Clinical Investigation Plan for

QP ExCELs U.S.

Sentus QP – Extended CRT Evaluation with Quadripolar Left Ventricular Leads

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U.S. specific amendment of

QP ExCELs

Sentus QP – Extended CRT Evaluation with Quadripolar Left Ventricular Leads

Protocol Version – February 1, 2017

PROTOCOL SIGNATURE PAGE

The signature below documents receipt and review of the QP ExCELs study protocol and any attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable guidelines.

Principal Investigator:

_____

Name (please print)

_____ _____

Signature Date

Summary

Title	Sentus **QP** – **Ex**tended **C**RT **E**valuation with Quadripolar Left Ventricular **L**eads
Acronym	QP ExCELs
Subject collective	Heart failure subjects with standard CRT-D indication according to clinical routine. Subjects need to be enrolled in the QP ExCELs clinical investigation prior to implantation with a BIOTRONIK Sentus QP left ventricular lead and US market released BIOTRONIK CRT-D with an IS4 port for the LV lead.
Design	Prospective, non-randomized, multi-center clinical investigation to satisfy FDA requirements for pre-market submission and post-approval registry of the Sentus OTW QP left ventricular leads.
Investigational device(s)	Sentus OTW QP L, Sentus OTW QP S, Sentus OTW QP S/49, and Sentus OTW QP L/49 left ventricular lead.
Objectives	Pre-market: Confirm the safety and effectiveness of the BIOTRONIK Sentus OTW QP left ventricular pacing leads. The evaluation of safety will be freedom from Sentus QP related complications at 6 months post-implant. The evaluation of effectiveness will be based on LV pacing capture thresholds. Post-approval: Confirm long-term safety of the BIOTRONIK Sentus OTW QP left ventricular pacing leads. The evaluation of safety will be freedom from Sentus QP related complications at 5 years post-implant.
Primary endpoints	Pre-market: 1. Sentus QP related complication-free rate through 6 months 2. Percentage of subjects with acceptable pacing threshold of Sentus QP lead in permanently programmed vector at 3 months Post-approval: 3. Sentus QP related complication-free rate through 5 years post-implant

Secondary endpoints	Pre-market: 1. Sentus QP pacing threshold in permanently programmed vector at 3 months per lead model 2. Sentus QP pacing threshold in novel vectors at 3 months 3. Sentus QP R-wave sensed amplitude at 3 months per lead model 4. Sentus QP pacing impedance at 3 months per lead model 5. Sentus QP time to first complication 6. Percentage of subjects successfully reprogrammed to resolve phrenic nerve stimulation or high LV pacing threshold during the study period Post-approval: 7. Sentus QP related complication-free rate through 5 years post-implant per lead model 8. Sentus QP Lead Safety – Individual 5-year adverse event rate
MultiPole Pacing (MPP) Sub-study: Primary Endpoint	Evaluation of the CRT responder status with the MPP feature
MultiPole Pacing Sub-Study: Secondary Endpoints	1. Freedom from MPP system-related complications at 6 months post MPP enrollment. 2. Clinical composite score + patient global assessment responder status 3. Clinical composite score responder status utilizing a modified responder classification
Sample Size	Pre-market study: up to 314 subjects enrolled worldwide Post-approval study: up to 1,754 subjects enrolled in U.S MPP sub-study: up to 100 subjects at up to 75 sites within the U.S. who are participating in the QP ExCELs study.
Investigational Sites	Pre-market: Up to 75 sites within the United States, up to 125 sites worldwide Post-approval: Up to 75 sites within the United States

Inclusion criteria	• Standard CRT-D indication according to clinical routine • *De novo* implantation or upgrade from existing ICD or pacemaker implant utilizing a BIOTRONIK CRT-D system with IS4 LV port and Sentus QP LV lead • Patient is able to understand the nature of the clinical investigation and provide written informed consent • Patient is able and willing to complete all routine study visits at the investigational site through 5 years of follow-up • Patient accepts BIOTRONIK Home Monitoring® concept • Age ≥ 18 years
Exclusion criteria	• Contraindication to CRT-D therapy • Currently implanted with an endocardial or epicardial left ventricular lead or had prior attempt to place a left ventricular lead • Cardiac surgical procedure, such as coronary artery bypass graft or valve surgery that is planned to occur within 6 months after implant or ablation that is planned to occur within 90 days after implant (ablations planned to occur prior to or at implant are not exclusionary) • Expected to receive a heart transplant or ventricular assist device within 6 months • Life expectancy less than 12 months • Participation in any other investigational cardiac clinical investigation during the course of the study • Presence of another life-threatening, underlying illness separate from their cardiac disorder • Pregnant or breast-feeding at time of enrollment

MultiPole Pacing Sub-Study: Inclusion Criteria	• Currently enrolled in the ongoing QP ExCELs study • Successfully implanted with a BIOTRONIK Ilivia 7 HF-T QP family CRT-D system, or future U.S. marketed CRT-D system with the MPP feature. Successful implantation is defined as having at least two LV pacing vectors with a measured pacing threshold of ≤ 5.0 V @ any pulse width (allowing for a minimum 2.5 V safety margin) without phrenic nerve stimulation at the final programmed pacing output at the time of enrollment into the MPP sub-study. • CRT Responder Assessment classification as "Worsened" or "Unchanged". • Standard continuous biventricular (BiV) pacing from implant until the 6-Month QP ExCELs follow-up visit. (Implant to 3-Month QP ExCELs follow-up for subjects with a HF hospitalization event prior to 3-Month follow-up) • Able to understand the nature of the sub-study and give informed consent • Available for an additional follow-up visit specific to the MPP sub-study at the investigational site • No evidence of non-compliance to their ongoing commitment in the QP ExCELs study
MultiPole Pacing Sub-Study Exclusion Criteria	• Have a life expectancy of less than 6 months • Expected to receive heart transplantation or ventricular assist device within 6 months • Chronic atrial fibrillation • Presence of another life-threatening, underlying illness separate from their cardiac disorder • Received MPP pacing prior to enrollment into the MPP sub-study
Follow-up period:	All subjects will be followed for 5 years post-implant of the Sentus QP LV lead
Sponsor	BIOTRONIK, Inc. Clinical Studies Department 6024 Jean Road Lake Oswego, Oregon 97035

1. INTRODUCTION

This clinical study protocol includes a pre-market study phase and an FDA required post-approval registry phase for BIOTRONIK's Sentus QP lead. During the study safety and effectiveness data will be collected and evaluated for the Sentus QP lead. The pre-market phase will enroll up to 314 subjects at up to 125 clinical study sites worldwide for pre-market analyses. Up to 75 study sites are planned within the United States. U.S. sites will enroll up to 1,754 subjects as part of a post-approval study. This clinical protocol additionally includes an FDA required post-approval MultiPole Pacing (MPP) sub-study to demonstrate the MPP feature can effectively convert a percentage of CRT non-responders to responders.

Subjects eligible for the study are receiving a new (*de novo*) implant or undergoing an upgrade from an existing ICD or pacemaker implant with no prior attempt at LV lead placement. Prior to enrollment, eligible subjects will be identified and will provide written informed consent. Post implant, subjects will be seen for a pre-hospital discharge or wound check evaluation plus in-office follow-ups at 3, 6, and 12 months. Thereafter, subjects enrolled in U.S. sites will continue to have follow-up visits every 6 months until 5 years post-implant.

Within the U.S., the Sentus QP LV leads are considered investigational devices. All other devices utilized in conjunction with this study are U.S. market approved and prescribed by physicians according to approved indications for use.

This clinical study protocol is a U.S. specific amendment for the QP ExCELs study and is only for U.S. study sites. The study sponsor for all U.S. sites is BIOTRONIK, Inc., Lake Oswego, OR, USA. Enrollment at non-U.S sites has ended with the last subject enrolled on February 29, 2016. It is anticipated that the Sentus QP LV lead will receive FDA approval during the course of the trial. BIOTRONIK will notify all sites when FDA approval is granted. The non-US subjects were enrolled and followed for the pre-market cohort only. These subjects end their study participation at the 12-month follow-up. The sponsor for all non-U.S. sites is BIOTRONIK SE & Co. KG, Berlin, Germany.

1.1 Background

Heart failure (HF) is a major public health issue with a current prevalence of 2-3% in the total and 10-20% in the aged population (Lloyd-Jones et al., 2010). The overall prevalence for heart failure is increasing due to aging population. Additional factors are the success of the modern therapies in prolongation of survival of patients suffering from coronary events and the effective prevention of death for patients being at high risk.

The overall mortality for the population is 50% in the first 4 years and 40% of the patients with HF-related hospitalizations have to be readmitted to hospital or die within one year (Dickstein et al., 2008).

Cardiac Resynchronization Therapy (CRT) is used in order to synchronize interventricular and intraventricular contraction pattern of the heart in patients with heart failure in whom there is evidence of electrical dyssynchrony (QRS width ≥120 ms). CRT with defibrillator function (CRT-D) is recommended to reduce morbidity and mortality in patients in NYHA class III-IV who are symptomatic despite optimal medical therapy and suffer from a reduced left ventricular ejection fraction (LVEF ≤ 35%, (Dickstein et al., 2008)). This indication has been recently extended to patients in NYHA class II (Dickstein et al., 2010).

Despite many improvements in techniques and equipment for this device therapy, phrenic nerve stimulation (PNS) or elevated pacing thresholds are still frequent issues (Crossley et al., 2010; Romeyer-Bouchard et al., 2010).

Phrenic nerve stimulation occurs when a device's electrical output inadvertently activates the diaphragm muscle and causes muscle twitching, hiccup, or shortness of breath. Phrenic nerve stimulation is found in 2 to 37% of implanted patients, depending on different factors including the type of the left ventricular lead (Moubarak et al., 2014). A higher incidence of PNS is found in the standard pacing configuration as compared to alternative configurations (Goetze et al., 2013). With unipolar and bipolar left ventricular leads, PNS may require surgery to reposition the lead or disable the CRT. With four electrodes on the left ventricular (LV) lead and 12 programmable pacing configurations, available with the Sentus QP left ventricular lead in combination with a corresponding CRT-D device, an occurrence of PNS or increased LV pacing thresholds may be resolved by non-invasive optimization of CRT delivery. Goetze et al., 2013 have shown that in 98% of patients presenting with phrenic nerve stimulation a reprogramming of the pacing vector could successfully terminate phrenic nerve stimulation without re-operation. Therefore, by using leads with multiple pacing options, the risk of surgical revision during follow up may be reduced.

Apart from limiting risks of CRT, quadripolar (QP) leads with multiple additional pacing vectors can also increase cardiac output compared to conventional bipolar LV leads (Cabrera-Bueno et al., 2013; Thibault et al., 2013) and thus enhance the overall benefit of CRT.

The combination of the new BIOTRONIK left ventricular lead family Sentus QP, containing 4 separate electrodes, with the corresponding Cardiac Resynchronization Therapy devices (CRT), provides additional pacing options to optimize cardiac resynchronization therapy, based on the individual anatomy and needs of heart failure patients as well as the occurrence of PNS and increased thresholds.

The QP ExCELs study aims to gather safety and effectiveness data on BIOTRONIK Sentus QP leads which will be used to satisfy US FDA requirements for pre-market submission of the Sentus over-the-wire (OTW) quadripolar (QP) left ventricular (LV) leads.

1.2 Devices

The investigational devices used in this clinical investigation are the Sentus OTW QP L LV lead, Sentus OTW QP S LV lead, Sentus OTW QP S/49 LV lead, and Sentus OTW QP L/49 LV lead.

Sentus OTW QP L, Sentus OTW QP S, Sentus OTW QP S/49, and Sentus OTW QP L/49 are quadripolar coronary sinus leads with IS4 connector. The leads are intended for permanent implantation in the coronary venous system and for left ventricular pacing with an appropriate triple chamber implantable pulse generator. The Sentus OTW QP L, Sentus OTW QP S, Sentus OTW QP S/49, and Sentus OTW QP L/49 will be further referred to as Sentus QP leads throughout this protocol. The Sentus QP leads will be utilized in conjunction with a US market released BIOTRONIK CRT-D with an IS4 port for the LV lead.

1.3 Investigational Device Description

1.3.1 Sentus QP Lead Design

The Sentus QP leads are 4.8 F transvenous, steroid-eluting, quadripolar coronary sinus leads intended for permanent pacing and sensing of the left ventricle during cardiac resynchronization therapy. The development of the Sentus QP lead (Figure 1) is based on the predecessor product Corox OTW BP. The new elements of the development include two additional ring electrodes along the distal portion of the lead, a standard IS4 quadripolar lead connector (Figure 2) and a small diameter.

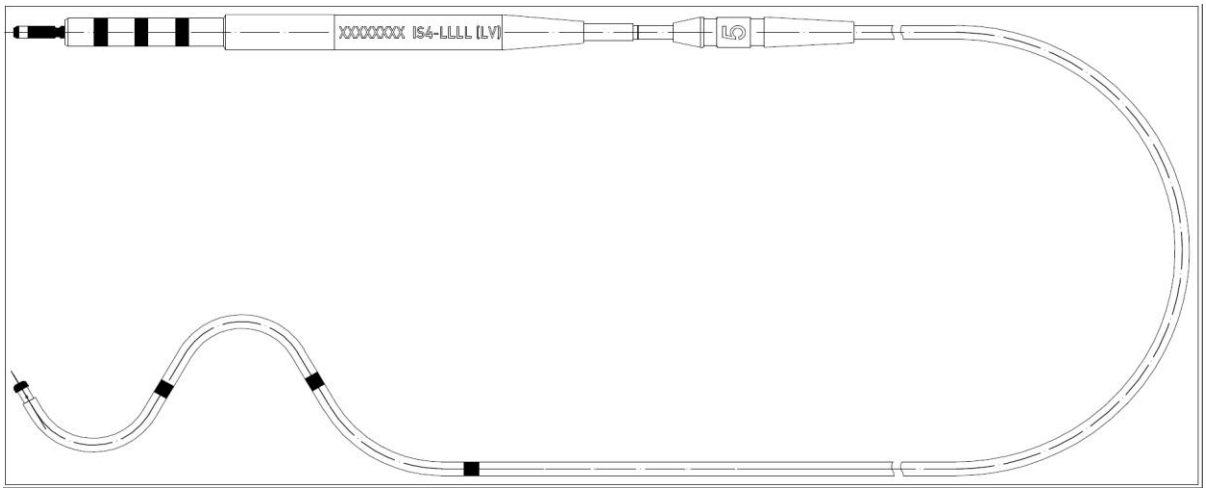


Figure 1: Sentus OTW QP Left Ventricular Lead (L model)

Figure 2: IS4 Connector of the Sentus QP Lead

A single steroid collar with 0.5 mg dexamethasone acetate (DXA) is located proximal to the lead tip. In the Sentus OTW QP L and Sentus OTW QP S models the distance between LV1-tip and LV2-ring is 21 mm, between LV2-ring and LV3-ring 20 mm and between LV3-ring and LV4-ring 20 mm. The additional Sentus OTW QP S/49 and Sentus OTW QP L/49 models have shorter pole spacing for short target vein anatomies with a distance of 21 mm between LV1-tip and LV2-ring, 15 mm between LV2-ring and LV3-ring, and 10 mm between LV3-ring and LV4-ring (Figure 3, Figure 4, and Figure 5). The tip and ring electrodes are coated with fractal iridium. The tantalum and platinum/iridium conductor coil is insulated with silicone, and then externally coated with polyurethane. Polyurethane improves the gliding capabilities of the lead when advanced through a left ventricular lead delivery catheter and through the coronary vasculature. The Sentus QP leads can be positioned in the target vein by using a guide wire via the over-the-wire technique or by using a stylet.

The Sentus QP has an outer diameter of 4.8 F and can be implanted with a CS lead delivery system.

Four Sentus QP lead models will be evaluated in this clinical investigation:

- Sentus OTW QP L and L/49 models are passive fixation leads utilizing a 2D dual-curve to achieve a stable position within the target vein.
- Sentus OTW QP S and S/49 models utilize a bend in the distal end enhanced with a silicone screw to provide passive fixation within the target vein.

