enrollment should occur within 12 months and sometimes it can be extended to 24-36 months based on circumstance. The longer enrollment actually makes it hard to complete, as new device will go to the market. The PAS reviewer contacted the firm to address the concern interactively. The firm also provided a comparison of the manufacturing processes of the previous devices to the proposed devices. The response clearly indicates the new processes and provides appropriate verification/validations for new processes. All concerns have been adequately addressed. The information, testing, and results provided in the submission demonstrate a reasonable assurance of safety and effectiveness for the proposed devices. I recommend approval of this PMA supplement.

Regulatory Background

The following table provides an overview of the regulator history for the ICDs and leads that are the subject of this PMA Supplement. The ICDs and leads are DF4 variants of devices with DF-1 variants which are already approved and marketed in the US.

Submission	Subject	Date	Comments
P980023/S038	Linox ^{smart} SD/TD (dual coil) ICD leads	September 17, 2010	Approval of DF-1 variants
P980023/S043	Linox ^{smart} S/T (single coil) ICD leads	February 28, 2011	Approval of DF-1 variants
P050023/S058	llesto/lforia families of ICDs/CRT-Ds	March 18, 2013	Approval of DF-1 variants
Q130538	DF4 ICDs and leads: canine study	April 29, 2013	The animal study protocol was amended to address FDA's comments. Responses to all of FDA's comments are provided in Section 10.6 .
Q130538/S01	DF4 ICDs and leads: bench testing	August 17, 2013	FDA feedback has been addressed in this PMA Supplement. Responses to all of FDA's comments are provided in Section 11.6 .

Indications for Use

The indications are unchanged from the approved DF-1 variants of the same device families.

Ilesto/Iforia ICDs

The Ilesto/Iforia Family of Implantable Cardioverter Defibrillators (ICDs) is intended to provide ventricular antitachycardia pacing and ventricular defibrillation, for automated treatment of life-threatening ventricular arrhythmias.

Ilesto/Iforia CRT-Ds

The Ilesto/Iforia CRT-Ds are indicated for use in patients with all of the following conditions:

- Indicated for ICD therapy
- Receiving optimized and stable Congestive Heart Failure (CHF) drug therapy
- Symptomatic CHF (NYHA Class III/IV and LVEF \leq 35%)
- Intraventricular conduction delay (QRS duration \geq 130 ms)

Protego Lead

The Protego steroid-eluting ICD lead is intended for use in the right ventricle of patients for whom implantable cardioverter defibrillators are indicated.

Contraindications

The contraindications are unchanged from the approved DF-1 variants of the same device families.

Ilesto/Iforia

The Ilesto/Iforia ICDs and CRT-Ds are contraindicated for use in patients with the following conditions:

- Patients whose ventricular tachyarrhythmias may have transient or reversible causes such as:
 - Acute myocardial infarction
 - Digitalis intoxication
 - Drowning
 - Electrocutation
 - Electrolyte imbalance
 - Hypoxia
 - Sepsis
- Patients with incessant VF/VT
- Patients whose only disorder is bradyarrhythmias or atrial arrhythmias

Protego Lead

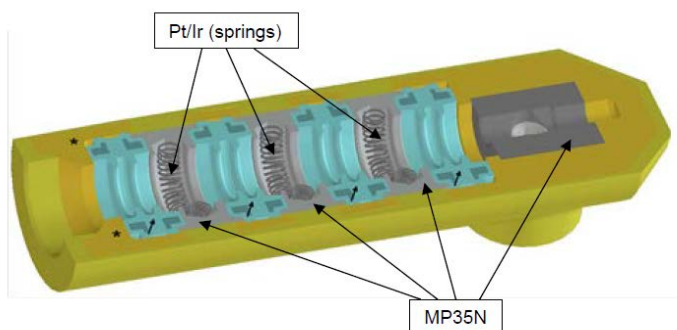
- Do not use the Protego Lead in patients with severe tricuspid valve disease or patients who have a mechanical tricuspid valve implanted.
- The Protego steroid-eluting leads with active fixation are additionally contraindicated for patients who cannot tolerate a single systemic dose of up to 1.3 mg of dexamethasone acetate (DXA).

- The Protego steroid-eluting leads with passive fixation are additionally contraindicated for patients who cannot tolerate a single systemic dose of up to 1.0 mg of dexamethasone acetate (DXA).

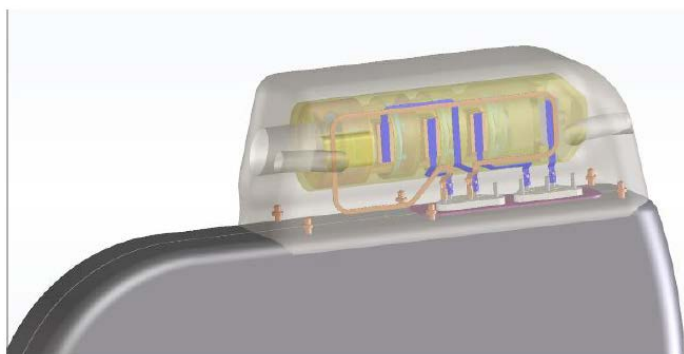
Device Description

Ilesto DF4 Design Differences

With this PMA Supplement, BIOTRONIK introduces DF4 variants of the current Ilesto family of ICDs/CRT-Ds. The only difference between the currently approved Ilesto devices (with DF-1 connector ports) and the proposed DF4 models is the header and respective device marking. The image below shows a cross-section of the DF4 port.



The DF4 module is integrated into the header of the Ilesto/Iforia DF4 variants. In addition to the DF4 module, the entrance bore of the header is modified to be compatible with the module and to comply with the ISO standard. Pin and spring contacts are connected using connection bands with the same ICD/CRT-D feed throughs and materials as in the DF-1 variants.



The geometry of the RF antenna in the DF4 header, used for Home Monitoring communication between the ICD and the CardioMessenger patient monitoring device, has been modified to accommodate the DF4 header dimensions and the modular design. The antenna is made of the same material. The main electrical components of the Ilesto ICDs are feedthroughs, high voltage capacitors, electronic modules, RF antennae and batteries. Differences in the RF antennae are described in Section 6.1.1.4. Otherwise, all of these electrical components are unchanged from the currently approved Ilesto devices (P050023/S058).