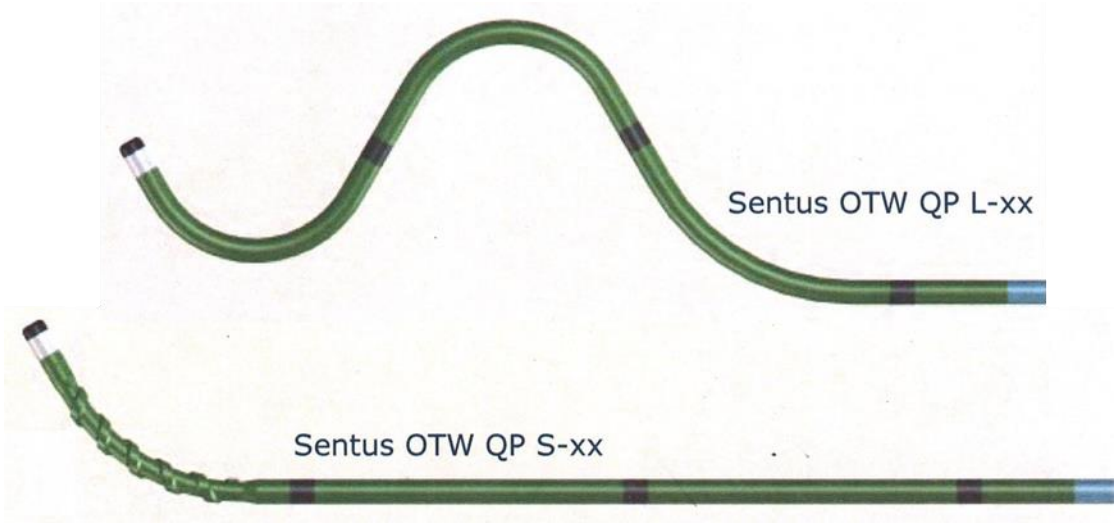


Figure 3: Sentus QP Lead Tip Design

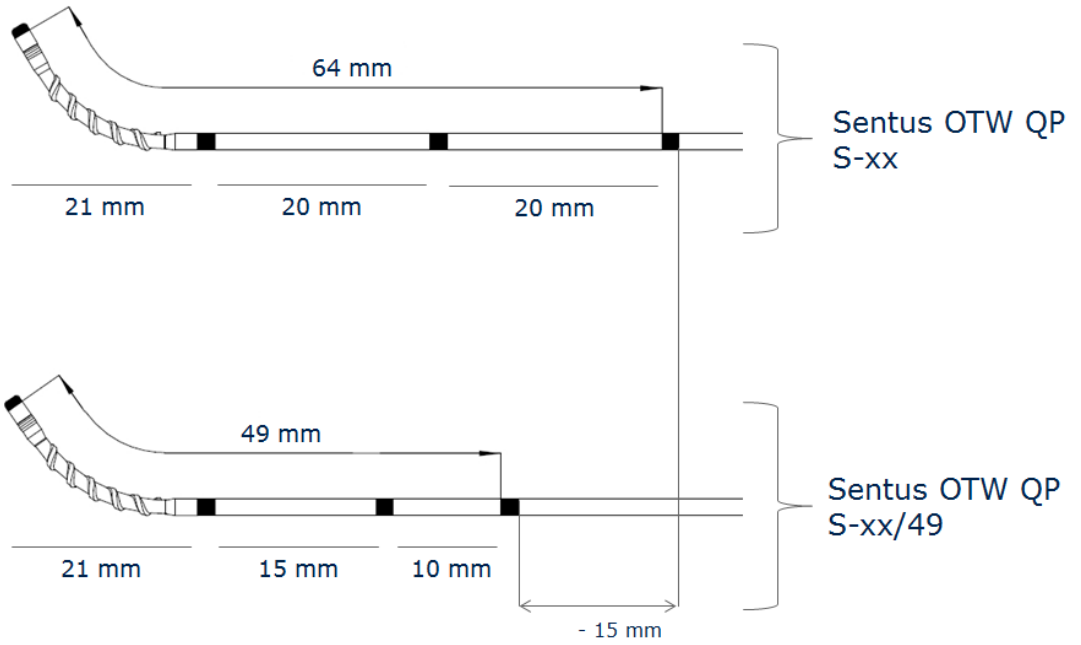


Figure 4: Pole Spacing with Sentus OTW QP S Models

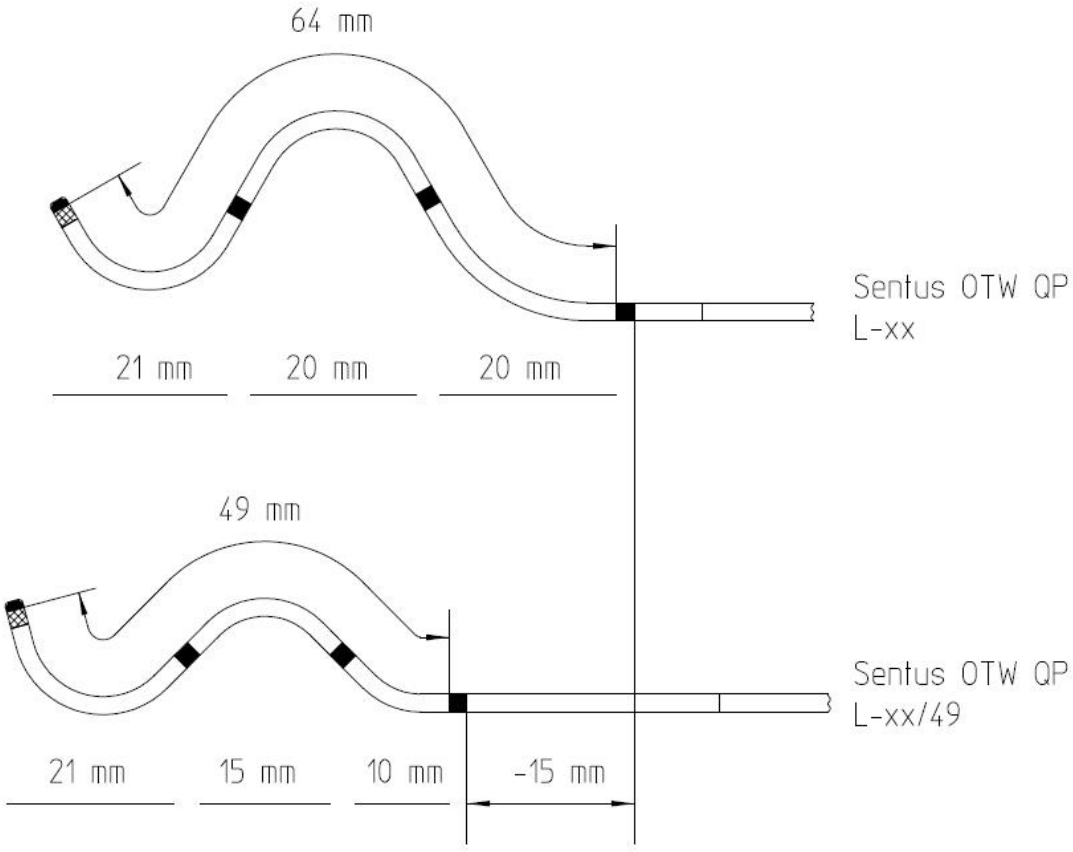


Figure 5: Pole Spacing with Sentus OTW QP L Models

The Sentus OTW QP is available in three lengths; L-75 (77 cm), L-85 (87 cm), and L-95 (97 cm). All three length variants carry a green marker ring to identify them as left ventricular CRT leads (Figure 2).

1.3.2 Pacing and Sensing Vector Options

When connected to a CRT-D device with an IS4 LV port, the Sentus QP leads offer more options in pacing and sensing configurations as compared with conventional bipolar systems.

The vectors are built between a cathode (From -) to an anode electrode (To +). Besides the four consecutively numbered LV electrodes of the quadripolar LV lead (LV1 tip, LV2 ring, LV3 ring, LV4 ring) the distal shock coil of the RV lead (RV coil) or the ICD housing (CRT-D) can be used as additional anode electrodes for the LV pacing and sensing configuration. This gives the Sentus QP leads a total of 12 LV pacing and 7 LV sensing vector options as described in Table 1.

Table 1: LV Pacing and Sensing Configurations

Pacing Vectors			Sensing Vectors		
#	From (-) →	To (+)	#	From (-) →	To (+)
1	LV1 tip →	LV2 ring	1	LV1 tip →	LV2 ring
2	LV1 tip →	LV4 ring	2	LV1 tip →	ICD
3	LV1 tip →	RV coil	3	LV2 ring →	LV3 ring
4	LV1 tip →	ICD	4	LV2 ring →	ICD
5	LV2 ring →	LV1 tip	5	LV3 ring →	LV4 ring
6	LV2 ring →	LV4 ring	6	LV3 ring →	ICD
7	LV2 ring →	RV coil	7	LV4 ring →	ICD
8	LV3 ring →	LV2 ring			
9	LV3 ring →	LV4 ring			
10	LV3 ring →	RV coil			
11	LV4 ring →	LV2 ring			
12	LV4 ring →	RV coil			

The vectors are chosen by selecting a cathode (From -) and an anode electrode (To +) during device interrogation and programming (Figure 6).

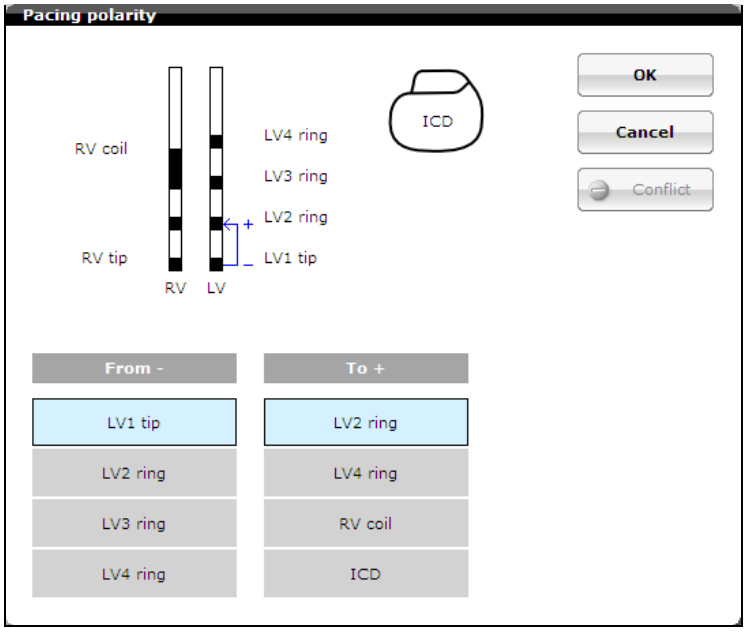


Figure 6: Programmer Display of LV Pacing Polarity

1.4 Prior Clinical Performance

BIOTRONIK, Inc. submitted the QP ExCELs Pre-Market Approval (PMA) Clinical Report in support of the PMA application to the FDA on November 23, 2016 and it is currently under FDA review. The PMA Clinical Report included all data collected since the first subjects were enrolled on December 16, 2014 (O.U.S.) and October 15, 2015 (U.S.) through September 9, 2016. A total of 635 subjects were enrolled and 576 successfully implanted with a Sentus QP lead. The cumulative implant duration was 341.8 years (mean implant duration: 0.6 ± 0.3 years).

The analyzed pre-market cohort is comprised of 299 subjects who were implanted on or before January 29th, 2016; the implant date for the 282nd subject to complete a 3 month follow-up. All pre-market primary endpoints were met with statistical significance and the results are summarized below.

1.4.1 Primary Endpoint 1 Results

The purpose of primary endpoint 1 is to evaluate the Sentus QP related complication-free rate through 6 months post-implant. Reported adverse events that were related to the implanted CRT-D system and/or implant procedure were adjudicated by the CEC. Events that occurred prior to or on the date of the 6 month follow-up and were adjudicated by the CEC as meeting the primary endpoint criteria were included in the calculation of the primary endpoint 1 complication-free rate. For the purposes of the primary endpoint 1 analysis, evaluable subjects are those who were included in the pre-market cohort and either completed a 6 month follow-up visit (n = 274), experienced an endpoint related adverse event but exited the study prior to reaching the 6 month follow-up

(n = 2), did not complete a 6 month follow-up visit but did complete a subsequent visit (n = 3), or had an unsuccessful implant due to a Sentus QP lead related complication (n = 0). Subjects in the pre-market cohort that did not have a successful Sentus QP implant were not included in the endpoint 1 analysis (unless, as noted above, the unsuccessful implant was due to a Sentus QP lead related complication). The total number of evaluable subjects for primary endpoint 1 was 279.

Analysis

Primary endpoint 1 was evaluated by performing an exact, binomial test comparing the observed proportion (complication-free rate at 6 months) to 90.0%.

Of the 279 evaluable subjects for primary endpoint 1, eight subjects had an event that met the primary endpoint criteria, were adjudicated by the CEC as related to the Sentus QP lead, and occurred prior to or on the date of the 6 month follow-up. The complication-free rate through 6 months post-implant is 97.1% (271/279), 95% CI of 94.4% to 98.8%, p<0.0001.

Table 2 provides a summary of the eight primary endpoint 1 adverse events.

Table 2: Primary Endpoint 1 Adverse Event Summary

Adverse Event Type	Subjects with AE	% with AE	Number of AEs	Rate (per subject year)
Lead dislodgement	4	1.43%	4	0.028
Extracardiac stimulation	3	1.08%	3	0.021
Lead impedance out of range, high	1	0.36%	1	0.007
Total	**8**	**2.87%**	**8**	**0.055**

Total number of implanted subjects = 279; Subject years since successful implant = 144.7

Conclusion

The results indicate that the complication-free rate through 6 months post-implant is greater than 90.0%; therefore, primary endpoint 1 is met.

1.4.2 Primary Endpoint 2 Results

The purpose of primary endpoint 2 is to evaluate the LV lead pacing threshold for the permanently programmed pacing vector at 3 months post-implant. Specifically, the percentage of subjects with an acceptable LV pacing threshold in the permanently programmed vector at the 3 month follow-up will be determined. An acceptable LV threshold was defined as being ≤ 2.5 V at a pulse width of 0.4 ms in the pacing vector programmed at the beginning of the 3 month follow-up.

For the purposes of the primary endpoint 2 analysis, evaluable subjects are those who were included in the pre-market cohort and either completed a threshold test at a pulse width of 0.4 ms at the 3 month follow-up (n = 276), did not have a threshold test at or missed the 3 month follow-up but had Home Monitoring data meeting specific consistency criteria available for imputation (n = 3), had a subsequent follow-up visit with threshold test at a pulse width of 0.4 ms (n = 7), or were not successfully implanted due to a Sentus QP lead related adverse event (n = 0). A total of 286 subjects were included in the evaluation of primary endpoint 2.

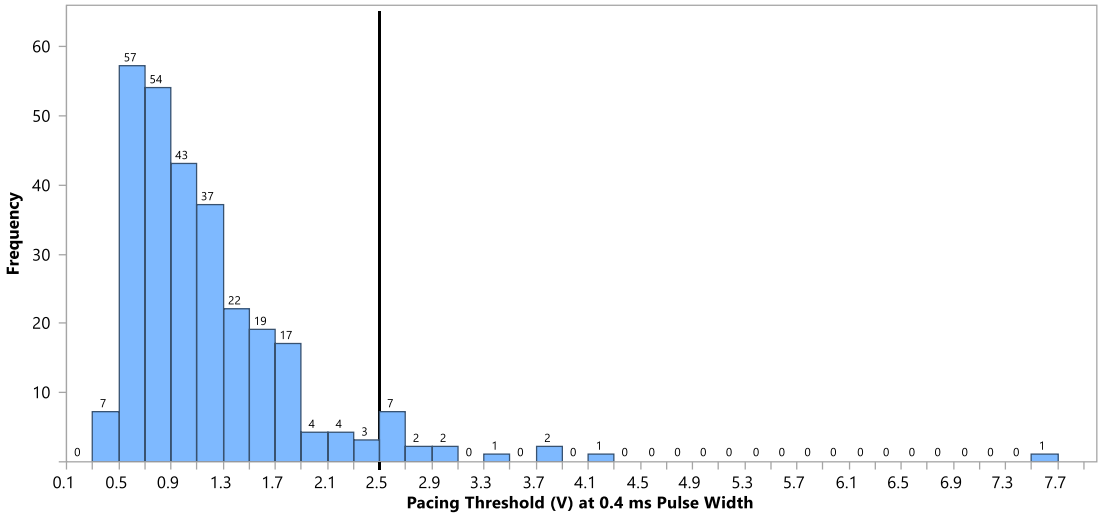
Analysis

Primary endpoint 2 was evaluated by performing an exact, binomial test comparing the observed proportion (rate of acceptable LV pacing thresholds at 3 months) to 88.0%.

Of the 286 evaluable subjects for primary endpoint 2, 267 subjects had an acceptable LV threshold for a rate of 93.4%, 95% CI of 89.8% to 96.0%, p=0.002.

Figure 7 provides a histogram showing the Sentus QP pacing threshold values in the permanently programmed vector at 3 months. The acceptable threshold maximum of 2.5 V is indicated by the vertical line. Three subjects had a result of no capture possible during the threshold test and are not displayed in Figure 7. These three subjects were considered as failures in the analysis of primary endpoint 2.

Figure 7: Sentus QP Pacing Threshold Values at the 3 Month Follow-up



Conclusion

The results indicate that the proportion of subjects with an acceptable threshold value in the permanently programmed vector at the 3 month follow-up is greater than 88.0%; therefore, primary endpoint 2 is met.

2. STUDY DESIGN

This is a multi-center, prospective, non-randomized clinical investigation. To document the clinical experience of the Sentus QP lead as required by the FDA to satisfy requirements for pre-market submission, the pre-market clinical investigation is designed to enroll up to 314 subjects whom will be followed for at least 12 months post-implant at up to 125 sites in total including up to 75 investigational sites within the United States. To satisfy U.S. requirements for a long term post-approval registry, the clinical investigation is designed to enroll up to 1754 U.S. subjects whom will be followed for 5 years post-implant. A sub-study is included (Section 11) to satisfy an FDA required post-approval study of the Multi-Pole Pacing feature (PMA P050023/S107) of the Ilivia HF-T QP family CRT-D system (PMA P050023/S103).

2.1 Objectives

The objective of this clinical investigation is to confirm the safety and efficacy of BIOTRONIK's Sentus QP leads in a clinical investigation to support regulatory approval as well as a long term post-approval evaluation of the devices in the United States. The safety objective of the clinical investigation is to assess the safety of the Sentus QP lead by the analysis of the lead related complications during 6 months after implantation. The efficacy (performance) objective of the clinical investigation is to assess if pacing thresholds of the lead are in an acceptable range at 3 months after implantation. The post-approval objective of the clinical investigation is to assess the safety of the Sentus QP lead by the analysis of the lead related complications through 5 years post-implant.

2.2 Study Endpoints and Hypotheses

The following endpoints have been defined to confirm the safety and efficacy of the investigational devices.

2.2.1 Primary Endpoint 1: Sentus QP Related Complication-Free Rate through 6 Months (Pre-Market Analysis)

The purpose of primary endpoint 1 is to evaluate the Sentus QP related complication-free rate through 6 months post-implant. The Sentus QP related complications that will be assessed in this primary endpoint are defined in Section 6.6.1. The parameter of interest $p_{Complication}^{SentusQP}$ is the complication-free rate per subject, which will be calculated by (1 - the number of subject with one or more complications divided by the number of subjects) in percent. The period of observation starts after successful implantation of the Sentus QP lead.

The following hypotheses have been defined to evaluate the primary endpoint "Sentus QP related complication-free rate through 6 months":

H_o: Complication-free rate through 6 months post-implant is ≤ 90.0%

H_a: Complication-free rate through 6 months post-implant is > 90.0%

A rejection of the null hypothesis (H_o) would demonstrate evidence that the complication-free rate is greater than 90.0%.

2.2.2 Primary Endpoint 2: Percentage of Subjects with Acceptable Pacing Threshold in Permanently Programmed Vector at 3 Months (Pre-Market Analysis)

The purpose of primary endpoint 2 is to evaluate the LV lead pacing threshold for the permanently programmed pacing vector at 3 months post-implant. Specifically, the percentage of subjects with an acceptable LV pacing threshold in the permanently programmed vector at the 3-month visit ($p_{acceptable}^{PaThres}$) will be determined. LV threshold values of ≤ 2.5V at 0.4 ms in the permanently programmed vector, defined as the permanent pacing vector at the beginning of the 3-month visit interrogation, will be considered acceptable.

The following hypotheses have been defined to evaluate the primary endpoint "Percentage of subjects with acceptable pacing threshold in permanently programmed vector at 3 months":

H_o: Acceptable LV threshold rate at 3 months post-implant is ≤ 88.0%

H_a: Acceptable LV threshold rate at 3 months post-implant is > 88.0%

A rejection of the null hypothesis (H_o) would demonstrate evidence that the rate of acceptable LV pacing thresholds is greater than 88.0%.

2.2.3 Primary Endpoint 3: Sentus QP Related Complication-Free Rate through 5 years (Post-Approval Analysis)

The purpose of primary endpoint 3 is to evaluate the long-term Sentus QP related complication-free rate through 5 years post-implant. The Sentus QP related complications that will be assessed in this primary endpoint are defined in Section 6.6.2. The parameter of interest $p_{Complication}^{SentusQP}$ is the complication-free rate per subject, which will be calculated by (1 - the number of subject with one or more complications divided by the number of subjects) in percent. The period of observation starts after successful implantation of the Sentus QP lead.

The following hypotheses have been defined to evaluate the primary endpoint "Sentus QP related complication-free rate through 5 years":

H_o: Complication-free rate through 5-years post-implant is ≤ 92.5%

H_a: Complication-free rate through 5-years post-implant is > 92.5%

A rejection of the null hypothesis (H_o) would demonstrate evidence that the complication-free rate is greater than 92.5%.