The body contact materials of the Ilesto/Iforia DF4 ICD/CRT-Ds are identical to those used in the predecessor Ilesto/Iforia ICDs/CRT-Ds, with the exception of the DF4 connector port seals (sealing rings). These rings are made of (b)(4) TS/CCI silicone, which is also used in

BIOTRONIK leads including the currently marketed Linx^{smart} ICD leads (P980023/S038, approved on September 17, 2010) and the Setrox S pacing leads (P950037/S042, approved on February 14, 2006).

It is noted that the firm did not provide a description of the CRT-D devices. However, the only major change to the device is the header to incorporate the DF4 connector port. In a phone call to the firm, March 24, 2014, I asked the firm to provide a comparison table of all the header configurations for both the ICDs and CRT-Ds. Specifically, I asked for a comparison of the currently approved headers compared to the proposed headers. The firm provided the table below.

	VR-T	VR-T	DK	HF-T
DF4				
DF-1				

In a review of table 5 in volume 1 of the submission it appears that the attachment footprint of the header to the can is not changing. This was confirmed by the firm in an email dated April 2, 2014. Therefore, I do not believe the attachment strength will be impacted by the proposed change.

During the review of this file modified capacitors were recently approved for the DF-1 models of the Ilesio/Iforia ICD family will also be used in the DF4 models, which are currently under review in this file. The capacitor changes were the subject of P050023/S075, which was approved on March 11, 2014.

Protego ICD Lead

The Protego ICD lead is a steroid-eluting lead for use with ICDs having a DF4 connector port conforming to ISO 27186. Protego leads are variants of currently marketed Linxsmart ICD leads with IS-1 and DF-1 connectors. The functionality of each lead is identical to the respective predecessor Linx^{smart} ICD lead.

The Protego S and Protego T leads have two pace/sense electrodes, (distal tip and ventricular ring electrode) and one defibrillation electrode (ventricular shock coil). The Protego SD and Protego TD Leads have two pace/sense electrodes (distal tip and ventricular ring electrode) and two defibrillation electrodes (ventricular and superior vena cava shock coils).

Differences between the currently approved Linxsmart leads and the Protego leads are limited to the replacement of separate DF-1 and IS-1 connectors with a DF4 connector. Implementation of the DF4 connector necessitated modification of the transition area between the connector and lead body (b)(4) TS/CCI). The components of Protego located from lead body to the lead tip remain unchanged compared to Linx^{smart} leads.

The DF4 connector of Protego ICD leads was designed in compliance with ISO 27186; the specifications such as geometry, tensile loads, etc., of the DF4 connector meet the requirements of this standard. The DF4 connector allows use with ICDs that have connector ports conforming to ISO 27186.

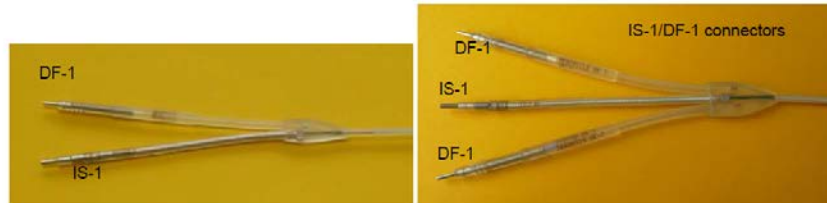
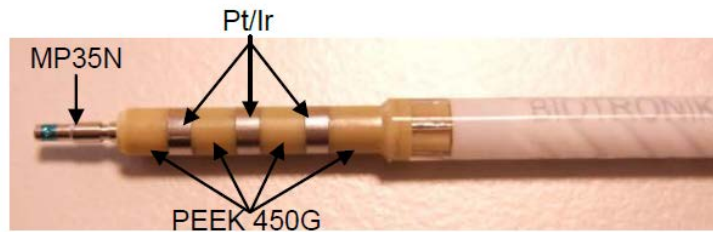


Figure 5. Protego DF4 Connector - Contacts and Transition Area



The transition from the flexible lead body to the rigid DF4 connector is designed in a spiral configuration. This structure helps to reduce the stress placed on conductor cables resulting from arm and shoulder movement.



Protego Lead Variants

The table below displays the difference variants of the Protego Leads.

Name	Fixation	Coils	Lead Length (cm)	SVC Coil – Tip Distance (cm)
Protego SD 60/16	Active	Dual	60	16
Protego SD 65/16	Active	Dual	65	16
Protego SD 65/18	Active	Dual	65	18
Protego SD 75/18	Active	Dual	75	18
Protego TD 65/16	Passive	Dual	65	16
Protego TD 65/18	Passive	Dual	65	18

Name	Fixation	Coils	Lead Length (cm)	SVC Coil – Tip Distance (cm)
Protego TD 75/18	Passive	Dual	75	18
Protego S 60	Active	Single	60	N/A
Protego S 65	Active	Single	65	N/A
Protego S 75	Active	Single	75	N/A
Protego T 65	Passive	Single	65	N/A

The differences between the Protego and the current Linxsmart leads do not result in the steroid collar being exposed to new processes, residues, vapors, or other manufacturing or packaging changes that could potentially affect the drug stability and/or performance. The Protego leads utilize the same steroid collars as their predecessors (P980023/S038, approved on September 17, 2010).

Materials used in the construction of the Protego ICD leads are the same as those used in the current FDA approved Linxsmart ICD leads (P980023/S038, approved on September 17, 2010), with the exception of the (b)(4) TS/CCI material used as the insulation material (b)(4) TS/CCI of the DF4 connector.

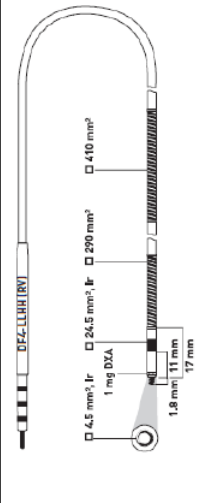
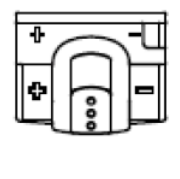
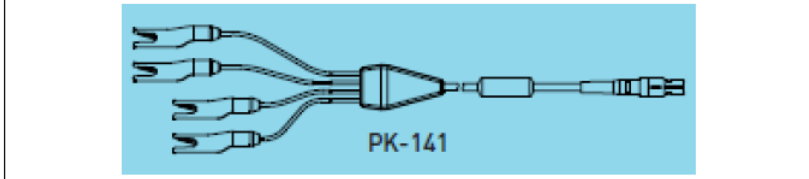
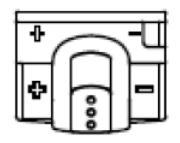
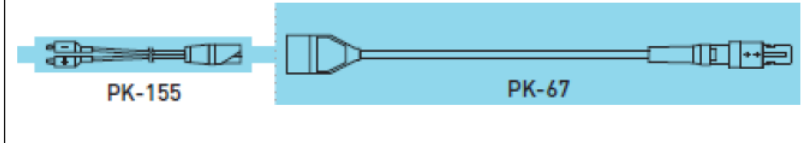
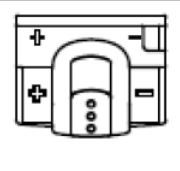
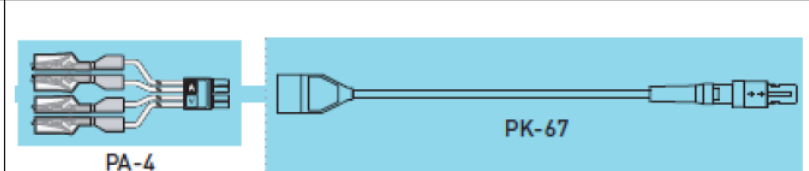
Accessories

With the introduction of DF4 connections, a new adapter and three modified accessories are introduced.

PA 10

The BIOTRONIK patient adapter PA 10 is used to connect a lead with DF4 connector to the alligator clips on one of the following legally marketed BIOTRONIK patient cables or patient adapters:

- PK-141
- PK-155 in combination with PK-67-S/-L
- PA-4 in combination with PK-67-S/-L

DF 4 lead	PA 10	Patient Cable/Adapter
		
		
		

PA 10 is used for transmission of sensing signals and pacing pulses for diagnostics and therapy during the implant procedure (i.e. connection to the pacing system analyzer). The PA 10 adapter does not contact the DF4 ring contacts of the shock coil conductors. The PA 10 is only provided as a separately available sterile accessory.

SG-IS4/DF4

The stylet guide SG-IS4/DF4 assists with the insertion of stylets into the leads. The dimension of SG-IS4/DF4 was adapted to the dimension of DF4 and IS4 connector in compliance with ISO 27186. In order to visually differentiate SG-IS4/DF4 from SG-UP, the SG-IS4/DF4 is blue in color, while the SG-UP is green. SG-IS4/DF4 will only be provided in the sterile package with the leads.

DH DF4

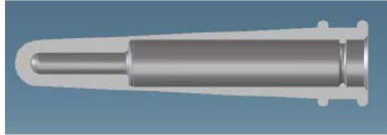
DH DF4 is used for extending and retracting the active fixation helix of BIOTRONIK's active implantable DF4 leads. DH DF4 is a successor of DH - the fixation tool for BIOTRONIK's active fixation leads with IS-1 connector. In order to visually differentiate DH-DF4 from DH, the DH-DF4 is blue in color, while the DH is white. See Figure below.



The DH DF4 will be provided in the sterile package with the active fixation leads, and also as a separately available accessory.

BK-IS4/DF4

BK-IS4/DF4 is used to seal unused leads with DF4 or IS4 connectors against the surrounding tissue in case an already implanted lead remains inside the body and is not going to be connected to an ICD or IPG. BK-IS4/DF4 is similar to BK-IS - blind cap for BIOTRONIK's leads with IS-1 connector.



The BK-IS4/DF4 will only be provided as a separately available sterile accessory.

LEAD REVIEWER COMMENTS: The PA 10 adapter, SG-IS4/DF4 stylet guide and the DH DF4 fixation tool have no patient contact. The BK-IS4/DF4 is constructed of the identical material as the current BK-IS. Therefore no biocompatibility testing is warranted for these accessories.

Clinical Impacts

Ilesto DF4 connector port

Limited clinical impact. Device functionality remains unchanged. A single DF4 connector may positively impact ease of use and the resulting pocket size during the implant procedure.

DF4 connector

Limited clinical impact. Device functionality remains unchanged as demonstrated by validation testing.

Modified Transition Area

No clinical impact. Validation testing demonstrates that the connector transition meets the established specifications for flex fatigue.

LEAD REVIEWER COMMENTS: Overall, I agree that the DF4 connector port will have limited clinical impact. As for the DF4 connector on the lead, I believe the removal of the trifurcation/bifurcation in the predecessor leads removes transition areas and potential points of failure. However, as the firm states above the over device functionality remains unchanged and from that standpoint I agree with the limited clinical impact.

Validation and Verification Testing

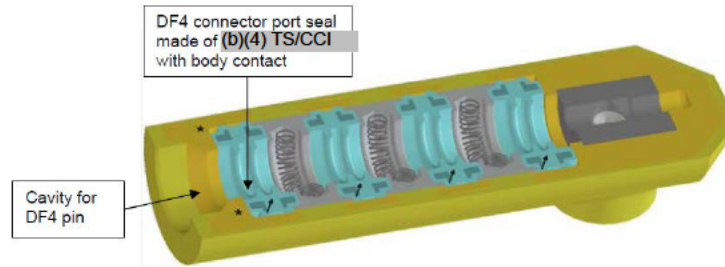
Biocompatibility

Ilesto DF4 Family

The body contact materials of the Ilesto DF4 ICDs are identical to those used in the predecessor Ilesto ICDs, with the exception of the 'DF4 connector port seal' (in some documents also named as 'seal coupler'). This is made of (b)(4) TS/CCI which is also used in BIOTRONIK steroid-eluting leads, including the currently marketed Linxsmart ICD leads (P980023/S038,

approved on September 17, 2010) and the Setrox S pacing leads (P950037/S042, approved on February 14, 2006).