2.2.4 Secondary Endpoints

The following secondary endpoints will be evaluated during this clinical investigation. There are no formal tests of hypothesis associated with the secondary endpoints. Secondary endpoints 1 through 6 will only be evaluated as

part of the pre-market analyses. Secondary endpoint 7 and 8 will be evaluated as part of the post-approval analyses.

2.2.4.1 Sentus QP pacing threshold in permanently programmed vector at 3 months per lead model

The purpose of the secondary endpoint is to evaluate the LV lead pacing threshold for the permanently programmed pacing vector at 3 months post-implantation in the four different lead types, Sentus OTW QP L, Sentus OTW QP S, Sentus OTW QP S/49, and Sentus OTW QP L/49. Specifically, the percentage of subjects with an acceptable LV pacing threshold in the permanently programmed vector at the 3-month visit will be determined for both leads. LV pacing threshold values of ≤ 2.5V at 0.4 ms in the permanently programmed vector, defined as the permanent pacing vector at the beginning of the 3-month visit interrogation, will be considered acceptable.

2.2.4.2 Sentus QP pacing threshold in novel vectors at 3 months

The purpose of this secondary endpoint is to evaluate the LV lead pacing threshold for the novel pacing vector at 3 months post-implantation. Specifically, the percentage of subjects with at least one acceptable LV pacing threshold in the novel vectors at the 3-month visit will be determined. LV pacing threshold values of ≤ 2.5V at 0.4 ms in the novel vectors will be considered acceptable. Novel vectors are defined as all vectors utilizing one of the two distal LV rings (LV3 or LV4).

2.2.4.3 Sentus QP R-wave sensed amplitude at 3 months per lead model

The purpose of this secondary endpoint is to evaluate the LV lead sensing amplitude at 3 months post-implantation. Specifically, the percentage of subjects with acceptable LV sensing amplitude at the 3-month visit will be determined. R-wave sensed mean amplitude of ≥ 2mV will be considered acceptable.

2.2.4.4 Sentus QP pacing impedance at 3 months per lead model

The purpose of this secondary endpoint is to evaluate the LV lead pacing impedance at 3 months post-implantation. Specifically, the percentage of subjects with acceptable LV pacing impedance at the 3-month visit will be determined. LV impedance values of >200 Ohms and <2000 Ohms will be considered acceptable.

2.2.4.5 Sentus QP Time to first complication

The purpose of this secondary endpoint is to evaluate the Sentus QP related complication-free rate through 6 months post-implant by the Kaplan-Meier method.

2.2.4.6 Percentage of subjects successfully reprogrammed to resolve phrenic nerve stimulation or high pacing threshold during the study period

The purpose of this secondary endpoint is to evaluate the effectiveness of electrical lead repositioning to resolve phrenic nerve stimulation or high LV pacing thresholds. Specifically, the percentage of subjects in which phrenic nerve stimulation or high LV pacing thresholds which could be resolved by vector reprogramming during the study period will be determined in relation to all subjects in which it was attempted to resolve phrenic nerve stimulation or high LV pacing thresholds by electrical repositioning.

2.2.4.7 Sentus QP Related Complication-Free Rate through 5 years per lead model

The purpose of this secondary endpoint is to evaluate the long-term Sentus QP related complication-free rate through 5 years post-implant per lead model. The Sentus QP related complications that will be assessed in this endpoint will be those defined in Section 6.6.2

2.2.4.8 Sentus QP Lead Safety – Individual 5-year adverse event rates

The purpose of this secondary endpoint is to evaluate each of the individual types of adverse events contributing to primary safety endpoint 3. The Sentus QP related complications that will be assessed in this endpoint will be those defined in Section 6.6.2.

2.2.5 Additional Data of Interest

Additional information will be collected to characterize the study population, implanted system, and progress of the clinical investigation. The collected data will include baseline demographics, comorbidities, implanted system and implantation experience, system revision, Sentus QP extractions, returned product analysis, and compliance. The data will be statistically analyzed, where appropriate. Specifically, further data of interest will include:

- Demographics, including age and gender
- Baseline New York Heart Association (NYHA) class
- Historical left ventricular ejection fraction (LVEF), if obtained within 6 months prior to enrollment
- Implanted devices, including pulse generator and other leads
- Implantation site and, if available, implant approach
- Approximate vessel diameter at Sentus QP lead tip (at final lead position, when this information is available from a routine venogram performed during implant)
- Reason for inability to place Sentus QP lead

- Adverse events related to implant procedure, pulse generator, or other implanted leads
- Sentus QP lead performance at 6 and 12 months post-implant plus at additional required follow-up visits (i.e., 18 months, 24 months), including R-wave sensing, pacing impedance, and pacing threshold
- Revisions to implanted system and reason for revision
- Results from returned product analysis
- Compliance to protocol requirements and study visit schedule
- Sentus QP pacing threshold in novel vectors (optional)

2.3 Statistical Design, Method, and Analytical Procedures

2.3.1 Pre-Market Analyses Cohort

A pre-market cohort for analysis of primary endpoints 1 and 2 and secondary endpoints 1 through 6 will be comprised at the time when 231 completed 6 month follow-ups and 282 completed 3 month follow-ups have occurred. Follow-ups will be considered complete once entered in the EDC system and case report forms are electronically signed by the investigator.

The pre-market analyses cohort is defined as the population of subjects who were implanted (or had an implant attempt) on or before the implant date of the last subject to reach the latter of the 231st completed 6 month follow-up or 282nd completed 3 month follow-up.

2.3.2 Primary Endpoint 1 Analysis

The analysis population for primary endpoint 1 will include all subjects who provided informed consent, met the enrollment criteria, and in whom a Sentus QP lead was successfully implanted. The common scenarios listed below will be taken into account for analysis of primary endpoint 1:

- Subjects who completed a 6 month follow-up or experienced an adverse event (as defined in Section 6.6.1) prior to reaching the 6 month follow-up time point will be included in the endpoint evaluation.
- Subjects without an adverse event (as defined in Section 6.6.1) who exit the study prior to the 6-month follow-up are excluded from the analysis population to avoid an overestimation of the complication-free rate.
- Subjects that were not successfully implanted due to a Sentus QP lead related complication (such as coronary sinus dissection caused by the Sentus QP lead) will be included in the population.
- Any subject with a missing 6 month follow-up, who completes a subsequent follow-up (e.g. 12 month follow-up or interim follow-up) will be included in the evaluation.

Primary endpoint 1 will be evaluated by performing an exact, binomial test comparing the observed proportion (overall complication-free rate at 6 months) to the performance goal of 90.0%. The lower, two-sided 95% confidence bound for the overall complication-free rate must be greater than 90.0%.

2.3.3 Primary Endpoint 2 Analysis

For primary endpoint 2, only subjects who provide informed consent, met the enrollment criteria, and in whom a Sentus QP lead was successfully implanted will be included. The common scenarios listed below will be taken into account for analysis of primary endpoint 2.

- Any subjects not successfully implanted due to a Sentus QP lead related adverse event will be included in the analysis for primary endpoint 2 as a failure.
- For successfully implanted subjects that missed a 3 month visit or did not undergo threshold testing of the LV lead at the 3 month visit, or completed threshold testing at a pulse width other than 0.4 ms, missing data points will be imputed according to Section 2.5.4.

Primary endpoint 2 will be evaluated by performing an exact, binomial test comparing an observed proportion (rate of acceptable LV pacing thresholds at the permanently programmed pacing vector at 3 months) to 88.0%. The lower, two-sided 95% confidence bound for the percentage of subjects with an acceptable LV pacing threshold in the permanently programmed pacing vector must be greater than 88.0%.

2.3.4 Primary Endpoint 3 Analysis

The analysis population for primary endpoint 3 will include all subjects who provided informed consent, met the enrollment criteria, and in whom a Sentus QP lead was successfully implanted. Only subjects who were successfully implanted and completed a 60-month month visit will be included in the endpoint analysis

Primary endpoint 3 will be evaluated by performing an exact, binomial test comparing the observed proportion (overall complication-free rate at 5 years) to the performance goal of 92.5%. The lower, two-sided 95% confidence bound for the overall complication-free rate must be greater than 92.5%.

2.3.5 Secondary Endpoints

The secondary endpoints of pacing threshold (programmed and novel pacing vectors), sensed amplitude, and impedance at the 3 month visit will be summarized using standard measures, including means, standard deviations, medians, minimum and maximums. In addition, the percentage of subjects with values within the acceptable range per lead model will be provided. Acceptable ranges for the lead measurements are provided in Section 3.2.5.

For secondary endpoints 1-4 only subjects who were successfully implanted, completed a 3 month visit, and have data for the specific endpoint being evaluated will be included in the endpoint analysis; however, additional data resources may be used for supplemental analysis.

For the endpoint 5, time-to-first-complication, the analysis set of the primary endpoint 1 and additionally also those subjects who drop out prior to the 6-month follow-up is used. Confidence intervals based on Kaplan-Meier estimates for freedom from complications together with the associated standard errors will be provided. For this estimate, subjects exiting the clinical investigation prior to the 6 month visit will be censored at the time of study termination.

For endpoint 7 and 8, only subjects who were successfully implanted and completed a 60-month month visit will be included in the endpoint analysis; however, additional data resources may be used for supplemental analysis.

2.3.6 Additional Data of Interest Analysis

For additional data of interest, descriptive summary statistics appropriate to the type of parameter, continuous or discrete, will be reported.

Pacing threshold, R-wave sensing and impedance measurements for the Sentus QP leads at pre-hospital discharge/wound check, 3, 6, and 12 months, plus additional required follow-up visits (i.e., 18 months, 24 months) will be summarized using standard measures, including means, standard deviations, medians, minimums, and maximums. Data will be provided as a total at each visit interval and per lead model at each visit interval.

2.3.7 Trend Analyses

The primary post-approval safety endpoint is evaluated at 5 years post-implant against a prespecified performance level (92.5% for overall freedom from Sentus QP related complications). To monitor the ongoing incidence of any potential AEs against the accumulating follow-up exposure post-implant, a Kaplan-Meier survival curve will be prepared at the reporting intervals for this safety outcome. Root causes for any failures, regardless of the incidence rates, will be investigated.

If the observed cumulative survival rate falls below the 5-year target value (92.5% of overall freedom from complications) at any time during the study, or is projected to fall below the target value, then BIOTRONIK will summarize the observed data and the results of the failure investigations, and report the findings to the FDA at or before the next scheduled reporting interval. If at any time a single unanticipated adverse event or device failure, or combination of events, is believed to have implications regarding the safety of current or future subjects, then this will be reported to the FDA within the statutory timeframes.

2.4 Estimated Sample Size

2.4.1 Pre-Market Analyses

The sample size required to evaluate primary hypotheses 1 and 2 was estimated using the following design criteria:

- Study design: non-randomized
- Test basis: exact binomial test
- Type I error, alpha: 2.5% (one-sided)
- Statistical power: 80% for acceptance of both primary Alternative hypotheses

For primary safety hypothesis (complication-free rate), the following assumptions apply:

- Expected complication-free rate through 6 months: 95.0%
- H_A: Complication-free rate through 6 months post-implant > 90.0%

For primary efficacy hypothesis (LV pacing threshold for permanently programmed vector), the following assumptions apply:

- Expected rate of acceptable LV pacing thresholds at 3 months: 93.0%
- H_A: Acceptable LV pacing threshold rate at 3 months > 88.0%

Based on the above criteria, a total of 231 evaluable subjects assessed at 6 months would be required to accept the primary safety alternative hypothesis (endpoint 1). For primary endpoint 2, a total of 282 evaluable subjects assessed at 3 months would be required to accept the primary efficacy alternative hypothesis.

An adjustment of 10% is used in the sample size estimation for both primary endpoints 1 and 2 to account for subjects that exit the clinical investigation prior to having a 6 month evaluation. Reasons that subjects may exit the clinical investigation include withdrawal of consent, mortality, device explant, change in physician, or subject moving. Therefore, up to 314 subjects (=282/.9) will need to be enrolled to account for premature study terminations.

2.4.2 Post-Approval Analysis

The sample size required to evaluate primary hypotheses 3 was estimated using the following design criteria:

- Study design: non-randomized
- Test basis: exact binomial test
- Type I error, alpha: 2.5% (one-sided)
- Statistical power: 80%
- Expected complication-free rate through 5-years: 94.75%

- H_A: Complication-free rate through 5-years post-implant > 92.5%

Based on the above criteria, a total of 979 evaluable subjects assessed at 5 years would be required to accept the primary 5-year safety alternative hypothesis.

An adjustment of 11% per year is used in the sample size estimation for primary endpoint 3 to account for subjects that exit the clinical investigation prior to having a 5-year (60-month) evaluation. Reasons that subjects may exit the clinical investigation include withdrawal of consent, mortality, device explant, change in physician, or subject moving. Therefore, up to 1754 evaluable subjects (=979/0.89^5) will need to be enrolled to account for premature study terminations.

2.4.3 Replacement of Subjects

For this study, a drop-out rate of 11% of subjects per year is expected in the QP ExCELs study. The additional enrollment of 11% (total subject number: n=979/0.89^5) is considered sufficient for the collection of the required primary endpoint 3 (n=979). However, to ensure sufficient primary endpoint 3 evaluable data, subjects who exit the clinical investigation prior to implantation of the LV lead, or by death, explant, lost-to-follow up may be replaced as long as enrollment is ongoing. This includes subjects in which it is determined that they are not eligible for the Sentus QP lead during implantation, as long as the subject did not come in contact with the Sentus QP lead. These subjects do not count to the overall U.S. planned subject number of 1754.

2.5 Other Statistical Considerations

2.5.1 Success Criteria

The proposed study will be considered a success (pre-approval) if the requirements set by the FDA for regulatory approval of the Sentus QP leads are fulfilled. The post-approval study will be considered a success if the post-approval requirements of the Sentus QP leads are fulfilled.

2.5.2 Provision for a Pivotal and Interim Analysis

An FDA pivotal analysis of the pre-market endpoint relevant data is planned after the minimum sample size for Primary Endpoints 1 and 2 has been met (Section 2.3.1). All enrolled subjects will be considered in an OUS Final Clinical Investigation Report, which is planned after all enrolled subjects outside of the U.S. have completed the 12 month follow-up period. Further interim analyses are not planned and there are no statistical criteria to stop the clinical investigation for superiority. Thus, no adjustment of the significance level is planned.

2.5.3 Specification of Subgroups

For primary endpoints, pooling of data from the Sentus OTW QP S, Sentus OTW QP S/49, Sentus OTW QP L, and Sentus OTW QP L/49 leads will be justified as part of the final data analysis. Potential differences in primary endpoint outcomes for the S lead models (Sentus OTW QP S or S/49) and the L lead models (Sentus OTW QP L or L/49) will be tested using an exact, Chi-square test. If no evidence is found of differences between the S and L lead models ($p > 0.05$), then the results will be considered poolable for the purposes of testing the hypothesis associated with each applicable primary endpoint. Based on the model mix of the Corox OTW-S and OTW-L in the CELESTIAL study, at least 30% of implants are expected to include the Sentus OTW QP S or S/49 lead models. However, as a minimum target, at least 100 subjects should be implanted with each of the two fixation curves (L or S) for the pre-market analyses, and at least 400 subjects with each fixation curve for the post-approval analyses (Note: the Sentus OTW QP L/49 lead model was not included in the study protocol prior to the pre-market analysis and will only contribute to the post-approval analysis). Additionally, gender subgroup analysis of the primary endpoints will be conducted with a p-value of 0.15 or less considered evidence of gender differences.

The distribution in complication-free rates across study centers will also be examined. The significance of differences in rates between centers will be initially tested using a Kruskal-Wallis test statistic, with an associated p-value of 0.15 or less considered evidence of center differences. In addition, a Cochran-Mantel-Haenszel test with continuity adjustment will be used to assess the poolability of data collected across the different centers. If evidence is found of center differences, then the reasons for the differences will be explored using Cox and logistic regression methods to determine if any baseline subject risk factors are explanatory.

Details on the data analysis plan for all endpoints and additional data of interest is provided in Section 2.3.

2.5.4 Handling of Missing, Unused, or Spurious Data

All possible steps will be taken to minimize missing data in the clinical investigation. This includes but is not limited to monitoring of study forms for completeness and supporting efforts to track and maintain contact with study subjects during the study period. If any data is missing, the reason will be documented.

In cases of missing data, a pre-planned supplemental procedure using BIOTRONIK Home Monitoring® data to impute the missing data points will be followed. When active, BIOTRONIK Home Monitoring® provides daily automatic LV pacing thresholds, R-wave sensing, and pacing impedance. When available, missing data will be imputed with BIOTRONIK Home Monitoring® values obtained from the day of a completed follow-up, due date of a missed follow-up, or the next closest day before or after.

For values imputed in support of primary endpoint 2, the consistency of the imputed value will be examined by comparing the selected value to the average value of the surrounding 6 values (typically 3 values prior to the selected value and 3 values after the selected value). The imputed value will be considered consistent if it is contained within the 95% confidence interval for the surrounding 6 values or if the difference between the minimum and maximum of the imputed value and surrounding values is ≤ 0.2 V.

Where BIOTRONIK Home Monitoring® data is not available for imputation of missing 3-month follow-up data in support of primary endpoint 2, the LV pacing threshold from the next completed follow-up after the 3-month time point may be used to impute the missing data.

Multiple analyses will be conducted as needed to assess the impact of missing and imputed data.

For purposes of the Kaplan-Meier survival analysis, described in Section 2.3.7, enrolled subjects exiting the clinical investigation prior to the 5 year visit will be censored at the time of study termination.

2.5.5 Maximum Number of Subjects per Site

For U.S. investigational sites, the maximum number of subjects per investigational site is 15% of the expected total number of subjects to be enrolled (n=1754), thus a maximum of n=263 subjects can be enrolled per center. OUS sites may enroll a maximum of 43 subjects per center for the pre-market analyses.

3. PROTOCOL REQUIREMENTS

3.1 Subject Population

The subject population consists of heart failure subjects with CRT-D indication according to clinical routine.

Up to 1754 subjects will be enrolled in the clinical investigation. The investigator is responsible for screening all potential subjects and selecting those who are appropriate candidates for implantation of a BIOTRONIK CRT system with Sentus QP lead. The subjects selected for participation should be from the investigator's general patient population with documented evidence of an indication for implantation of a BIOTRONIK CRT-D system according to clinical routine and according to the inclusion and exclusion criteria described below. Decision for implantation of the respective BIOTRONIK devices is based on medical decisions alone and should not be influenced by the possible enrollment to this clinical trial. If a Sentus QP implantation was planned but the investigator decided after depiction of the coronary sinus system that the Sentus QP lead is not suitable for the vessel anatomy he/she is not bound to the lead choice.

The implanting investigator is responsible for choosing the fixation and length variant. For the indications, we recommend following the respective current guidelines of the Heart Rhythm Society (HRS), the American College of Cardiology (ACC), and the American Heart Association (AHA), as well as those of other national cardiology associations.

Investigators are strongly encouraged to seek equal enrollment between men and women at their site. This will help ensure women are adequately represented in the study population and enable meaningful analyses of results by gender.