The DF4 connector port seal is located in the header of Ilesio DF4 ICDs. The figure below shows a schematic drawing of the DF4 module, with connector port seal indicated. When implanted, the lead connector pin fills the cavity, except a small surrounding gap. Therefore, the body contact to the DF4 connector port seal is only realized via bodily fluid which penetrates through this small gap.



The DF4 connector port seal is (b)(4) TS/CCI with (b)(4) TS/CCI by BIOTRONIK SE & Co. KG (b)(4) TS/CCI. Biocompatibility studies per ISO 10993-1 were conducted on this material. Testing included:

Table 20. Biocompatibility Studies for Silastic 7--6860

Test name	Test report VER-111-09-1841
1. Cytotoxicity Tissue culture tests with extract and elastomer (direct contact)	Attachment 01 Attachment 11
2. Sensitization Test for delayed-type hypersensitivity (b)(4) TS/CCI polar and non-polar extract, elastomer in direct contact)	Attachment 02
3. Acute Systemic toxicity and Intracutaneous reactivity (USP (b)(4) TS/CCI plastic extractables study with (b)(4) TS/CCI tracts of different polarity)	Attachment 03
4. material mediated Pyrogenicity (Rabbit Pyrogen test)	Attachment 04
5. Repeated exposure systemic toxicity (subacute, subchronic chronic toxicity in the rat)	Attachment 05
6. Genotoxicity (Bacterial Reverse Mutation assay (AMES test); polar and non-polar extract)	Attachment 06
7. Implantation (local tissue response) – Implantation period: short term response – 14 days – Implantation period: steady state response - 90 days – - Implantation period: 7, 30 and 90 days	Attachment 07 Attachment 08 Attachment 09
8. Hemolysis (elastomer in direct contact, saline extract)	Attachment 10

In addition to the test reports listed above, biocompatibility tests were performed on representative seal samples of (b)(4) TS/CCI using the same process as for the DF4 connector port seal. These test samples were further processed at BIOTRONIK in the same way as the final DF4 connector port seal including sterilization and are therefore representative for the final material in its final application in the Ilesio ICDs.

Since the firm chose to conduct biocompatibility testing on only the new material as a component, an assessment was conducted for possible interactions of (b)(4) TS/CCI with other materials and processes. To confirm that there are no influences of toxicological concern during the manufacturing process, BIOTRONIK performed a sensitive cytotoxicity assay using fibroblasts with samples of finished Ileso DF4 ICDs

LEAD REVIEWER COMMENTS: Materials used in the manufacture of the Ileso DF4 ICDs with body contact, besides silicone (b)(4) TS/CCI, have already been used in FDA approved ICDs. (b)(4) TS/CCI which is used for the DF4 connector port seal, is also used in BIOTRONIK's FDA approved implantable leads. Although this material is currently used in implantable leads manufacturing processes for the header may differ and introduce biocompatibility concerns. I commend the firm for the analysis of the potential effects the manufacturing process may have on the biocompatibility of this material. The analysis did not raise any concerns. Additional biocompatibility tests were performed with (b)(4) TS/CCI material which was processed (b)(4) TS/CCI using the same process as DF4 connector port seal. These tests confirmed the biocompatibility of (b)(4) TS/CCI when processed (b)(4) TS/CCI c. Biocompatibility tests were also performed with finished Ileso DF4 devices. There was no evidence for toxicity of materials or for interactive chemistry observed. The biological evaluation was adequate, appropriate, and demonstrated that there were no concerns from a biocompatibility perspective.

Protego Lead Family

The materials used in the construction of the Protego ICD leads with body contact are the same as those used in the current FDA approved Linx^{smart} ICD leads (P980023/S038, approved on September 17, 2010), with the exception (b)(4) TS/CCI is the material of the 'DF4 connector housing' (in some test reports, also named as '(b)(4) TS/CCI the DF4 connector'). In this location (b)(4) TS/CCI permanent tissue contact.

For the new material (b)(4) TS/CCI biocompatibility tests were performed. For these tests, the (b)(4) TS/CCI samples were fully processed as in Protego leads, including sterilization. In addition, some tests were performed with finished Protego leads including (b)(4) TS/CCI material. For these tests the lead samples were fully processed, including sterilization, prior to testing.

Biocompatibility tests according to ISO 10993-1 were performed with (b)(4) TS/CCI samples which were subjected to all stages of the manufacturing process including (b)(4) TS/CCI (b)(4) TS/CCI materials were supplied (b)(4) TS/CCI and was (b)(4) TS/CCI by (b)(4) TS/CCI. It was assured that the test samples are processed in the same way as the final connector housing, and are therefore representative for the final material in its final application in the Protego ICD leads. Testing included:

Test name	Result report
1. Cytotoxicity - Tissue culture test with extract	(b)(4) TS/CCI (b)(4) TS/CCI
2. Sensitization – test for delayed-type hypersensitivity (b)(4) TS/CCI (b)(4) TS/CCI polar and non-polar extract)	
3. Intracutaneous reactivity - Intracutaneous Injection test (polar and non-polar extract)	
4. Acute Systemic toxicity - Acute Systemic Toxicity in the mouse (polar and non-polar extract)	
5. material mediated Pyrogenicity - Rabbit Pyrogen test	
6. Repeated or continuous exposure systemic toxicity (subacute, subchronic chronic toxicity) – subacute / subchronic systemic toxicity in the rat (14 days)	
7. Genotoxicity – Reverse Mutation assay using Bacteria (AMES test) – In vitro Mouse Lymphoma cell gene mutation assay – In vivo Mouse Peripheral Blood Micronucleus Study	
8. Implantation (local tissue response) – Implantation period: short term response - 2 weeks – Implantation period: steady state response - 90 days – Implantation period: long term response - 180 days	
9. Compendium of tests for Hemocompatibility evaluation	
10. Assessment of biocompatibility of (b)(4) TS/CCI according to ISO 10993-1:2009	

Since the firm chose to conduct biocompatibility testing on only the new material as a component, an assessment was conducted for possible interactions (b)(4) TS/CCI with other materials and processes.