3.1.1 Indications for Use

The Sentus OTW QP left ventricular pacing lead is a 4.8 French (5 F introducer) quadripolar steroid-eluting lead intended for permanent implantation in the left ventricle via the coronary veins to provide pacing and/or sensing when used in conjunction with a compatible IS4 pulse generator.

3.1.2 Contraindications

Implantation of this lead is contraindicated in the following cases:

- Coronary sinus anomalies
- Tissue in the coronary sinus area that has been damaged by an infarction
- Any anomalies of the venous system that preclude transvenous implantation of the lead
- Patient cannot tolerate a single systemic dose of up to 0.5 mg of dexamethasone acetate (DXA)

3.1.3 Inclusion Criteria

All of the following inclusion criteria have to be fulfilled for study participation:

- Standard CRT-D indication according to clinical routine
- *De novo* implantation or upgrade from existing ICD or pacemaker implant utilizing a BIOTRONIK CRT-D system with IS4 LV port and Sentus QP LV lead
- Patient is able to understand the nature of the clinical investigation and provide written informed consent
- Patient is able and willing to complete all routine study visits at the investigational site through 5 years of follow-up
- Patient accepts BIOTRONIK Home Monitoring® concept
- Age ≥ 18 years

3.1.4 Exclusion Criteria

None of the following exclusion criteria can be fulfilled for study participation:

- Contraindication to CRT-D therapy
- Currently implanted with an endocardial or epicardial left ventricular lead or had prior attempt to place a left ventricular lead
- Cardiac surgical procedure, such as coronary artery bypass graft or valve surgery that is planned to occur within 6 months after implant or ablation that is planned to occur within 90 days after implant (ablations planned to occur prior to or at implant are not exclusionary)
- Expected to receive a heart transplant or ventricular assist device within 6 months
- Life expectancy less than 12 months
- Participation in any other investigational cardiac clinical investigation during the course of the study
- Presence of another life-threatening, underlying illness separate from their cardiac disorder
- Pregnant or breast-feeding at time of enrollment

3.2 Methods

3.2.1 eCRFs

During the course of the clinical investigation all clinical procedures are performed according to clinical routine. All parameters and measurements that are recorded within the clinical investigation are described in this section and are documented on the following electronic Case Report Forms (eCRFs). Information

from electronically delivered source data (e.g. programmer interrogations, adverse event documentation) will be uploaded to the appropriate eCRF, then captured and stored in a validated environment until the end of the study. The investigator will be required to use an electronic signature to approve the content of the data reported in the eCRFs listed below.

- Informed Consent
- Enrollment
- Demographics Indications
- Comorbidities Medication
- Implantation
- Device Measurements
- Follow-up Visit (routine and interim)
- Threshold Test
- Study Termination
- Adverse Event
- Device Complaint
- Informed Consent Update
- Protocol Noncompliance
- Study Termination
- System Revision

BIOTRONIK, Inc. will audit and monitor the content of the eCRFs as described in Section 9. The required procedures and corresponding time schedule for eCRF completion is described in Section 3.4

All data have to be available for source data verification during monitoring visits of the sponsor. Subjects have to consent to the use of their medical data prior to enrollment by signing the informed consent form.

3.2.2 Subject Demographics, Comorbidities and Medications

After the informed consent has been obtained, demographic information including year of birth, gender, height and weight should be gathered for all subjects.

Furthermore, details regarding illnesses, ECG diagnostics (if obtained within 6 months prior to enrollment), most recent LVEF, the assessment of the current NYHA class, the device therapy indication, comorbidities and current cardiovascular medication should be collected.

3.2.3 Implantation Information

All devices are identifiable by a unique 8-digit serial number which will be collected on the implantation eCRF. In addition, the following implantation information will also be collected:

- Implanted devices (manufacturer, model, serial number)
- Implantation site and, if available, implant approach
- Upgrade information from pacemaker/ICD
- Information about LV lead implantation (date of implantation)
- Sentus QP lead implant success
- Approximate vessel diameter at Sentus QP lead tip (at final lead position, when this information is available from a routine venogram performed during implant)

Note: The implantation of the Sentus QP LV lead is considered **'unsuccessful'** if an attempt was made to place the lead but it could **not** be placed in a stable position for any reason.

3.2.4 Device Settings

The device programming must be medically reasonable. Recommended device settings for participation in this clinical trial are summarized in the following table (Table 3):

Table 3: Recommended Device Settings

Parameter	Recommended device settings
BIOTRONIK Home Monitoring®	ON
Capture control LV lead	ON or ATM
Pacing configuration	BiV
LV MultiPole Pacing	OFF*

***In order to support the CRT responder assessment for enrollment into the MPP sub-study, the MPP feature should not be programmed ON prior to the 6-month follow-up (or the 3-Month follow-up for subjects consented for the MPP sub-study due to a HF hospitalization event).**

3.2.5 CRT Based Lead Measurements

At implantation, pre-hospital discharge/wound check, 3-, 6- and 12-month follow-up, and the additional required visits every 6 months to 60 months post-implant, documentation of the mean sensing amplitude, the pacing threshold and the impedance is required for the LV channel at beginning of device interrogation. The pacing threshold can be measured either manually or triggered automatically.

The LV pacing threshold is considered **elevated** if the threshold is greater than 2.5 V at 0.4 ms. The LV lead impedance is considered '**out of range**' if a measurement is < 200 Ohms or > 3000 Ohms. The LV sensing threshold is considered '**out of range**' if a measurement is lower than 2 mV.

The electronic programmer file with the stored measurements is used for source data verification.

3.2.6 LV Pacing Threshold Measurement in Novel Vectors

At pre-hospital discharge/wound check and 3-month follow-up the LV pacing threshold at each of the following novel pacing vectors (vectors utilizing the two proximal LV rings) at 0.4 ms may be determined (optional).

Table 4: Novel Pacing Vectors

Sentus QP Novel Pacing Vectors From (-) → To (+)
LV1 tip → LV4 ring
LV2 ring → LV4 ring
LV3 ring → LV2 ring
LV3 ring → LV4 ring
LV3 ring → RV coil
LV4 ring → LV2 ring
LV4 ring → RV coil

The physician is free to test the other vectors, including the available standard vectors. All measured values can be documented in the eCRF. A maximum of 12 vectors are available for testing (see Section 1.3.2).

Please note: Following completion of the pacing threshold test, the permanent pacing vector can be programmed according to physicians' medical opinion independent of the threshold measurement test.

3.2.7 Adverse Events and Device Complaints

The investigator has to record any reportable adverse event, or device complaint which occurs during study duration on the corresponding eCRF. The adverse event will be classified according to the seriousness, the relation to the investigational devices and to the procedure. Reportable adverse events and the definitions event classification are described in Section 6.

3.3 Number of Investigational Devices to be Used

In the QP ExCELs study, 314 Sentus QP leads are expected to be successfully implanted for the pre-market cohort, which equals one device per subject. However, additional investigational devices may be used due to left ventricular lead exchange during the study. Additional Sentus QP leads will be implanted

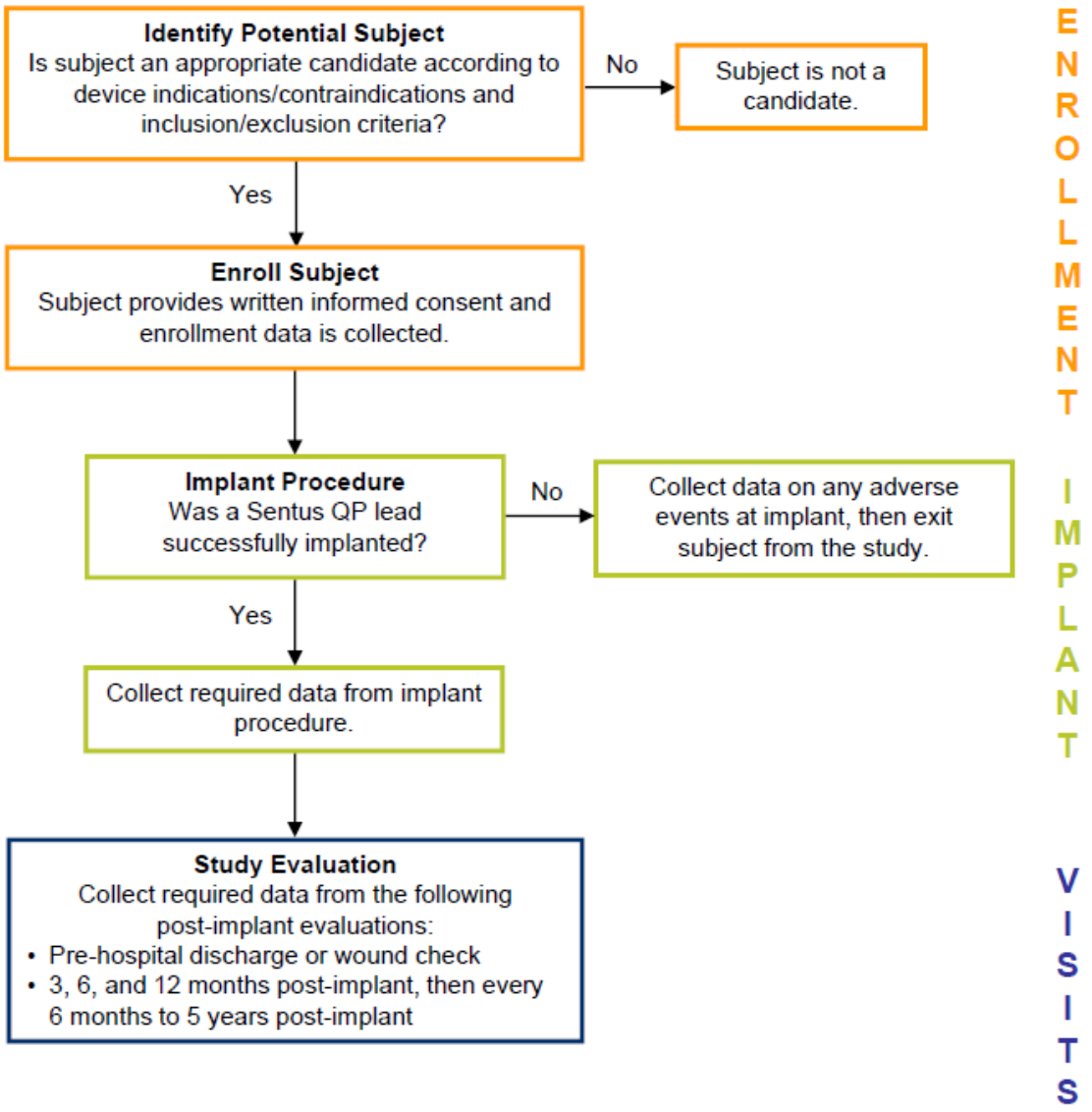
during the IDE to satisfy the post-approval cohort. All Sentus QP leads implanted during the ongoing IDE are considered investigational until FDA approval of the Sentus QP lead is received.

3.4 Study Procedures

Subjects who have a successful lead implant will be evaluated at pre-hospital discharge or wound check and then seen for in-office evaluations at 3, 6, and 12 months post-implant. Thereafter, subjects enrolled will be seen for follow-up visits every 6 months until 60 months post implant.

Figure 8 provides an overview of the clinical study design. Details of subject eligibility requirements are noted in Sections 3.1.3 and 3.1.4. Details of other specific study procedures and collected data are noted in Section 3.2.

Figure 8: Clinical Study Design



Assessments of the lead performance are required at pre-hospital discharge or wound check, 3 months post-implant, 6 months post-implant, 12 months post-implant, and every 6 months until 60 months post-implant. The windows associated with each visit are provided below in Table 5. This schedule should be followed as closely as possible. If circumstances prevent the presence of the subject at the follow-up visit, the reason for the missed follow-up has to be indicated on the eCRF. In addition interim evaluations for Sentus QP lead-related complications or system revisions will be performed.

Table 5: Required Visit Windows

Visit Type	Window	Days post-implant
Pre-hospital discharge or wound check	N/A	0 to 45
3 months post-implant	± 30 days	61 to 121
6 months post-implant	± 45 days	137 to 227
12 months post-implant	± 45 days	320 to 410
18 months post-implant	± 45 days	503 to 593
24 months post-implant	± 45 days	685 to 775
30 months post-implant	± 45 days	868 to 958
36 months post-implant	± 45 days	1051 to 1141
42 months post-implant	± 45 days	1234 to 1324
48 months post-implant	± 45 days	1417 to 1507
54 months post-implant	± 45 days	1600 to 1690
60 months post-implant	± 45 days	1783 to 1873

3.4.1 Overview of Study Procedures

Table 6 displays an overview about the study procedures at the different visits which are described in detail afterwards.

Table 6: Procedures by Visit Type

Procedures	Enrollment	Implant	Pre-hospital discharge & 3 Month Follow-up	6 Month Follow-up through 60 Month Follow-up*	Interim Follow-up†
Informed consent	X				
Verification of inclusion and exclusion criteria	X				
Demographic data and comorbidities	X				
NYHA class and heart failure symptoms	X				
ECG and ECHO values (if performed routinely)	X				
Co-morbidities	X				
Cardiovascular medication	X				
CRT-D implantation		X			
Implantation information		X			X
Vessel diameter at lead tip		X			
Programming of device settings		X			
Standard device evaluation		X	X	X	X
Extended device evaluation with novel pacing vector (optional)			X		
Adverse event reporting	X	X	X	X	X
Completion of eCRFs	X	X	X	X	X

† Interim follow-ups may be collected when related to an AE or a system revision. Implant information only needs to be collected if a system revision has occurred.

3.4.2 Enrollment

Prior to enrollment, the physician selects potential candidates which are eligible for the clinical investigation. If the potential subject meets all inclusion and exclusion criteria (see Sections 3.1.3 and 3.1.4), the potential subject is informed on the study and asked to read and sign an Informed Consent Form. The potential subject should be provided with sufficient time to consider participation in the trial. Afterwards a detailed recording of data being evaluated during the clinical investigation is possible. A subject is considered enrolled in the QP ExCELs study upon signing the Informed Consent Form and meeting the inclusion/exclusion criteria at time of consent. Enrolled subjects must be entered in the subject enrollment log. The consent process should be documented within the subject's medical record.

After informed consent has been obtained, the following data should be collected for baseline evaluation:

1. Demographic characteristics (year of birth, gender, height, weight)
2. Device therapy indication
3. ECG diagnosis, if routinely performed
4. Current NYHA class and most recent LVEF
5. Comorbidities and cardiac medications

The Enrollment eCRF needs to be completed using the data collected during the enrollment visit.

3.4.3 Implantation

Implantation occurs after enrollment of the subject.

At implantation, the following procedures/data are required:

1. Implanted devices (manufacturer, model, serial number).
2. Implantation procedure information (see Section 3.2.3).
3. Sentus QP lead implant success.
4. Approximate vessel diameter at Sentus QP lead tip (at final lead position, when this information is available from a routine venogram performed during implant).
5. Activation of the recommended device settings as listed in Section 3.2.4.
6. Sentus QP lead evaluation from implant procedure:
   - Determine LV lead impedance
   - Determine LV mean R-wave sensing amplitudes
   - Determine LV pacing threshold at 0.4 ms pulse width for the pacing vector programmed at the end of implantation
7. Plexa ICD lead evaluation from implant procedure (if Plexa ICD lead is implanted with initial Sentus QP lead):
   - Determine Plexa ICD lead R-wave sensing amplitude
   - Determine Plexa ICD lead pacing threshold at 0.4 ms pulse width
   - Determine Plexa ICD lead pacing impedance
   - Determine Plexa ICD lead shock impedance
8. Device programming and settings at end of implantation procedure.
9. Store the electronic procedure data (including final device settings, measurements, episodes) of the BIOTRONIK programmer on an appropriate USB flash drive.

10. Complete the Implantation eCRF using data collected during implant and information from the end of procedure device evaluation.
11. Document any reportable adverse event (e.g. phrenic nerve stimulation, high LV pacing threshold, etc.) or device complaint during the procedure by using the respective eCRF. Please adhere to the reporting timelines listed in Section 10.2.

Please note:

1. If a Sentus QP implantation was planned but not performed or the implant procedure was initiated but the Sentus QP lead did not come in contact with the subject, the subject will be exited from the clinical investigation using a Study Termination eCRF.
2. If an attempt to implant a Sentus QP lead was made and the lead came in contact with subject but implantation was not successful, reportable adverse events related to the implant attempt will be collected and the subject will be exited from the clinical investigation using a Study Termination eCRF.
3. If the investigator decided to repeat the implantation of the Sentus QP lead, the final successful implantation is documented on the Implantation eCRF. Please complete Adverse Event or Device complaint eCRF for the first unsuccessful attempt (attempt = Sentus QP lead came in contact with subject).

3.4.4 Pre-hospital Discharge/Wound Check and 3-month Follow-up

As the analysis of secondary endpoint 2 is complete, additional LV pacing threshold testing using the novel pacing vectors is optional at the pre-hospital discharge/wound check and the 3 month post-implant follow-up. The pre-hospital discharge/wound check visit occurs after successful device system implantation and either prior to the subject's discharge from the hospital or at a routine wound check visit (occurring no later than 45 days after implantation). Three (3) months (± 30 days) after implantation, subjects return to the investigational site for an in-office assessment of their implanted system. For both visits the CRT-D system should be assessed.

The following requirements have to be fulfilled and the data have to be documented on the Pre-hospital Discharge/Wound Check eCRF or 3-month Follow-up eCRF, respectively:

1. Standard Sentus QP lead evaluation:
   - Determine LV lead impedance
   - Determine LV lead R-wave sensing
   - Determine LV pacing threshold at 0.4 ms pulse width for the pacing vector programmed at the beginning of the device interrogation
2. Plexa ICD lead evaluation from implant procedure (if Plexa ICD lead is implanted with initial Sentus QP lead):
   - Determine Plexa ICD lead R-wave sensing amplitude
   - Determine Plexa ICD lead pacing threshold at 0.4 ms pulse width

- Determine Plexa ICD lead pacing impedance
- Determine Plexa ICD lead shock impedance

3. Novel pacing vector evaluation, if performed
   - Measure the LV pacing threshold with 0.4 ms pulse width
4. Check the activation of the recommended device settings (Section 3.2.4).
5 Screen/Enroll subject for MPP Sub-Study if prior HF Hospitalization event (3-month Follow-up Only) → Refer to Protocol Section 11
6. Device programming and settings at end of follow-up.
7. At pre-hospital discharge or wound check, register the subject in the Home Monitoring Service Center.
8. Store the electronic procedure data (including final device settings, measurements, episodes) of the BIOTRONIK programmer on an appropriate USB flash drive.
9. Complete the electronic Pre-hospital Discharge/Wound Check or 3-month Follow-up eCRF.
10. Document any reportable adverse event (e.g. phrenic nerve stimulation, high LV pacing threshold, etc.) or device complaint by using the respective eCRF. Please adhere to the reporting timelines listed in Section 10.2.

    Please note: Phrenic nerve stimulation occurring during the left ventricular threshold test and not leading to any serious medical symptoms are not considered adverse events and thus do not need to be reported in an Adverse Event eCRF.

In order to support the CRT responder assessment for enrollment into the MPP sub-study, the MPP feature should not be programmed ON prior to the 6-month follow-up (or the 3-month follow-up for subjects consented for the MPP sub-study due to a HF hospitalization event).

3.4.5 6-month Follow-up and 12-month Follow-up

Six (6) months (± 45 days) and 12 months (± 45 days) after implantation, subjects return to the investigational site for an in-office assessment of their implanted system.

The following data should be collected:

1. Standard Sentus QP lead evaluation:
   - Determine LV lead impedance
   - Determine LV lead R-wave sensing amplitude
   - Determine the LV pacing threshold at 0.4 ms pulse width for the

programmed pacing vector

2. Plexa ICD lead evaluation from implant procedure (if Plexa ICD lead is implanted with initial Sentus QP lead):
   - Determine Plexa ICD lead R-wave sensing amplitude
   - Determine Plexa ICD lead pacing threshold at 0.4 ms pulse width
   - Determine Plexa ICD lead pacing impedance
   - Determine Plexa ICD lead shock impedance
3. Screen/Enroll Subject for MPP Sub-Study (6-Month Follow-up Only) → Refer to Protocol Section 11
4. Device programming and settings at end of follow-up.
5. Store the electronic procedure data (including final device settings, measurements, episodes) of the BIOTRONIK programmer on an appropriate USB flash drive.
6. Complete the appropriate Follow-Up eCRF.
7. Document any reportable adverse event (e.g. phrenic nerve stimulation, high LV pacing threshold, etc.), or device complaint by using the respective eCRF. Please adhere to the reporting timelines listed in Section 10.2.

Any subject not enrolled into the MPP sub-study may only have the MPP feature activated at the investigator's discretion any time after the 6-Month follow-up if the subject is determined by the investigator to be a non-responder.

3.4.6 Additional Visits Required Every 6 Months to 60 Months

After completion of the 12-month follow-up visit, subjects enrolled at U.S. study sites will be followed every 6 months until 60 months post-implant. For subjects utilizing BIOTRONIK Home Monitoring®, study sites will have the option to substitute a BIOTRONIK Home Monitoring® evaluation for up to every other of these additional visits. BIOTRONIK Home Monitoring® evaluations will be accompanied by a phone assessment that is designed to document clinical signs and symptoms that identify a potential reportable adverse event, or device complaint. The phone assessment should occur within 7 days of the date of the BIOTRONIK Home Monitoring® report. Subjects utilizing BIOTRONIK Home Monitoring® assessments are still expected to be evaluated in-office at least once per year.

The data collected for these additional visits is the same as required for the 6 and 12 month evaluations (Section 3.4.5). For BIOTRONIK Home Monitoring® evaluations, a Summary Report created in the Home Monitoring Service Center will be used to store the required electronic procedure data.

3.4.7 Interim Follow-up

Interim follow-ups may occur anytime during the clinical investigation; however, those interim evaluations in support of lead or system related adverse events or system revisions may be collected in the clinical investigation. Interim follow-ups can be visits scheduled by physicians according to clinical routine, visits scheduled by the physician due to BIOTRONIK Home Monitoring® alerts or trends, or visits initiated by the subject.

3.4.7.1 Adverse event related interim follow-up

For interim follow-ups related to an adverse event, the data collected on the Interim Follow-up eCRF is the same as the 6 and 12 month evaluations (Section 3.4.50).

3.4.7.2 System Revision

For interim evaluations that involve a system revision (even if the Sentus QP lead is not directly affected), the following data is required:

1. Implantation procedure information (date of intervention, information about new implanted devices).
2. Revised device (manufacturer, model, serial number).
3. Sentus QP lead measurements during procedure:
   - Determine LV lead impedance
   - Determine LV lead R-wave sensing amplitudes
   - Determine LV pacing threshold at 0.4 ms pulse width for the pacing vector programmed at the end of intervention.
4. Device programming and settings at end of intervention.
5. Plexa ICD lead measurements during procedure (if Plexa ICD lead is implanted with initial Sentus QP lead):
   - Determine Plexa ICD lead R-wave sensing amplitude
   - Determine Plexa ICD lead pacing threshold at 0.4 ms pulse width
   - Determine Plexa ICD lead pacing impedance
   - Determine Plexa ICD lead shock impedance
6. Store the electronic procedure data (including final device settings, measurements, episodes) of the BIOTRONIK programmer on an appropriate USB flash drive.
7. Complete the electronic System Revision eCRF.
8. Document any reportable adverse event (e.g. phrenic nerve stimulation, high LV pacing threshold, etc.), or device complaint during the procedure by using the respective eCRF. Please adhere to the reporting timelines listed in

Section 10.2.

Please note:

1. If the Sentus QP lead is explanted and the subject does not receive a new Sentus QP lead, the subject will be withdrawn from the clinical investigation.
2. If the Sentus QP lead is replaced with another Sentus QP lead, the subject will continue participation in the clinical investigation based on the original implantation date and visit schedule.
3. The subject will continue participation and time schedule will be unchanged if any other lead is replaced or if the CRT-D is replaced (even if replacement CRT-D is not BIOTRONIK).
4. Please notice, whenever possible, BIOTRONIK devices that are explanted must be returned to BIOTRONIK, Inc. for analysis.

3.4.8 Study Termination

The Study Termination eCRF must be completed to determine the end date and reason for study termination of the individual subject. The expected study termination for all subjects should not be earlier than the 60 month follow-up visit. Reasons for early study termination are described in Section 3.5.2.

3.5 Study Participation Expectations

3.5.1 Point of Enrollment

A subject is considered enrolled in the QP ExCELs study upon signing the Informed Consent Form and meeting the inclusion/exclusion criteria at time of consent.

3.5.2 Reasons for Study Termination

Once a subject is enrolled and successfully implanted, every effort should be made to continue to follow the subject in the clinical investigation. However, it is inevitable that some subjects will decline to participate further, change geographic location, or become non-compliant with the visit schedule.

3.5.2.1 No implant attempt

If a Sentus QP implantation was planned but not performed or the implant procedure was initiated but the Sentus QP did not come in contact with the subject, the subject is exited. The reason for study termination must be provided.

3.5.2.2 Unsuccessful implant

If a Sentus QP lead came in contact with the subject but could not be implanted, an adverse event or device complaint should be completed and the subject exited. Data for subjects that have a Sentus related adverse event according to the listing provided in Section 6 will be included in analysis.

3.5.2.3 Withdrawal of subject consent

Subjects may withdraw their consent for study participation at any time without stating the reason and without any unfavorable consequences. All data, which are collected until the date of withdrawal will be used for analysis. A Study Termination eCRF has to be completed by the investigator in which the reasons for withdrawal should be documented if willingly provided by the subject.

3.5.2.4 Subject death

In the event of subject death during study participation, personnel at the investigational site are requested to notify BIOTRONIK, Inc. immediately by completing an Adverse Event eCRF (if applicable) and a Study Termination eCRF.

The following information will be required for any subject death:

- Death certificate, death report signed by the investigator, or relevant medical records that include:
  - Date of death
  - Primary cause of death
  - Any other circumstances surrounding the death
  - Whether death was device or procedure related
- Sentus QP lead return status, if available

Whenever possible, devices that are explanted must be returned to BIOTRONIK, Inc. for analysis.

3.5.2.5 Sentus QP lead extraction

Any subject who has the Sentus QP lead explanted and not replaced with another Sentus QP lead will be withdrawn from the clinical investigation. After documentation of the system revision procedure (see Section 3.4.7.2), a Study Termination eCRF should be completed.

Whenever possible, devices that are explanted must be returned to BIOTRONIK, Inc. for analysis.

3.5.2.6 Lost to follow-up

Subjects lost to follow-up are those for whom contact is lost despite the investigator's best efforts to locate the subject. Study sites should attempt to contact these subjects in order to maintain study visit compliance and all contact attempts should be documented. At a minimum, the site should make two attempts to contact the subject by phone and one attempt by certified mail.

In the event the subject cannot be contacted using the above methods, the subject is terminated from the clinical investigation by completing a Study Termination eCRF.

3.5.3 Date of Study Termination

The expected study termination for all subjects should not be earlier than the 60 month follow-up visit.

For all early study terminations, the following rules apply:

- In case of withdrawal of consent, date of study termination is the date of withdrawal of consent.
- In case of subject death, the date of study termination is the date of death.
- If subject is lost to follow-up, date of termination is the date of last documented contact with the subject.
- If a Sentus QP implantation was planned but was never attempted, the date of termination is the date of decision not to implant.
- If a Sentus QP implantation was initiated but not completed and the Sentus QP did not come in contact with the subject, date of unsuccessful implantation is date of study termination.
- If an attempt to implant Sentus QP lead was made and lead came in contact with subject but implantation was ultimately not successful, date of study termination is date of unsuccessful implantation.
- If the Sentus QP is explanted and not replaced with another Sentus QP, the date of study termination is the date the lead is explanted.

Study related procedures and documentation should end at the day of study termination for the respective subject.

4. ADDITIONAL STUDY CONDITIONS

4.1 IRB Approval

Institutional Review Board (IRB) approval is required for each study site according to local requirements and investigator prior to participation in this clinical study. Subject enrollment may not begin until both the IRB and BIOTRONIK, Inc. have granted approval for the study site. If IRB approval is withdrawn, BIOTRONIK, Inc. must be notified by the investigator within 5 working days.

4.2 Subject Consent

Subject participation in this study is voluntary. All subjects must sign an IRB approved Informed Consent Form (ICF) prior to participation in the study. Subject informed consent must be obtained prior to enrollment or any protocol related procedures. To assist with the consent process, BIOTRONIK, Inc. will provide a template subject ICF to participating sites. Subjects that qualify for the MPP sub-study (Section 11) must sign a separate ICF prior to participating in the MPP sub-study.

4.3 Data Collection

4.3.1 Electronic Data Capture (EDC)

MedNet Solutions Incorporated is a privately-held company that specializes in web-based clinical data management technology. MedNet will host the EDC system and provide a secure environment that is accessible to authorized individuals through the internet. BIOTRONIK, Inc. will implement a study specific configuration using this software to meet the data collection requirements of the protocol. It is the platform for electronic case report form (eCRF) data entry, query management, and access to clinical data for parties authorized by BIOTRONIK, Inc.

4.3.2 Electronic Case Report Forms (eCRFs)

Original data will be collected from each investigational site and recorded into the EDC system via completion of eCRFs. The investigator will be required to use an electronic signature to approve the content of the data reported in the eCRFs. BIOTRONIK, Inc. will audit and monitor the content of the eCRFs as described in Section 9.

Information from electronically delivered source data (e.g. programmers) will be captured and stored in a validated environment until the end of the study.

4.3.3 BIOTRONIK Home Monitoring® Data

In the QP ExCELs study, data of the study subjects will be accessible to the sponsor via transfer from the Home Monitoring Service Center during the course

of study participation of the respective subject. BIOTRONIK Home Monitoring® data might be used for evaluation and publication if desired by the sponsor.

All data are transferred to the sponsor in a pseudonymized form. Data includes all information transmitted from the device (e.g. IEGMs, statistics, lead information).

4.4 Confidentiality of Subject Data

Information sent to BIOTRONIK, Inc. pertaining to study subjects will be kept confidential at BIOTRONIK, Inc. and is subject to audit by IRB and other regulatory authorities. For reporting purposes, data collected from U.S. sites will be shared with BIOTRONIK SE & Co. KG. Information shared with BIOTRONIK SE & Co. KG will be kept confidential. Reports submitted to physicians and data presented in publications of study results will not make any reference to subject name.

In order to verify the study data and ensure study integrity, monitors from BIOTRONIK, Inc., authorized personnel from BIOTRONIK SE & Co. KG, regulatory authorities, and the reviewing IRB may review and/or copy the study records.

4.5 Data Quality Control

BIOTRONIK, Inc. will regularly review study data. At any time, reports can be generated on entered or missing data by BIOTRONIK, Inc. or by approved research personnel at each investigational site. The EDC system will be used to track received and expected visit data and eCRFs for each subject. This system also provides the capability to monitor the status, volume, and disposition of data. In addition, all study data will undergo extensive automatic edit and plausibility checks that provide information to the investigational sites to help improve and maintain data quality control procedures designed to detect inaccuracies and inconsistencies.

4.6 Deviations from Clinical Investigation Plan

The investigator is required to conduct this study in accordance with the signed investigator agreement and clinical protocol. The investigator shall notify BIOTRONIK, Inc. and reviewing IRB in writing no later than 5 working days after any significant deviation from the clinical protocol that has occurred to protect the life or physical well-being of a subject in an emergency. Except in such emergency situations, prior approval by BIOTRONIK, Inc. is required for significant deviations from the clinical protocol.

BIOTRONIK, Inc. categorizes protocol non-compliance instances as either protocol violations or protocol deviations. Both protocol violations and deviations will be reported in the interim and final clinical progress reports.

4.6.1 Protocol Violations

Protocol violations are defined as instances where the protocol requirements and/or regulatory guidelines were not followed, and are generally more serious in nature. Protocol violations are considered to potentially affect the scientific soundness of the study and/or the rights, safety, or welfare of subjects. Protocol violations include, but are not limited to, failure to obtain consent, unapproved investigator implanting an investigational device, and subject inclusion/exclusion violations.

The investigator must notify the reviewing IRB of all protocol violations per the reporting requirements. In some instances, such as failure to obtain consent, the investigator should also seek guidance from the IRB to ensure the subject received appropriate information to consider their participation in the study.

4.6.2 Protocol Deviations

Protocol deviations are defined as instances where the requirements of the protocol were not followed in such a manner whereby data is unusable or unavailable. Protocol deviations are less serious in nature and may not require IRB notification as long as they do not affect the rights, safety, or welfare of the study subject.

4.7 Subject Retention

BIOTRONIK, Inc. will provide additional tools to the sites in an effort to minimize the number of subjects that are lost to follow-up. This includes an overview of each subject's visit schedule, including the windows for each visit as they become due. The visit schedule reporting allows research personnel to become alerted to and track all study subjects that should be scheduled for upcoming study evaluations.

In addition, BIOTRONIK, Inc. monitors will review subjects, including those that may be lost to follow-up, to ensure protocol and study visit compliance.

4.8 Study Completion

BIOTRONIK, Inc. will notify the U.S. study site upon completion or termination of the clinical investigation or of the investigator's participation. BIOTRONIK, Inc. will provide a Clinical Investigation Report to each investigational site. BIOTRONIK, Inc. will also determine which sites will have an on-site close out visit and provide details on closure activities to all investigators to ensure the investigator understands any applicable regulatory requirements, including those related to record retention.

4.9 Labeling and Control of the Investigational Devices

For all sites, the investigational leads and associated components will have a label that will be visible on the pertinent shipping cartons and storage containers. The required labels or manuals will bear the following information:

- Model and serial number of the investigational device (where appropriate)
- Name of the investigational device and the address of BIOTRONIK SE & Co. KG as the manufacturer
- Labeling statement: Caution: Investigational Device. Limited by United States law to investigational use.
- All relevant contraindications, hazards, adverse device effects, interfering substances or devices, warning and precautions.

BIOTRONIK, Inc. will control the investigational devices within the U.S. by distributing those devices only to approved investigational centers and approved investigators. BIOTRONIK, Inc. will also keep records that indicate the place and date of shipment. Devices are not transferrable between investigators unless prior approval is obtained from BIOTRONIK, Inc.

Upon receipt of FDA approval of the Sentus QP lead, this section will no longer be applicable.

5. STUDY OVERSIGHT

5.1 Clinical Events Committee

A Clinical Events Committee (CEC) consisting of at least 3 independent Electrophysiologists or Cardiologists (with CRT experience) will be established to review and adjudicate all protocol defined adverse events reported by the investigational sites related to:

1. Lead or generator adverse event resolved by surgical reposition, surgical explanation, surgical replacement, surgical abandonment, or if other lead-related surgery is performed
2. Adverse event related to clinical lead failure, electrical lead failure, or mechanical lead failure, regardless of action taken. This includes PNS resolved by electrical abandonment and disabled pacing
3. Any major implant procedure related event that meets the criteria of a serious adverse event
4. (MPP Sub-Study Only, see Section 11.3.4) MPP sub-study related events.

Protocol defined adverse events that do not meet these criteria for CEC adjudication (e.g. reprogramming pacing output due to high LV threshold without a suspected or confirmed lead failure) will be included in the clinical report based on site-reported information.

The CEC will be blinded to the investigational site and subject identity, and to minimize bias members will not participate as investigators. The CEC will create a study specific charter defining the adverse event adjudication process, specifically detailing review guidelines along with appropriate response timelines.

Adverse events meeting the criteria described above will be adjudicated by the Clinical Events Committee. The Clinical Events Committee (CEC) will have the responsibility to adjudicate the classification, category, seriousness, and resolution of each reported adverse event In addition, the CEC will also indicate whether the adverse event is related, possibly related, not related, or has an unknown relation to the Sentus QP lead or Plexa ICD lead. The CEC will decide for each event on the inclusion to the primary endpoint 3 analysis according to the definition for endpoint 3 relevant adverse events as documented in Section 6.6.2.

The Clinical Events Committee is responsible for:

- Endpoint adjudication of adverse events meeting the criteria above
- Adjudication meetings, as needed, via telephone conference or face-to-face
- Final decision on inclusion of each adverse event in the primary endpoint 3 analysis according to the definition provided in Section 6.6.2.
- Regular reporting of adjudication results to the sponsor

The Clinical Events Committee will be supported by members of the sponsor in pre-selection of device complications from non-device related adverse events (e.g. broken leg, headache, cancer) and in organizational tasks.

6. ADVERSE EVENTS

In the course of the clinical investigation, undesired medical events can occur in participating subjects, which are called adverse events (AEs). Furthermore, device deficiencies (DD) or complaints may also be observed. All AEs and device complaints of the investigational device shall be assessed by the investigator and shall be documented and reported throughout the clinical investigation.

The investigator shall submit to the sponsor all reportable events using the respective eCRFs provided within the EDC system.

Based on literature research, the adverse events listed in Appendix B may possibly occur as medical complications of a cardiac rhythm management system implant.

6.1 Definitions

6.1.1 Definition of Adverse Event

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons whether or not related to the investigational medical device. This includes:

- Events related to the investigational medical device or the comparator
- Events related to the procedures involved
- For users or other persons, this definition is restricted to events related to the investigational medical devices.

6.1.2 Definition of Adverse Device Effect

An adverse device effect (ADE) is an AE that is related to the use of an investigational medical device. This includes any AE resulting from insufficient or inadequate instructions for use or the deployment, implantation, installation, or operation, or any malfunctioning of the investigational device and any event resulting from use error or from unintentional misuse of the investigational device.

Adverse events, which result from the required medical procedures involved, when implanting, using or testing the respective investigational device, even if not directly related to the device (e.g. anesthetic complications, wound healing disturbances, lead perforation, etc) are considered ADEs.

Three categories for classification of relationship to the investigational device and/or procedure are available:

- Clearly not related: A relationship of the AE to the investigational device and / or procedure can be excluded.