LEAD REVIEWER COMMENTS: The materials used in the manufacture of Protego leads with body contact, besides (b)(4) TS/CCI already been used in FDA approved ICD leads. The biocompatibility according to ISO 10993-1 was previously proven. The major concern with this submission is the proximal end of the lead and not the blood contacting distal end. (b)(4) TS/CCI (b)(4) TS/CCI is used for the DF4 connector, was adequately investigated for biocompatibility according to ISO 10993-1. There was no evidence for toxicological potential found. Additionally, Based on the potential material interaction analysis and finished device testing on representative samples of the (b)(4) TS/CCI material subjected to the same processing as the leads, it is appears that biocompatibility of the Protego Leads has been established. The biological evaluation was adequate, appropriate, and demonstrated that there were no concerns from a biocompatibility perspective.

Lead Adapter and Accessories

The PA 10 adapter, SG-IS4/DF4 stylet guide and the DH DF4 fixation tool have no patient contact. The BK-IS4/DF4 is constructed of the identical material as the current BK-IS. Therefore no biocompatibility testing is warranted for these accessories.

LEAD REVIEWER COMMENTS: I agree with the assessment for the lead adapter and accessories and there are no further concerns.

DF4 Family Verification and Validation

Verification and Validation testing summary was provided in Table 23 as well as the appended test reports are the same as the respective summaries and reports that were included in

P050023/S058 (Approved March 14, 2013). As directed by FDA in response to Q130538/S001, this information is also included within this submission. Much of the testing was agreed upon during the review of Q130538/S001.

Validation Testing:

- Header and Housing User Tests After Environmental Preconditioning
- Confirmation of Successful Production End Test

- Environmental Preconditioning:
 - Protection from temperature, pressure and moisture changes
 - Transport test
 - Drop test
- Handling with Packaging
- Completeness of the Sales Unit
- Visual Inspection Packaging
- Visual Inspection Product
- Protection from Damage Caused by External Pressure Changes Storage 500h @ 50°C

Verification Testing:

To demonstrate conformance to the ISO 27186 standard, samples were subjected to the verification testing. For the verification tests, test samples were the “DF4 modules” (internal name (b)(4) TS/CCI test headers using the standard manufacturing process including sterilization. In some of the documents the test headers are also named header dummies. Test headers represent the relevant header geometries, but offer additional features to enable testing (b)(4) TS/CCI (b)(4) TS/CCI

- Insertion/Withdrawal force test
- Retention Force
- Electrical Isolation Initial and after 10days
- Dielectric Strength
- Current Carrying
- Withdrawal force after Current Carrying test
- Visibility of Insertion Indicator
- Contact Resistance
- Pitting/Crevice Corrosion Test
- Passivation/Re-passivation
- Seal Zone Creep
- Contact Resistance Stability: Static no-load contact resistance
- Contact Resistance Stability: Dynamic contact resistance

LEAD REVIEWER COMMENTS: Overall, the testing was a mirror of that approved under P050023/S058. Sample sizes were appropriate and testing was adequate for verifying/validating this change. The animal study results will be reviewed separately to demonstrate system performance. Verification testing demonstrated conformance to ISO 27186. While typically with a header change, I would expect to see header attach strength testing from

a static and dynamic load, I do not feel it is necessary based on the scope of this change. The firm confirmed that there are no changes to the attachment foot print of any models subject to this submission. The firm did conduct shear testing of the CRT-D models. The testing was adequate and demonstrated no degradation in attachment strength for the new DF4 headers. All testing passed the required specifications.

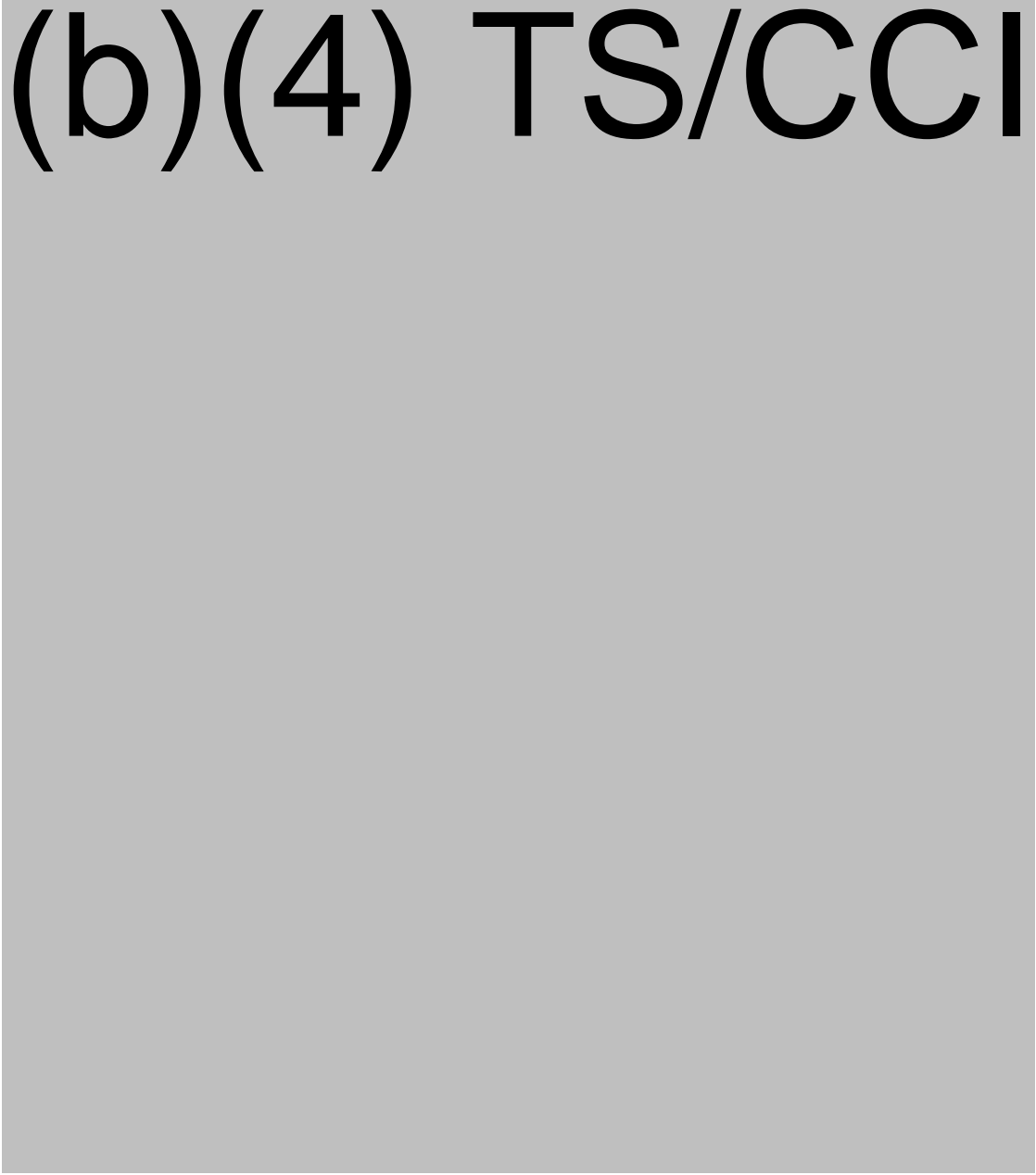
Protego Lead Family Verification and Validation