- Possibly related: It cannot be excluded that there is a connection with the device under investigation and / or the procedure.
- Clearly related: A relationship of the AE to the investigational device and/or procedure is likely/sure.

6.1.3 Definition of Unanticipated Adverse Device Effect

As defined in 21 CFR Part 812.3, an unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

A listing of previously identified adverse events along with anticipated frequency is provided in Appendix B. It is important to note that random component failures or problems caused by misuse of the product are not considered unanticipated adverse device effects.

6.1.4 Serious AEs, ADEs, and UADEs

AEs, ADEs, and UADEs are classified as serious if one or more of the following consequences are fulfilled:

- led to death
- led to serious deterioration in the health of the subject, that either resulted in
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

In-patient hospitalization is defined as at least one overnight stay (change of date) in a hospital. Events for which subjects are hospitalized for less than 24 hours without change of date will not be documented as serious, unless one or more of the other seriousness criteria are fulfilled.

6.1.5 Definition of Device Complaint

Device complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety,

effectiveness, or performance of a device after it is released for distribution [21 CRF 820 3(b)].

6.2 Reporting Adverse Events

The investigator shall report to the sponsor, by completing the appropriate eCRF, the following types of events:

- all adverse events related to or possibly related to
  - investigational device
  - implanted system
- any major adverse events related to procedures involved with implanting, using, or testing the investigational device (see examples in Section 6.3 and definitions in Appendix A: Definition of Terms)
- any adverse device effects, regardless of severity and including both previously reported and unanticipated adverse events
- (MPP Sub-Study Only, see Section 11.5.4) any cardiovascular hospitalizations and any other hospitalizations in which cardiovascular symptoms occur on or before the date of the 12-Month follow-up
- (MPP Sub-Study Only, see Section 11.5.4) all adverse events that require additional invasive intervention to resolve, specifically related to the MPP feature of the CRT-D. These adverse events include any software issues related to MPP programming for any adverse event that occurs while MPP is enabled and that may be attributed to the use of the MPP feature.

(**Please note:** Phrenic nerve stimulation is an expected event during left ventricular threshold testing. As the Sentus QP lead allows for measurements in up to 12 different vectors, phrenic nerve stimulation might be a common observation in this study. Therefore phrenic nerve stimulation during threshold testing is only considered a reportable adverse event if serious medical symptoms occur.

Events will be reported on an Adverse Event eCRF or a Device Complaint eCRF, as appropriate. Events should be reported as information is available, even if this results in an incomplete eCRF. The investigator must follow-up all ongoing reportable events either as long as the subject participates in the clinical investigation, the clinical investigation is terminated, or until the event has been resolved, whatever comes first.

The investigator must characterize each event by a single primary diagnosis. The primary diagnosis may describe an event consisting of several clinically recognizable features, symptoms or secondary diagnoses. Note: The observed symptoms and secondary diagnoses must be properly documented in the respective eCRF.

Multiple events may occur simultaneously in one subject. For each medically independent event with a primary diagnosis an individual report must be provided.

In addition, the action taken/treatment should also be provided with any supportive documentation available.

The investigator has to ensure that all relevant information is available. This also includes information from other parties (family, other hospitals, etc.).

If a patient dies during the clinical investigation, the investigator shall document the cause of death, circumstances and place of death. All actions taken, which were initiated to gain further information must be documented in writing and provided to BIOTRONIK, Inc.

Investigators are required to adhere to applicable regulations and reviewing IRB reporting requirements for adverse events.

6.3 Examples of Reportable Adverse Events

The following are examples of potential reportable adverse events and do not limit the required adverse event reporting as defined in Section 6.2.

Examples of reportable lead related events

- Ablation sequelae (such as lead dislodgement or damage during an ablation)
- Cardiac perforation occurring post implant
- Clinical lead failure
- High pacing threshold
- Extracardiac stimulation (e.g. phrenic nerve stimulation)
- Electrical lead failure
- Intermittent capture
- Lead abrasion
- Lead dislodgement or migration (not occurring during a procedure)
- Lead impedance out of range, high impedance
- Lead impedance out of range, low impedance
- Lead fracture or insulation damage
- Lead undersensing
- Lead-related thrombosis
- Loss of sensing
- No capture
- Mechanical lead failure
- Muscle or nerve stimulation
- Twiddler's syndrome
- Unsuccessful Sentus QP lead implant (unless due to a device complaint not leading to AE)
- Lead repositioned, explanted, or replaced for any other reason

Examples of reportable system or pulse generator related events

- Device extrusion
- Device migration
- Inappropriate detection of arrhythmias
- Inappropriate therapy or shocks
- Inability to defibrillate or pace
- Myopotential sensing
- Pacemaker mediated tachycardia
- Premature battery depletion
- Pulse generator failure
- Shunting current or insulating myocardium during defibrillation with internal or external paddles
- Skin erosion
- Pulse generator repositioned, explanted, or replaced for any other reason

Examples of reportable major implant related events

- Air embolism
- Anesthetic complications
- Allergic reaction to components used at implant or during lead testing, or to components of the lead
- Arrhythmias associated with implant
- Arteriovenous fistula
- Body rejection phenomena
- Cardiac perforation with or without tamponade associated with lead implant
- Chronic nerve damage
- Coronary sinus dissection
- Damage to lead during a procedure
- Fluid accumulation
- Heart valve damage
- Major Hematoma
- Infection
- Keloid formation/fibrotic tissue formation
- Lead dislodgement of chronic leads that occurs during a procedure
- Loose set-screw
- Myocardial damage
- Non-healing pocket dehiscence or other wound healing disturbance
- Pericardial effusion
- Pericarditis
- Phlebitis
- Pleural effusion
- Pneumothorax associated with lead implant
- Pulmonary embolism associated with the implant procedure
- Respiratory arrest
- Venous occlusion associated with the implant procedure

- Hemothorax
- Incorrect lead connection with pulse generator

6.4 Adverse Event Reporting Timelines

If an unanticipated adverse device effect occurs, then the investigator is required to notify the sponsor and the reviewing IRB as soon as possible but no later than 10 working days after the investigator first learns of the event. If the event is serious or life threatening, the sponsor must be notified within 2 calendar days. The sponsor will conduct an immediate evaluation of any unanticipated adverse device effects. Devices that are returned to BIOTRONIK, Inc. will be sent to BIOTRONIK SE & Co. KG in Berlin, Germany for analysis. Those analyses will be trended (as appropriate) and reported to FDA as soon as they are available. The sponsor will notify the FDA, all reviewing IRBs, and participating investigators within 10 working days after notification of the event by the investigator, as required by FDA regulations.

All other events should be reported to the sponsor as soon as information is available.

6.5 Sponsor Reporting

To ensure reporting requirements are met during the study, adverse event information reported for all study sites, will be reviewed by BIOTRONIK to ensure specific reporting requirements are met.

As such, unanticipated adverse device effects identified will be reported to FDA, all reviewing IRBs, and participating investigators per the standard requirements and timelines.

6.6 Adverse Events for Primary Endpoint Analysis

The complication-free rate calculated for primary endpoint 1 will be based on the total number of subjects with at least one ADE. For the primary endpoint analysis, the AE classification, category, resolution and relation to the investigational device (Sentus QP lead) for each individual event will be determined by the Clinical Events Committee (CEC) (see Section 5.1).

All adverse events that meet the primary endpoint criteria (Section 6.6.1) and for which the CEC determines the event is related or possibly related to the Sentus QP lead will be included in the primary endpoint event analysis. Adverse events with a final CEC adjudicated relation of not related or unknown will not contribute to or be included in the evaluation of the primary safety endpoint.

6.6.1 Adverse Events Included in Primary Endpoint 1

ADEs related to the Sentus QP lead and resolution combinations that will be analyzed as part of the primary endpoint 1 ($p_{Complication}^{SentusQP}$) are presented in Table 7.

Combinations marked with an "X" will be included but are not limited to the primary endpoint 1 analysis. All Sentus QP related ADEs meeting the below criteria occurring after successful implantation until the 6-month post-implantation visit will be included.

Table 7: Adverse Event/Resolution Combinations for Primary Endpoint 1 Analysis

Resolution	Clinical lead failure	Electrical lead failure	High pacing threshold	Extracardiac stimulation	Intermittent capture	Lead dislodgement	Lead impedance out of range, high	Lead impedance out of range, low	Lead undersensing	Lead-related thrombosis	Loss of sensing	Mechanical lead failure	No capture
Lead surgically repositioned	X	X	X	X	X	X	X	X	X	X	X	X	X
Lead surgically explanted	X	X	X	X	X	X	X	X	X	X	X	X	X
Lead surgically replaced	X	X	X	X	X	X	X	X	X	X	X	X	X
Lead surgically abandoned	X	X	X	X	X	X	X	X	X	X	X	X	X
Other lead-related surgery performed	X	X	X	X	X	X	X	X	X	X	X	X	X
Lead pacing polarity or mode reprogrammed*		X										X	
Lead electrically abandoned and pacing disabled	X	X										X	
Lead use continued based on medical judgment	X	X										X	

*Adverse events resolved by reprogramming of pacing polarity or pacing mode are only included in primary endpoint 1 analysis in cases of electrical or mechanical lead failure. Other adverse events, such as extracardiac stimulation, which are resolved by reprogramming are excluded.

In addition, the following procedure-related adverse events will be included in the analysis of primary endpoint 1:

- Pneumothorax directly associated with the Sentus QP lead

- Cardiac perforation with or without tamponade caused by the Sentus QP lead
- Coronary sinus dissections directly caused by the Sentus QP lead (e.g., dissections caused by lead delivery device are excluded)

Finally, subject deaths resulting from a Sentus QP lead-related AE will be included in the primary endpoint analysis.

6.6.2 Adverse Events Included in Primary Endpoint 3

ADEs related to the Sentus QP lead and resolution combinations that will be analyzed as part of the primary endpoint 3 ($p_{Complication}^{SentusQP}$) are presented in Table 8.

Combinations marked with an "X" will be included but are not limited to the primary endpoint 3 analysis. All Sentus QP related ADEs meeting the below criteria occurring after successful implantation until the 60-month post-implantation visit will be included.

Table 8: Adverse Event/Resolution Combinations for Primary Endpoint 3 Analysis

Resolution	Clinical lead failure	Electrical lead failure	High pacing threshold excluding events within 45 days of implant or lead revision	Extracardiac stimulation	Intermittent capture excluding events within 45 days of implant or lead revision	Lead dislodgement >45 days post-implant or lead revision	Lead impedance out of range, high	Lead impedance out of range, low	Lead undersensing	Lead-related thrombosis	Loss of sensing	Mechanical lead failure	No capture excluding events within 45 days of implant or lead revision
Lead surgically repositioned	X	X	X	X	X	X	X	X	X	X	X	X	X
Lead surgically explanted	X	X	X	X	X	X	X	X	X	X	X	X	X
Lead surgically replaced	X	X	X	X	X	X	X	X	X	X	X	X	X
Lead surgically abandoned	X	X	X	X	X	X	X	X	X	X	X	X	X
Other lead-related surgery performed	X	X	X	X	X	X	X	X	X	X	X	X	X
Lead pacing polarity or mode reprogrammed*		X										X	
Lead electrically abandoned and pacing disabled	X	X										X	
Lead use continued based on medical judgment	X	X										X	

*Adverse events resolved by reprogramming of pacing polarity or pacing mode are only included in primary endpoint 3 analysis in cases of electrical or mechanical lead failure. Other adverse events, such as extracardiac stimulation, which are resolved by reprogramming are excluded.

In addition, the following adverse events will be included in the analysis of primary endpoint 3:

- Pneumothorax directly associated with the Sentus QP lead
- Cardiac perforation with or without tamponade caused by the Sentus QP lead
- Coronary sinus dissections directly caused by the Sentus QP lead (e.g., dissections caused by lead delivery device are excluded)

Finally, subject deaths resulting from a Sentus QP lead-related AE will be included in the primary endpoint analysis.

7. OTHER INSTITUTIONS AND PHYSICIANS

This clinical study is not transferable to other institutions attended by the investigator unless prior approval is obtained from both BIOTRONIK, Inc. and the appropriate IRB. Only approved investigators are authorized to participate in the clinical investigation. However, there are certain situations where an investigator might not be immediately available to provide the necessary medical care for a subject enrolled in the clinical investigation (such as a subject emergency room visit for medical treatment) in these instances a protocol deviation will not be issued and all available data will be utilized.

In case technical support is needed the service hotline of BIOTRONIK, Inc. is available 24 hours a day. Phone: 1-800-547-0394.

8. RISKS AND BENEFITS OF THE DEVICE AND CLINICAL INVESTIGATION

8.1 Anticipated Clinical Benefits

With the participation in this clinical investigation, the subject receives a modern device with many clinical benefits. The clinical status of the subject will be intensively supervised within study participation. The different available LV sensing and pacing configurations of the QP systems will be tested in order to find the best suitable setting for the CRT therapy. The investigational devices meet the current state of medical science and technology and are used according to their intended use.

With the CRT therapy, a significant improvement in quality of life is achieved in 75-85% of patients (Bristow et al., 2004).

CRT devices are three chamber devices, requiring the implantation of the left ventricular lead. As a standard, left ventricular leads are implanted in a transvenous approach through the coronary sinus. Due to the diversity of the individual venous anatomy a range of different coronary sinus leads is required, e.g. leads with a larger diameter for larger caliber target veins and smaller diameter leads for small caliber target veins (Hansky et al., 2006; Minden, 2011). The Sentus OTW QP L, Sentus OTW QP S, Sentus OTW QP S/49, and Sentus OTW QP L/49 are quadripolar, 4.8 F left ventricular leads, which can be used in combination with CRT devices. Due to the thin diameter, this leads might allow easier left ventricular positioning in patients with small coronary arteries compared to leads with a larger diameter.

However, since the establishment of CRT in the last 10 years some pitfalls are still remaining as there are notable non-responder rates, high pacing thresholds and phrenic nerve stimulation (PNS). Electronic repositioning as discussed for the first time by Gurevitz et al., 2005 has been revealed as means of choice to overcome at least high pacing thresholds and PNS adequately. The available approach to extend the choice of pacing vectors due to the use of a quadripolar LV lead has shown the superiority over a standard bipolar system in several studies (Goetze et al., 2013; Moubarak et al., 2014). The quadripolar left ventricular leads like the Sentus QP together with the corresponding CRT-D device offer more pacing and sensing configuration for CRT therapy compared to the bipolar LV leads. Due to multiple pacing options, the treating physician is able to overcome most cases of high pacing thresholds and PNS during implantation or at follow-up. A very important benefit of the QP system is the option to maintain lead stability in case of distal PNS and to avoid pacing from within scar areas by selecting near-site stimulation. Therefore the number of re-intervention procedures can be reduced with the new systems which may lead to reduce patient risks and costs.

The use of Home Monitoring® functionality offers the physicians the possibility to monitor their patients remotely whenever it is deemed necessary. The automatic

early detection of arrhythmia and device anomalies allows earlier medical intervention as compared to conventional in-office follow-ups. The results of the TRUST clinical study demonstrated the safety and effectiveness of the remote monitoring (Varma et al., 2010).

The individual benefit of study participation for the subject is an intensified medical supervision of his clinical status, an optimal adaptation of the left ventricular pacing configuration and the supervision of the success of the CRT therapy.

8.2 Anticipated Risks

8.2.1 Anticipated Adverse Events

Implantation of the Sentus QP LV lead does not differ from the procedures applicable for comparable devices. Thus, no additional risks or burdens concerning device implantation derive from participation in the clinical investigation.

8.2.2 Risk Associated with Participation in the Clinical Investigation

Subjects included in the QP ExCELs study have an indication for CRT-D therapy and will be implanted with an implantable cardiac rhythm management device as well as a left ventricular lead independently from the clinical investigation. As implantation of the investigational devices used in this clinical investigation does not differ from standard operation procedure, no study specific risks are associated with the implantation procedure.

In some cases the Sentus QP might not be suitable for implantation due to the individual anatomy of the coronary venous system. The physician will determine if the lead is appropriate for a specific subject during the implantation procedure. In most cases the decision can be made during visualization of the coronary veins, thus the Sentus QP lead will only be implanted in those subjects most likely eligible for the LV lead. However, in single cases unsuccessful positioning of a Sentus QP lead might occur, requiring lead exchange during implantation. Unsuccessful positioning of a left ventricular lead and exchange of the lead during implantation is common in about 7% to 19% of subjects during CRT implantation (Nof et al., 2008) and can therefore not be accounted for as additional risk of Sentus QP implantation.

At pre-hospital discharge/wound check and 3-month follow-up testing of the pacing threshold of the Sentus QP lead is planned for a pre-specified testing order. These measurements will increase the duration of the follow-up by about 10 minutes. Furthermore threshold tests of the left ventricular lead in some cases may lead to reversible phrenic nerve stimulation, therefore potentially resulting in hiccups or muscle contractions (Metha et al., 2012; Shetty et al., 2011). In addition, palpitations during the measurements might be experienced. However, threshold tests are a common procedure at device follow-ups and are therefore also expected during device implantation outside of clinical studies.

All other conducted examinations are part of clinical routine. Depending on the specific clinics' routine, the timing of the in-office follow-ups might deviate slightly from the routine. However, otherwise no additional burden for the subject due to the study participation is expected.

8.2.3 Possible Interactions with Concomitant Medical Treatments

For CRT-D therapy, no interactions with concomitant medication or other medical treatment are expected.

The subject's individual cardiovascular medication may have to be adapted to the subject's needs.

8.3 Steps to Control or Mitigate the Risks

As with any implantable device, there are always potential risks that accompany the device. The risks can be minimized through the utilization of strict aseptic technique, compliance with the technical manual, compliance with this clinical investigation plan and technical procedures, adhering to the guidelines for selection of subjects, close monitoring of the subject's physiologic status during the procedures, and by promptly supplying BIOTRONIK, Inc. with all pertinent information required by this clinical investigation plan.

8.4 Risk-to-benefit Rationale

Subjects are provided with the new quadripolar left ventricular lead which will be implanted in combination with the newest available BIOTRONIK CRT-D technology. Only the Sentus QP LV leads are investigational. All other devices used in this study are approved for the U.S. market. The implantation procedure does not differ from other comparable CRT-D system implantations, thus resulting in no additional risk for the subject.

The Sentus QP lead is the successor of the well-proven Corox OTW BP LV lead.

The use of the quadripolar Sentus QP LV lead and the corresponding CRT-D device with IS4 connection offers more programming options due to 12 available pacing vectors. This might be beneficial in avoiding phrenic nerve stimulation. It also offers more possibilities to reprogram the device in case of elevated pacing thresholds. The testing of the enhanced LV pacing options during the study visits is reduced as testing is only performed until a suitable pacing configuration is determined. Hence, the measurement of the LV pacing thresholds in all 12 pacing vectors is not required. However, the measurements might increase duration of the follow-ups by about 10 minutes and may result in reversible hiccup or palpitations. As threshold tests are common procedures during device follow-up, this cannot be counted as additional burden due to the study participation. Beyond the predefined measurements, the physician is not limited in testing other vectors during follow-up. The physician can test and program the CRT-D system according to the subjects' individual needs.