This Section summarizes the lead validation testing conducted for the Protego leads. Note that differences between the currently approved Linox^{smart} leads and the Protego leads are limited to the replacement of DF-1 and IS-1 connectors with a DF4 connector and a modified transition area between connector and lead body. The components of Protego located from lead body to the lead tip remain unchanged compared to Linox^{smart} leads. The testing was conducted according to the plans that were included in Q130538/S001. The testing plans appeared appropriate under the pre-submission for evaluating the changes proposed to the lead. The main concerns for this testing were to address:

- Connector Requirements of ISO 27186
- Functional Testing with the new connector
- Axial and Fatigue Strength of the new transition section

Below is a flow chart of the initial leads testing (prior to accelerated aging) followed by the testing conducted on the DF4 connector (ISO 27186)

(b)(4) TS/CCI



(b)(4) TS/CCI



LEAD REVIEWER COMMENTS: The test plan for evaluating the modified lead was very comprehensive and complete. Appropriate preconditioning was conducted prior to all tests. FDA and Biotronik have multiple discussions related to mechanical preconditioning (i.e., tortuous anatomy, off set insertion, simulated implant handling, etc.) While it has been discussed that the offset insertion test is not entirely what FDA is looking for it does impart stress on the lead in the area behind the connector. FDA has provided feedback to Biotronik that this activity is acceptable the connector should be fully seated in the header then bent +/- 90°. Representative sample sizes of each model of the leads were tested per the plan. Testing of the DF4 connector demonstrated conformance to ISO 27186. Following Bending testing the firm cross sectioned leads for an abrasion analysis. The inner cables and coil did not show signs of abrading through the insulation. I do not believe that long term flex testing is necessary for the proposed changes. Appropriate testing was also conducted following accelerate aging. Overall, I have no concerns with the testing conducted. All test met appropriate pre-specified acceptance criteria.

Drug Component

The modifications do not result in the steroid collar being exposed to new processes, residues, vapors, or other manufacturing or packaging changes that could potentially affect the drug stability and/or performance. The Linox^{smart} DF4 leads use the same steroid collars as their predecessors (P980023/S038, approved on September 17, 2010). As with the current Linox^{smart} leads, the steroid collar is attached to the lead after all manufacturing processes have been completed. Afterwards, the lead containing the steroid collar is sterilized; the sterilization process remains unchanged and the lead packaging is identical to that used with the Linox^{smart} leads.

LEAD REVIEWER COMMENTS: Since changes presented are limited to the proximal end of the lead I agree there does not appear to be any effect on the drug component of these leads.

Lead Adapter and Accessories Verification and Validation Testing

Finished device samples were sterilized, and then subjected to environmental preconditioning; including temperature, pressure and moisture changes, transport simulation and drop tested prior to validation testing.

Validation Testing for PA 10 and the lead accessories Included:

#	Test Title	Test Description	Samples Tested
1.	Packaging	The packaging is checked for conformity to the product specification.	(b)(4) TS/CCI
2.	Integrity test of sterile package	For validation of the integrity of the sterile package (SteriClin bag) according to ISO 11607-1:2006 and ISO 11607-2:2006 following tests are performed: 1. Visual inspection of packaging 2. Visual inspection of seal seam (non-destructive) 3. Visual inspection of seal seam, peel characteristic (destructive) 4. Peel test 5. Seal leaks test (Dye penetration test) 6. Bubble emission test	
3.	Connection of the lead	The characteristics for connecting a DF4 lead are tested for conformity to requirements of product specification.	
4.	Connection of the patient cables	The characteristics for connecting the patient cables are tested for conformity to requirements of product specification.	
5.	Electrical measurements	Test of electrical measurements with DF4 lead and patient cables attached to the adapter. Impedance, pacing and sensing measurements are performed.	
6.	Operation on limits of environmental conditions	Test of functionality of the product within the range of operation conditions. The handling is checked with OR gloves for simulating real conditions.	
7.	Removing the adapter	The removal and reconnection of the adapter from/to the lead is tested.	

Testing was also conducted following accelerated aging for all accessories.

Table 33. PA 10 Validation Testing after accelerated aging

#	Test Title	Test Description	Samples Tested
1.	Sterile package integrity after accelerated aging	<ol style="list-style-type: none"> 1. Visual inspection of Packaging 2. Visual inspection of seal seam (non-destructive) 3. Visual inspection of seal seam, peel characteristic (destructive) 4. Peel test 5. Seal leaks test (Dye penetration test) 6. Bubble emission test 	(b)(4) TS/CCI
2.	Functional test after accelerated aging	<ol style="list-style-type: none"> 1. Visual inspection of Packaging and product 2. Functional test of product 3. Electrical measurement of product (impedances) 	

Table 34. Lead Accessory Validation Testing

#	Test Title	Test Description	Samples Tested
1.	Validation testing for DH DF4	After environmental preconditioning, the documentation is checked. Then, samples are inspected for handling with sales and sterile packaging, dimensions and geometric control, and clamping function.	(b)(4) TS/CCI
2.	Validation testing for BK-IS4/DF4	After environmental preconditioning, the documentation is checked. Then, samples are inspected for handling with sales and sterile packaging, dimensions and geometric control, and mechanical compatibility with specified connectors.	(b)(4) TS/CCI

LEAD REVIEWER COMMENTS: Testing for PA 10 and the lead accessories was adequate and appropriate. Samples sizes were more than adequate for this testing based on the risk analysis. Testing demonstrated that the accessories are compatible with the new DF4 connector and function as intended even after accelerated aging. Sterile packaging was evaluated following accelerated testing to demonstrate the sterile barrier remains intact and the devices/components remain sterile at the proposed shelf life. All specifications were met and all testing passes pre-specified acceptance criteria.

Packaging

The packaging controls and materials used with the Ilesto DF4 devices, Protego leads and accessories are identical to those used in the approved Ilesto devices, Linxsmart leads and accessories (P050023/S058, P980023/S038).

The Ilesto devices and Protego leads are sealed within a double sterile blister package consisting of (b)(4) TS/CCI). The blister packs are sealed with (b)(4) TS/CCI).

For the Protego leads, there is a silicone part in the inner blister that secures the distal end of the lead in place during shipping. Standard positioning stylets and other accessories are also contained within the inner (b)(4) TS/CCI blister package. A ring made of (b)(4) TS/CCI secures the stylets within the inner blister.

Stylets, DH DF4 and BK-IS4/DF4 are also available as separately packaged accessories. Each separately packaged accessory is provided within a double sterile bag. These bags have a clear (b)(4) TS/CCI) foil front and a medical paper backing.

LEAD REVIEWER COMMENTS: The changes proposed to these devices do not appear to impact the approved packaging for predecessor devices. As such testing on the predecessor device packaging remains applicable and there are no concerns.

Sterilization

The Ilesto DF4, Protego, PA 10, DH DF4 and BK-IS4/DF4 devices are sterilized (b)(4) TS/CCI to achieve a sterility assurance level (SAL) of 1×10^{-6} . The environmental controls, sterilization process, and sterility assurance procedures for the subject devices are identical to those used in the current legally marketed devices (Ilesto, P050023/S058, Linx^{smart} SD/TD and accessories, P980023/S038).

LEAD REVIEWER COMMENTS: The proposed changes to both the market approved header and the leads do not appear to increase the burden for sterilization. All processes remain identical to achieve and appropriate SAL. There are no further concerns with this section of the review.

Shelf Life

The shelf life for the Ilesto ICDs is 19 months, which is unchanged from the currently marketed Ilesto devices. BIOTRONIK assigns an expiration date, "Use Before Date" (UBD), based on device longevity and internal battery characteristics. The UBD is assigned as the last date of the nineteenth month after battery connection is made during the manufacturing process. It is guaranteed that the projected longevity of the device remains valid until implantation. Sterility is not a factor when determining the UBD, because sterility duration exceeds the device electrical characteristics duration.

LEAD REVIEWER COMMENTS: Since the proposed changes do not appear to affect the packaging, device electrical component, materials, or battery, labeling these devices for a 19month shelf life is appropriate.

The proposed shelf-life for the Protego leads is 24 months, which is the same as all of BIOTRONIK's other leads. As with the current Linxsmart leads (P980023/S038), the labeled storage conditions are "Storage at temperatures up to 25° C (77° F); excursions permitted from 5° to 55° C (41° to 131° F)." Shelf life testing was provided to support this proposal.

LEAD REVIEWER COMMENTS: The proposed changes do not appear to affect the drug component of this lead, packaging, or the majority of the lead materials. Therefore, I believe that accelerated testing is sufficient for supporting the 24month shelf life. The accelerated testing included adequate representative samples of each lead. Following sterilization and aging testing included: handling, visual inspection, introducer compatibility, mechanical compatibility, simulated implant, extension/retraction of helix, tensile testing. Overall, the testing was adequate and appropriate and supports the proposed 24month shelf life.

The shelf life for the accessories is also 24 months, which is the same as the predecessor devices. Shelf life testing was provided to support this proposal.

LEAD REVIEWER COMMENTS: The accelerated testing included adequate representative samples of each accessory. Finished device samples were sterilized, and then subjected to environmental preconditioning, including temperature, pressure and moisture changes, transport simulation and drop testing. Following accelerated aging testing included: Sterile package integrity after accelerated aging, functional test after accelerated aging, validation testing for DH DF4, Validation testing for BK-IS4/DF4. The testing was adequate and appropriate and supposed the proposed 24month shelf life for these accessories.

Labeling

The Ilesto Family Technical Manual was updated to add information specific to the DF4 variants, and is provided in Appendix 90. To facilitate review, Appendix 91 included a comparison of the updated Ilesto Manual with the current manual (affected pages). The Iforia Family Technical Manual is not appended since the only difference is the trade name of the device.

The Protego manual is provided in Appendix 92. This manual is largely based on the OUS manual. Compared to the current Linxsmart manual, information was added that is specific to the DF4 connector of the Protego leads, as well as information for new/modified accessories. In addition, several sections of the manual, including warnings and precautions, were updated for clarity and for consistency with manuals used outside the US. Due to the number of formatting and editorial differences, a comparison of the Protego Manual to the current Linxsmart Manual is not provided. The current Ilesto and Linxsmart manuals were approved on July 30, 2013, in P050023/S067, bundled with P980023/S056.

The technical manual (English section only) for the PA 10 adapter is provided in Appendix 93.

LEAD REVIEWER COMMENTS: The changes to the labeling were appropriate based on the new header design and DF4 connector change to the lead. All other changes were made for consistency between manuals. Warning and precautions were appropriate and did not raise any concerns. Package labels were also provided and have been updated appropriate to reflect the changes in header design and lead connector design. Overall, the labeling remains largely unchanged from approved versions of the devices and are acceptable.