The implantation of a Sentus QP lead is limited to those subjects with an appropriate structural anatomy of the coronary veins. The thin, flexible lead might allow easy and successful implantation in small diameter coronary veins and thus might be beneficial for a specific subset of subjects with the respective structural properties of the coronary veins.

In total, no additional burden for the subject exists during the clinical investigation, besides potential slight time changes of follow-ups in the clinical routine, increase of follow-up duration at pre-hospital discharge/wound check and 3-month follow-up, and possible hiccup or palpitation experiences during threshold measurements.

In summary the potential benefits of the study participation of the subject exceed the potential risks, which is for the most part limited to a possible exchange of the LV lead during implantation, which is a common procedure during CRT implantation.

9. MONITORING

9.1 Summary

The responsibility of BIOTRONIK, Inc. as sponsor is to ensure protocol and regulatory compliance through proper monitoring of the clinical investigation in sites. BIOTRONIK, Inc. is also required to ensure that the investigational device is used under the immediate direction of an investigator. As the investigator, the physician is responsible for conducting the clinical investigation in accordance with the signed Investigator Agreement, the study protocol, applicable laws, and FDA and/or local regulations and any conditions of approval imposed by the reviewing IRB. The principal investigator must also accept responsibility for all aspects of the clinical investigation including the actions of any co-investigators participating in the clinical investigation at the investigational site.

BIOTRONIK utilizes a risk-based monitoring strategy consistent with FDA's Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, August 2013. Risk-based monitoring starts with performing a study risk assessment of the identified critical data and processes. The resulting monitoring plan focuses on targeted source data verification and trend analyses to improve oversight and data quality, while integrating predefined triggers for additional on-site monitoring. The detailed QP ExCELs risk-based monitoring plan developed by BIOTORNIK, Inc. focuses on a combination of centralized and on-site monitoring.

Monitors will visit the study site periodically during the clinical investigation in accordance with the monitoring plan. Sites are required to support these on-site monitoring visits and the study monitoring effort. On-site monitoring visits will also provide an assessment of the continued acceptability of the facilities to continue participation in the study.

Centralized monitoring is conducted via investigator locked electronic case report forms (eCRFs) through the source data verification of source documents uploaded to the eCRF. Some examples of data that may be monitored remotely include: informed consent forms, enrollment, eligibility, implant, study termination, device data and adverse events reported in the EDC system. Sites are required to support centralized monitoring by providing source documents to BIOTRONIK in order to source data verify data reported in the EDC system and resolving queries in a timely manner. Uploaded source documents should meet ALCOA principles of attributable, legible, contemporaneous, original, and accurate. It is critical that the fully executed informed consent form and all necessary source documentation are uploaded to the EDC in a timely manner.

The entries in the eCRF will be reviewed and source data verified by on-site or centralized monitors (authorized BIOTRONIK, Inc. personnel, or by authorized BIOTRONIK, Inc. designees) to ensure that the investigator and the clinical investigation team conducts the clinical investigation in accordance with the clinical investigation protocol and applicable FDA and local laws and regulations

to ensure adequate protection of the rights, safety and wellbeing of subjects and the quality and integrity of the resulting data. In addition, BIOTRONIK, Inc. may require the presence of personnel from BIOTRONIK, Inc. at implant and/or follow-up visits outlined in this protocol in order to assist the investigator and other site personnel.

9.2 Monitors

Monitors are trained, qualified, and designated by BIOTRONIK, Inc. management to oversee the progress of a study at the clinical site. Additional monitors may be appointed as necessary.

If a monitor becomes aware that an investigator is not complying with the signed Investigator Agreement, the study protocol, applicable laws, and FDA and/or local regulations and any conditions of approval imposed by the reviewing IRB, the monitor is obliged to notify BIOTRONIK, Inc. study management. BIOTRONIK, Inc. will evaluate the non-compliance and issue corrective actions, discontinue enrollment or as a last measure close the clinical investigation site.

10. RECORDS AND REPORTS

10.1 Investigator Records

Investigators are required to maintain the following accurate, complete and current records relating to this study:

- All correspondence relating to the study with another investigator, an IRB, BIOTRONIK, Inc., a monitor, or any regulatory agency (e.g., a letter sent from the investigator to the IRB)
- Records showing receipt, use, and disposition of all investigational devices, including:
    - Date, quantity, and serial numbers of devices received
    - Names of subjects implanted with the investigational device
    - Information and serial numbers of devices return to BIOTRONIK, Inc. and the reason(s) for return
    - Information and serial numbers of devices that are discarded (not returned to BIOTRONIK, Inc.)
- All clinical forms and documentation, including:
    - A copy of all signed Informed Consent Forms
    - All procedure and visit report forms, including supporting documents
    - Records of any adverse device effect, including supporting documentation
    - Records pertaining to subject deaths during the study
    - Protocol with documentation and rationale for any deviations from the clinical protocol
    - Any other records required by BIOTRONIK, Inc.

The investigator must retain records related to the study according to FDA regulations and IRB requirements.

10.2 Investigator Reports

Investigators are required to prepare and submit to BIOTRONIK, Inc. the following complete, accurate and timely reports on this study, when necessary:

- Notification of a subject death during the study
- Any unanticipated adverse device effects
- Notification of the withdrawal of IRB approval
- Annual progress reports prepared for the IRB

- Notification that informed consent was not obtained from a subject
- Final summary report prepared for the IRB
- Any other information upon the request of an IRB, regulatory authority, or BIOTRONIK, Inc.

Table 9 outlines the responsibilities, including time constraints, for submitting the above reports.

Table 9: Investigator Reports

Type of Report	Prepared by Investigator for:	Time Constraints of Notification
Subject death during study	BIOTRONIK, Inc., IRB	As soon as possible and as required by reviewing IRB
Unanticipated adverse device effect	BIOTRONIK, Inc., IRB	Within 10 working days after notification of effect
Serious or life-threatening unanticipated adverse device effect	BIOTRONIK, Inc., IRB	Within 2 working days after notification of effect
Subject withdrawal	BIOTRONIK, Inc.	Within 5 working days after notification of withdrawal
Withdrawal of IRB approval	BIOTRONIK, Inc.	Within 5 working days of receipt of notice of withdrawal of approval
Progress report(s)	BIOTRONIK, Inc., IRB	Submitted no less than yearly
Significant deviations from study plan	BIOTRONIK, Inc., IRB	Within 5 working days after emergency to protect life or physical well-being of subject, otherwise prior approval by BIOTRONIK, Inc. is required
Informed consent not obtained	BIOTRONIK, Inc., IRB	Within 5 working days of occurrence
Final summary report	BIOTRONIK, Inc., IRB	Within 3 months after completion or termination of the study

10.3 Sponsor Records and Reports

BIOTRONIK, Inc. will maintain the following records:

- All correspondence with the investigator(s), IRBs, and FDA that pertains to the study
- Investigational device shipment and inventory reconciliation reports
- Investigator agreements, financial disclosures, and current curriculum vitae
- Name and address of each investigator and each IRB that is involved with the investigation
- Adverse events and complaints

- Adverse device effects (whether anticipated or unanticipated)
- Electronic Case Report Form data
- Confirmation of completed subject informed consent forms
- Clinical investigation protocol and report of prior investigations
- Screening visit reports
- Monitoring reports
- Clinical progress reports
- Statement of the extent to which the good manufacturing practice regulation in part 21 CFR 820 will be followed in manufacturing the device

BIOTRONIK, Inc. is responsible for preparing the following reports, when necessary:

Table 10: Sponsor Reporting Responsibilities

Type of Report	Prepared by BIOTRONIK for	Time Constraints of Notification
Unanticipated adverse device effect	FDA, all reviewing IRBs, participating investigators	Within 10 working days after notification of effect
Withdrawal of IRB approval	FDA, all reviewing IRBs, participating investigators	Within 5 working days of receipt of notice of withdrawal of approval
Withdrawal of FDA approval	Reviewing IRBs, participating investigators	Within 5 working days
Current investigator list	FDA	Names and addresses of participating investigators at 6 month intervals
Progress report	FDA, all reviewing IRBs	Submitted at least annually
Recall and disposition	FDA, all reviewing IRBs	Within 30 working days and will include reasons for any request that an investigator return, repair, or otherwise dispose of any investigational leads
Final report	FDA, all reviewing IRBs, participating investigators	Notification within 30 working days of the completion or termination of the investigation. A final report will be submitted within 6 months after completion or termination of the study.
Informed consent not obtained	FDA	Within 5 working days of notification of occurrence

11. MULTIPOLE PACING SUB-STUDY

11.1 Introduction

This QP ExCELs clinical sub-study is an FDA required post-approval study for the US market released BIOTRONIK MultiPole Pacing (MPP) feature (PMA P050023/S107) of the Ilivia HF-T QP family CRT-D system (PMA P050023/S103).

11.1.1 Sub-Study Overview

Since the initial PMA approvals of Cardiac Resynchronization Therapy (CRT) devices, features have evolved to provide additional programmability designed to maximize patient benefit. Despite the proven benefit of CRT in the indicated population, up to one-third of patients do not respond to the therapy.[1]

In the field of CRT, the adaption of the IS4 connector standard was the most prominent improvement within the recent past. This IS4 connector allows the usage of left ventricular (LV) leads that offer four separate poles which results in an increased number of effectively different pacing polarities. Along with the quadripolar (QP) LV lead comes the possibility of stimulating more than one LV pacing site within one cardiac cycle.

Studies have shown that multiple point LV pacing via a QP LV lead may be an alternative approach to improve CRT response by delivering multiple LV pacing pulses, simultaneously recruiting a larger volume of myocardium.[2] A recent IDE study from St. Jude Medical showed that quadripolar multiple point LV pacing (MultiPoint™ Pacing algorithm) was non-inferior to standard quadripolar biventricular pacing.[3]

QP ExCELs is a prospective, non-randomized, multi-center clinical investigation designed to satisfy U.S. Food and Drug Administration (FDA) requirements for pre-market submission of the Sentus OTW QP LV leads. The QP ExCELs study enrolls subjects with a standard CRT-D indication prior to implantation with a BIOTRONIK Sentus QP LV lead and US a market released BIOTRONIK CRT-D with an IS4 port for the LV lead.

11.1.2 MultiPole Pacing (MPP) Description

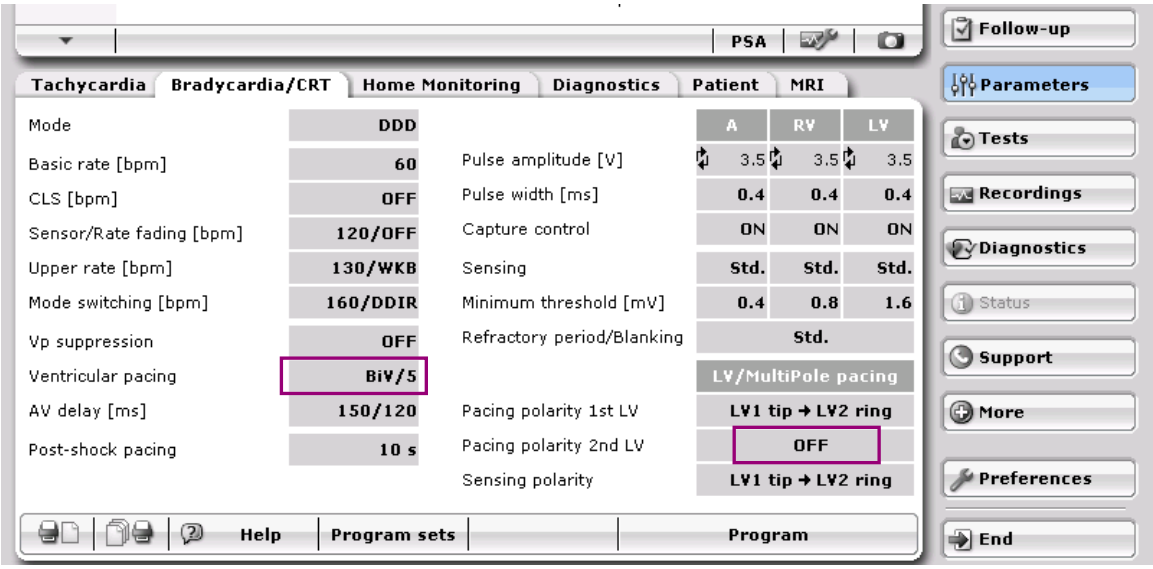
The US market released MultiPole Pacing feature of the Ilivia HF-T QP family CRT-D systems allows left ventricular pacing in two different vectors within a single cardiac cycle using the same quadripolar lead in order to improve synchronization of the contraction pattern. Both left ventricular stimuli will either be before the right ventricular pace (1st LV – 2nd LV - RV) or after the right ventricular pace (RV-1st LV – 2nd LV). The second LV stimulus will only be capable of delivering the second pacing stimulus in the left ventricle; sensing and timing will not be affected by 2nd LV. The delay between the two left ventricular paces is programmable between 0 ms and 50 ms in 5 ms steps. All 12 currently approved pacing configurations are available for both pacing stimuli. However, the same pacing vector cannot be used for both stimuli. Pacing output and interventricular delays can be programmed independently. There is no change to the same parameter ranges available for pacing amplitude and pulse width (0.5 to 7.5 V and 0.4 to 1.5 ms, respectively). The programmable parameters for the MultiPole Pacing feature are listed in 11.

Table 11: Programmable Parameters for MultiPole Pacing

Parameter	Programmable range
LV MultiPole stimulation	OFF, 1st LV-2nd LV-RV, RV-1st LV-2nd LV
LV stimulation amplitude (1st LV and 2nd LV)	0.5 to 7.5 V
LV stimulation width (1st LV and 2nd LV)	0.4 to 1.5 ms
Interval 1st LV – 2nd LV	0 to 50 ms
Stimulation configuration (1st LV and 2nd LV)	LV1 Tip → LV2 Ring LV1 Tip → LV4 Ring LV1 Tip → RV Coil LV1 Tip → ICD LV2 Ring → LV1 Tip LV2 Ring → LV4 Ring LV2 Ring → RV Coil LV3 Ring → LV2 Ring LV3 Ring → LV4 Ring LV3 Ring → RV Coil LV4 Ring → LV2 Ring LV4 Ring → RV Coil

MultiPole Pacing is programmable using programmer software that can be used with one of BIOTRONIK's programmers, either the ICS 3000 (P950037/S035, dated May 18, 2005) or the Renamic (P950037/S089, dated April 15, 2011). The user accesses the feature from the Bradycardia/CRT parameters tab (Figure 9).

Figure 9: Programming MultiPole Pacing



As shown in Figure 9 and Figure 10 the polarity, pulse amplitude, and pulse width for the two LV stimuli can be programmed independently.

Figure 10: Programming 1st LV Stimulus

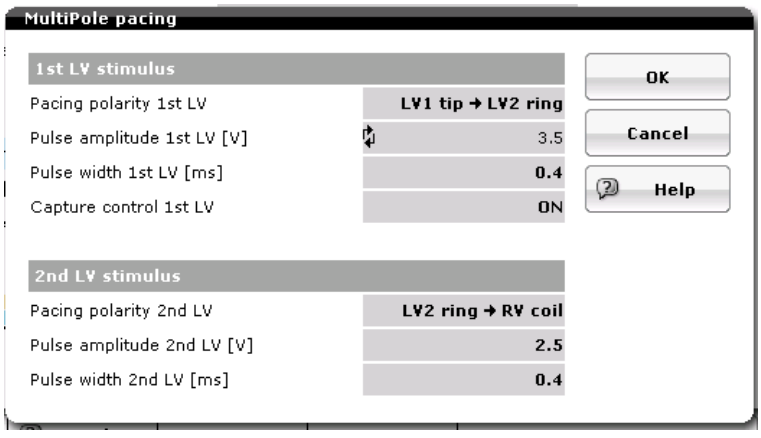


Figure 11: Programming 2nd LV Stimulus

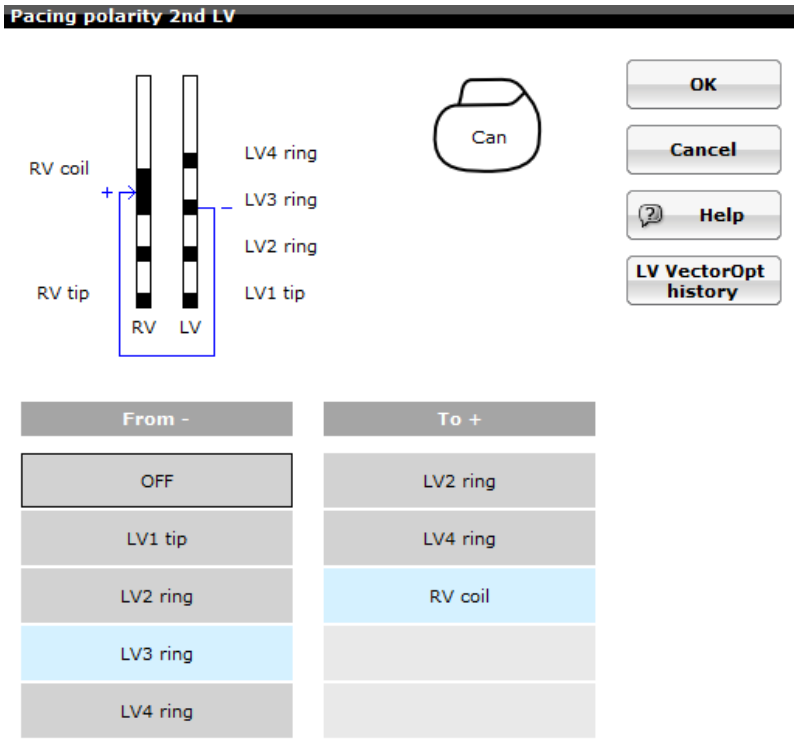


Figure 11 and Figure 12 compare the timing of the ventricular stimuli depending on which chamber is selected to be initially paced. When the right ventricle is paced first, the LV-LV delay starts after the V-V delay, whereas the V-V and LV-LV delays start simultaneously when the left ventricle is paced first.