Manufacturing

The firm provided the following site information regarding manufacturing:

Manufacturing Site	Name and Address	Registration Number
Manufacturer	BIOTRONIK SE & Co. KG Woermannkehre 1, Berlin, Germany	9610139
Contract Manufacturer	BIOTRONIK AG Ackerstraße 6 8180 Bülach, Switzerland	8043892
Contract Sterilizer	(b)(4) TS/CCI	

LEAD REVIEWER COMMENTS: From my review of this submission, this is the only information I could locate on manufacturing. These sites appear to be unchanged from previously approved devices. The firm should provide a detailed description of how the manufacturing process has changed based on the proposed changes in this submission. The DF4 connector for the leads is new to Biotronik and a process flow with appropriate validations should be submitted. Additionally, the manufacturing process for the new pulse generators should also be submitted. In subsequent sections of the submission the firm has provided an analysis of how manufacturing processes may impact the drug component or new materials. While this information is helpful, it was recommended the following be sent to the firm.

- 1. FDA was unable to locate information regarding the manufacturing processes for both the Ilest/Iforia DF4 ICD/CRT-Ds and Protego DF4 Leads. Please provide a description of the manufacturing process, including a process flow diagrams and appropriate process verification and validation activities for the manufacturing of each of the referenced devices. Please also indicate processes that remain identical or unchanged from the previously approved devices for which the design of these proposed devices are based.*

The above deficiency was sent to the firm in an email dated April 08, 2014. The firm responded, April 17, 2014 via email. The firm provided adequate descriptions of the changed manufacturing processes to support the new DF4 connector in both the lead and header. Appropriate process validations and verifications were provided to support the changes. Processes having results that are easily verified during production do not require validation. There are no further concerns with this above question.

Animal Studies

The preclinical animal study was reviewed by a veterinarian in a review memo dated April 1, 2014. The chronic GLP study involved 2 cohorts: DF4, test and DF-1, control groups to study the safety and efficacy of the DF4 System compared to its predecessor, the DF-1 system. All acceptability criteria and study endpoints were met. Pathological observations were in keeping with device studies of this nature with the exception of one animal (#65008, DF4) whose lead dislodged one week prior to study termination. This animal had endocardial abrasions and secondary organizing mural thrombi that resulted in multifocal pulmonary thromboemboli, downstream occlusions, and collateral ischemia infarctions. The pathologist attributed these lesions to study design (excess lead slack and dislodgement); the reviewer agreed with the assumption. The study data support the premise that the DF4 System is safe and performs similar to the DF-1 system. The reviewer indicated that this preclinical study supports a recommendation of approval.

LEAD REVIEWER COMMENTS: I agree with the reviewer's recommendation for this submission. However, the reviewer stated that this is the second animal study from Biotronik that has been reviewed that used this study design; in both studies, when lead dislodgement occurred significant tissue damage followed. Following review of the first submission we recommended that they reconsider their preclinical study design. I suspect that this study was underway as we reviewed the first submission. This concern will be conveyed to the sponsor via email as a general recommendation for pre-clinical studies submitted in the future.

Post Approval Study (PAS)

The initial review of the proposed PAS was conducted in a review memo dated April 4, 2014. The reviewer noted that while the PAS contained much of the required elements for which we would expect for a new or substantially modified lead, there were a few minor concerns. The concerns from the review memo are highlighted below:

1. In the section 10.1.3 Lead-Related Adverse Events (Page 43, Version 31-DEC-2013), the list of adverse events (AEs) classified as lead-related is not complete. Several critical AEs (in bold) appear to be missing. Please revise the AE list as follows:
 - a. Extracardiac (Diaphragmatic) stimulation
 - b. **Cardiac perforation**
 - c. Lead (conductor) fracture
 - d. Lead dislodgement
 - e. No lead capture / Intermittent capture
 - f. High pacing threshold*
 - g. Lead impedance out of range, high/low impedance*
 - h. Lead oversensing
 - i. Lead undersensing or loss of sensing
 - j. Lead-related thrombosis
 - k. **Lead-related infection**
 - l. **Other unexpected complications that are identified (by image) and considered related to the RV lead or DF4 connector**

***The criteria of high pacing threshold and lead impedance out of range should be pre-specified in the protocol.**

2. There is no timeline included in the PAS protocol. The detailed timeline should be provided in order to objectively assess the progress of the study. Please be sure that the study timeline includes the following information:
 - a. Expected date of study initiation
 - b. Expected monthly number of study sites with IRB approvals
 - c. Expected number of subjects enrolled per month
 - d. Expected date of enrollment completion
 - e. Expected date of study follow-up completion
 - f. Expected date for Final Report submission

The above deficiency was sent to the firm in an email dated April 08, 2014. The firm responded, April 14, 2014 via email. The PAS reviewer indicated that the firm addressed most of the concerns except one deficiency. The sponsor proposed to complete the enrollment in 59 months which is too long according to our guidelines according to the reviewer. It normally requests to complete enrollment in 12 months and sometimes it can be extended to 24-36 months based on circumstance. The longer enrollment actually makes it hard to complete as new device will go to the market. The reviewer contacted the sponsor interactively to resolve the enrollment time frame. FDA had a teleconference with the firm April 30, 2014 to discuss the enrollment timeline. FDA indicated that the firm could increase the number of participating sites to speed up enrollment. The firm expressed the proposed time line was not feasible based on sites and patients willingness to participate as well as projected sales. FDA asked the firm to provide sales projections of the lead to determine if the sample size and enrollment rate was appropriate based on those numbers. From the sales projection it appears that (b)(4) TS/CCI the projected sales would be enrolled with in 24months if the firm were to agree to the FDA enrollment time line of 24months. FDA also explored other options that included leveraging data from the ongoing GALAXY study as well as trying to develop a Bayesian type analysis for the PAS. The alternative options did not prove to be viable. Therefore based on the sales projection and firms rationale FDA agreed that the firm could conduct the proposed study as is. All PAS concerns have been addressed.

Recommendation

The initial review identified concerns with the manufacturing information provided in the submission, as well as minor concerns noted with the proposed PAS. Since much of the testing for the proposed devices appears appropriate and adequate, I recommended proceeding interactively to address the noted concerns. The concerns were sent to the firm April 08, 2014.

The firm provided adequate responses to the concerns noted though out this memo. The information, testing, and results provided in the submission demonstrate a reasonable assurance of safety and effectiveness for the proposed devices. I recommend approval of this PMA supplement.