Figure 12: V-V Delay, LV First

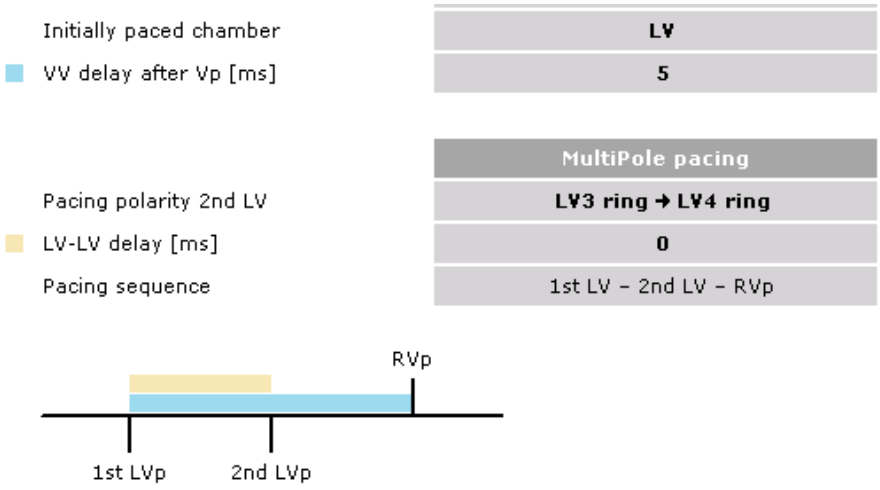
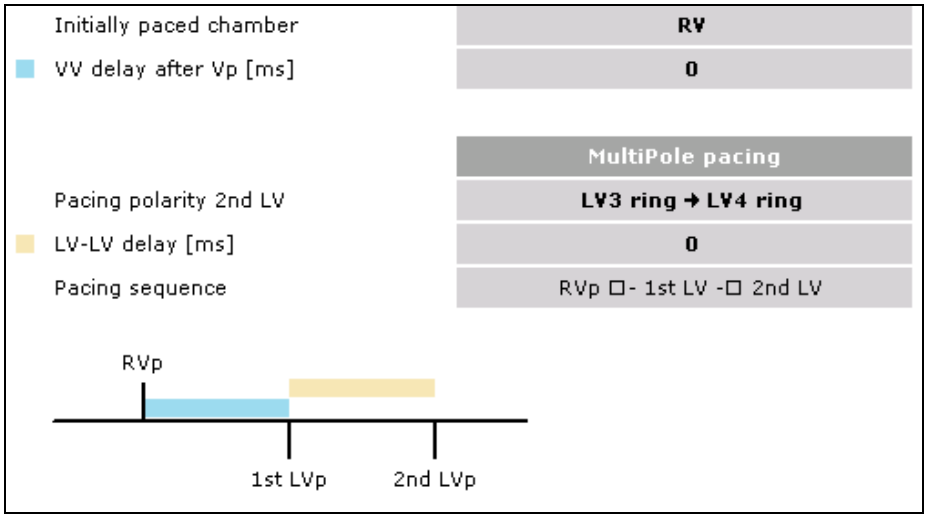


Figure 13: V-V Delay, RV First



11.1.3 Published Results for Multipoint LV Pacing

Forleo et. al, 2016 evaluated the experience of the St. Jude Medical MPP-capable CRT-D devices (Unify Quadra MP or Quadra Assura MP) connected to a quadripolar LV lead (Quartet™). A total of 507 patients in whom these devices had been successfully implanted were enrolled between August 2013 and May 2015. The analyses included: (i) current clinical practices for the management of such patients, and (ii) the impact of MPP on heart failure clinical composite response and on the absolute change in ejection fraction (EF) at 6 months. Multipoint pacing was programmed to 'ON' in 46% of patients before discharge. Methods of optimizing MPP programming were most commonly based on either the greatest narrowing of the QRS complex (38%) or the electrical delays between the electrodes (34%). Clinical and echocardiographic follow-up data were evaluated in 232 patients whom data were available both at the baseline and the 6-month follow-up examination. These patients were divided into two groups according to whether MPP was programmed to 'ON' (n = 94) or 'OFF' (n = 138) at the time of discharge. At 6 months, EF was significantly higher in the MPP group than in the biventricular-pacing group (39.1 ± 9.6 vs. 34.7 ± 7.6%; P < 0.001). Even after adjustments, early MPP activation remained an independent predictor of absolute increase in LVEF of ≥5% (odds ratio 2.5; P = 0.001). At 6 months, an improvement in clinical composite score was recorded in a greater proportion of patients with MPP-ON than in controls (56 vs. 38%; P = 0.009). On comparing optimal MPP and conventional vectors, QRS was also seen to have decreased significantly (P < 0.001).[2]

The recent MultiPoint™ Pacing (MPP) IDE Study from St. Jude Medical showed that quadripolar multiple point LV pacing (MultiPointTM Pacing algorithm) was non-inferior to standard quadripolar biventricular pacing. The multicenter study enrolled and followed 506 subjects with a standard CRT-D indication who were implanted with a CRT-D system (Quartet™ LV lead with a Quadra CRT-D) capable of delivering either quadripolar biventricular pacing or MPP. Quadripolar Bi-V pacing was activated at implant. At 3 months post-implant, patients' responder status was assessed, both responders and non-responders were randomized, and 1:1 randomization (Bi-V or MPP) was stratified by responder status. The primary efficacy endpoint (freedom from system-related complications through 9 months) was 93.2%, (97.5% lower confidence bound 90.4%) was greater than the objective performance criterion of 75%. The primary efficacy endpoint was met for both intention-to-treat and as-treated populations in 381 randomized patients (ITT, p=0.013 and as-treated, p=0.008, respectively). For patients in the MPP arm programmed with wide cathode spacing and the shortest intraventricular timing delay (5ms), MPP provided significantly higher clinical responder rate (between 3 and 9 months) up to 87% (p=0.003 vs <30mm) and converted 100% non-responders to responders (p=0.006 vs <30mm).[3]

11.2 Sub-Study Design

The objective of this MultiPole Pacing sub-study is to demonstrate that the MPP feature is effective by converting a percentage of CRT non-responders to responders. Each subject's responder status will be assessed using a Clinical Composite Score (CCS)[4] including three components: NYHA Class, heart failure (HF) hospitalizations, and cardiovascular death.

The MPP sub-study is a single-arm, multi-center, prospective trial within the ongoing QP ExCELs study. Eligible patients will have been enrolled in QP ExCELs and successfully implanted with the BIOTRONIK Ilivia HF-T QP family CRT-D system, or future-marketed CRT-D system with the MPP feature, and have received standard biventricular (BiV) pacing (i.e. without MPP) prior to a 6-Month CCS assessment or at the time of the QP ExCELs 3-month follow-up with a HF hospitalization event.

Visit intervals below are specified according to time since implant to minimize confusion between the differing enrollment timing into the QP ExCELs study and MPP sub-study.

At the QP ExCELs 6-month Follow-up, a CCS assessment will be completed for all QP ExCELs enrolled subjects who are currently receiving BiV pacing, including NYHA class and HF hospitalization status. Additionally, a Patient Global Assessment (PGA) will be collected. A responder status will be derived classifying these subjects as "Improved", "Worsened", or "Unchanged" using the following definitions:

CRT Responder Classification at QP ExCELs 6-Month Follow-up (evaluated compared to QP ExCELs Enrollment Visit)*:

- "Improved":
  - No HF hospitalization has occurred, AND
  - NYHA class is improved
- "Unchanged":
  - No HF hospitalization has occurred, AND
  - NYHA class is unchanged
- "Worsened":
  - HF hospitalization has occurred, OR
  - NYHA class is worsened

Classification of prior "HF hospitalization" event at the time of MPP screening/enrollment and NYHA class will be determined and reported by the investigator.

Those subjects responder classification determined to be "Worsened" or "Unchanged" may be approached for enrollment into the MPP sub-study. These subjects must sign a separate MPP sub-study Informed Consent prior to enrollment. Those that decline enrolling into the MPP sub-study will continue to be followed according to the primary QP ExCELs protocol.

After enrollment into the MPP sub-study, the MPP feature will be programmed ON and an MPP optimization procedure may be performed for all subjects according to the site's optimization method (see Section11.3.3.1).

At a 9-Month Follow-up† (90 ± 30 days post-MPP enrollment), each subject will repeat the NYHA classification, PGA, and HF hospitalization status, in addition to the standard QP ExCELs required lead testing.

At a 12-Month Follow-up† (180 ± 30 days post-MPP enrollment), each subject will repeat the NYHA classification, PGA, and HF hospitalization status. Following the 12-Month Follow-up, all subjects may be programmed to MPP or standard BiV pacing, per physician discretion.

Subjects enrolled in the MPP sub-study will rejoin the main QP ExCELs study at the 12-Month Follow-up†; however, no further CCS will be assessed.

11.2.1 Study Endpoints

This sub-study includes the assessment of one primary effectiveness endpoint, as well as three secondary endpoints. The hypothesis associated with the primary endpoint is in a superiority format.

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* Subjects may be enrolled in the MPP sub-study at the 3-Month QP ExCELs follow-up if the subject received continuous standard biventricular (BiV) pacing from implant to the 3-Month follow-up with a HF hospitalization event and will be followed for 6 months in the MPP sub-study with MPP sub-study data collected at a 6-month follow-up and 9-month follow-up.

11.2.1.1 Primary Endpoint 1

The purpose of primary endpoint 1 is to evaluate the CRT responder status with the MPP feature within the Ilivia 7 HF-T QP family CRT-D, or future-marketed CRT-D system, compared to a pre-specified performance goal.

The associated hypothesis is evaluated based on a CCS determining a responder classification based on changes in NYHA class, HF hospitalization, and cardiovascular death.

A responder status will be derived classifying these subjects as “Improved”, “Worsened”, or “Unchanged” using the following definitions:

Responder Classification at 12-Month Follow-up (evaluated compared to MPP Enrollment Visit occurring at 6 months)[†]:

- “Improved”:
  - No HF hospitalization or cardiovascular death, AND
  - NYHA class is improved
- “Unchanged”:
  - No HF hospitalization or cardiovascular death, AND
  - NYHA class is unchanged
- “Worsened”:
  - HF hospitalization or cardiovascular death has occurred, OR
  - NYHA class is worsened

Ho: The proportion of subjects (P) who are classified as “Improved” is not superior to a performance goal (PG) of 3%.

$PG \geq P$

Ha: The proportion of subjects who are classified as “Improved” is superior to a performance goal of 3%.

$PG < P$

A rejection of the null hypothesis would indicate that the proportion of subjects classified as “Improved” is superior to 3%.

11.2.1.2 Secondary Endpoint 1- Freedom from MPP system related adverse events requiring additional invasive intervention to resolve at 6 months

The purpose of Secondary Endpoint 1 is to evaluate adverse events that require additional invasive intervention to resolve, specifically related to the MPP feature of the Ilivia HF-T QP family, or future-marketed CRT-D system with the MPP feature. These adverse events include any software issues related to MPP programming or any adverse event that occurs while MPP is enabled and that may be attributed to the use of the MPP feature.

[†] Evaluated at 9-month follow-up if MPP sub-study enrollment visit occurred at 3 months.

11.2.1.3 Secondary Endpoint 2 - Evaluate CCS + PGA Responder Status utilizing a modified CCS that incorporates the Patient Global Assessment

The purpose of Secondary Endpoint 2 is to evaluate a modified CCS, determining a responder classification based on changes in NYHA class, Patient Global Assessment (PGA), HF hospitalization, and cardiovascular death, where the PGA will ask subjects to assess how their overall status has changed since prior to receiving CRT therapy (markedly better, better, unchanged, worse, markedly worse).

Modified Responder Classification (CCS + PGA) at 12-Month Follow-up‡:

- "Improved":
  - No HF hospitalization or cardiovascular death, AND
  - Neither NYHA class is worsened or PGA is worsened ("worse" or "markedly worse"), AND
  - NYHA class is improved or PGA is improved ("better" or "markedly better")
- "Unchanged":
  - No HF hospitalization or cardiovascular death, AND
  - NYHA class is unchanged, AND
  - PGA is unchanged ("unchanged")
- "Worsened":
  - HF hospitalization or cardiovascular death has occurred, OR
  - NYHA class is worsened or PGA is worsened ("worse" or "markedly worse")

11.2.1.4 Secondary Endpoint 3: Evaluate CCS Responder Status utilizing a modified Responder Classification

The purpose of Secondary Endpoint 3 is to evaluate a modified Responder Classification in which both "Improved" and "Unchanged" subjects will be classified as responders. At the time of enrollment into the MPP sub-study, MPP sub-study subjects have already been found to have no change or worsening in their HF status with BiV pacing. Since HF is a chronic and progressive condition, these subjects may be expected to continue to worsen during the MPP follow-up period or remain stable with careful management. In this secondary endpoint, a status of "Unchanged" (in addition to "Improved") during the MPP follow-up period will be considered a responder to MPP.

‡ Evaluated at 9-month follow-up if MPP sub-study enrollment visit occurred at 3 months.

11.2.1.5 Additional Data of Interest

Additional information will be collected to characterize the study population, implanted system, and progress of the clinical investigation. The data will be statistically analyzed, where appropriate. Further data of interest will include:

- Patient Global Assessment (PGA) at each visit
- MPP programmed settings
- Adverse events attributed to MPP feature
- Device initial and final programmed settings
- Methods utilized to optimize MPP, AV and/or V-V timing

11.2.2 Study Size and Duration

The MPP sub-study will enroll up to 100 subjects at up to 75 sites within the United States who are participating in the QP ExCELs study. Subjects in the MPP sub-study will be followed for 6 months (180 ± 30 days post-MPP enrollment). Subjects enrolled in the MPP sub-study will rejoin the main QP ExCELs study after completion of their 12-month MPP follow-up[§].

11.2.3 Sample-Size Analysis

The investigation is designed to limit the number of patients involved while still exposing the device to a sufficiently large patient population in order to ensure a representative and statistically meaningful sample.

Primary Endpoint 1 Sample Size

The estimated sample size requirements are based on a superiority comparison of the proportion of responders to a performance goal of 3%, chosen based on the assumption that any conversion of non-responders to responders is clinically relevant. A performance goal of 3% was chosen rather than 0% to account for variability ("noise") around 0%, for example, due to infrequent subjects who are late responders to CRT or improve regardless of MPP. The expected result is estimated at a 10% conversion of non-responders to responders.

There is limited published data available for mid- to long-term follow-up CRT response with multiple point LV pacing in any population. Additionally, no published data could be found related to CRT response with multiple point LV pacing in an "all-comer non-responder" population. The St. Jude Medical MultiPoint Pacing IDE Study[3,5] ("St. Jude IDE study", NCT01786993) evaluated CRT response based on a Clinical Composite Score (CCS) after 3 months of BiV pacing. Subjects were then randomized to the MultiPoint™ Pacing treatment arm

[§] If an MPP sub-study subject was enrolled at the 3-Month QP ExCELs follow-up, they will re-join the main QP ExCELs study after completion of their 9-month MPP follow-up.

or to continue on with BiV pacing. The study showed that 70.1% of subjects were responders to MultiPoint™ Pacing. However, both responders and non-responders after 3 months of BiV pacing were included in the MultiPoint™ Pacing treatment arm. Additionally, the St. Jude IDE study only randomized subjects with acute "equal or better" EA velocity time integral (VTI) with MultiPoint™ Pacing vs. BiV pacing per echocardiogram at the 3-Month Visit. There were 52 subjects that did not meet this criterion and were not randomized. Thus, subjects that may likely have not responded to multiple point LV pacing therapy were not randomized which certainly led to a higher response rate to MultiPoint™ Pacing.

BIOTRONIK proposes to allow enrollment of any QP ExCELs subject meeting non-responder criteria (“all-comer non-responders”) at the 6-Month Follow-up into the MPP sub-study as it is not standard of care to perform echocardiograms on CRT subjects to determine if they are responding to standard CRT therapy. As such, we estimate that the proportion of non-responders at 6-months that will be converted to responders at 12-months will be less than that observed in the St. Jude IDE study. There are three additional studies which have published results for CRT response with MPP measured via CCS or NYHA improvement with mid- to long-term follow-up (6 to 12 months)[2,6,7]. However, these studies also did not limit multiple point LV pacing treatment to non-responders, and thus the results are not directly applicable to the proposed BIOTRONIK study design.

Assumptions:

- Study Design: Superiority Trial
- Type I error (alpha): 0.025 (one-sided)
- Statistical power: 80%
- Performance Goal: 3%
- Expected: 10%

A total of 90 evaluable subjects would be required to demonstrate superiority to a performance goal of 3%.

11.2.4 Data Analyses

Classification of “HF hospitalization” and “cardiovascular death” events for use in primary endpoint 1, secondary endpoint 2, and secondary endpoint 3 analyses will be determined by a Clinical Events Committee (Section 11.3.4).

Descriptive statistics will be used to present and summarize the data collected in the clinical study. Frequency distributions and cross tabulations will be presented for discrete variables. Means, standard errors, and ranges will be presented for continuous variables.

For primary endpoint 1, the lower, one-sided, exact 97.5% bound for the observed proportion of responders (“improved”) would have to exceed 3% for rejection of the null hypothesis.

Additional related analyses to be performed for the endpoint include:

- Descriptive statistics for observed changes in NYHA class and frequency tabulations for the other components of the Clinical Composite Score.

11.2.4.1 Adjustments to Overall Study Sample Size

Assuming a 10% loss to follow-up rate during the study for reasons unrelated to the study outcomes, a total enrollment of 100 subjects (90/0.9) would be required to achieve an evaluable study population of 90 subjects.

11.2.4.2 Replacement of Missing Data

The last observation carried forward (LOCF) principle will be utilized for the analysis of NYHA Classification and Patient Global Assessment for primary endpoint 1 and secondary endpoints 2 and 3.

Missing NYHA and patient global assessment data at either the enrollment or follow-up visits affects the number of subjects that can be included in the analysis. It is possible that subjects or investigational personnel may either forget or choose not to answer one or more of the questions related to NYHA classification or patient global assessment.

11.2.4.3 MPP Programming

Subjects are expected to remain programmed with the MPP feature ON from MPP enrollment through the completion of the sub-study. Subjects who have the MPP feature permanently turned OFF prior to completion of the sub-study will be required to report a protocol violation. Subjects with MPP permanently turned OFF prior to completion of the stub-study will be analyzed as intent to treat.

Subjects may have the MPP feature temporally turned OFF due to a lead revision procedure and these short durations with MPP will not be reported as a protocol violation or analyzed differently. Additionally, any QP ExCELs subject that does not enroll into the MPP sub-study but receives MPP due to the physician's determination will not be analyzed towards the MPP study endpoints.

11.3 Protocol Requirements

11.3.1 Patient Population

The investigator is responsible for screening all potential patients and selecting those who are appropriate for study inclusion. The patients selected for participation should be from the investigator's general patient population currently participating in the QP ExCELs study according to the inclusion and exclusion criteria described below.

11.3.1.1 Inclusion Criteria

To support the objectives of this investigation, the inclusion criteria at the time of patient enrollment for this investigational study include the following requirements:

- Currently enrolled in the ongoing QP ExCELs study
- Successfully implanted with a BIOTRONIK Ilivia 7 HF-T QP family CRT-D system, or future-marketed CRT-D system with the MPP feature. Successful implantation is defined as having at least two LV pacing vectors with a measured pacing threshold of ≤ 5.0 V @ any pulse width (allowing for a minimum 2.5 V safety margin) without phrenic nerve stimulation at the final programmed pacing output at the time of enrollment into the MPP sub-study.
- CRT Responder Assessment classification as “Worsened” or “Unchanged”
- Standard continuous biventricular (BiV) pacing from implant until the 6-Month QP ExCELs follow-up visit. (Implant to 3-Month QP ExCELs follow-up who qualify due to a HF hospitalization event)
- Able to understand the nature of the sub-study and give informed consent
- Available for an additional follow-up visit specific to the MPP sub-study at the investigational site
- No evidence of non-compliance to their ongoing commitment in the QP ExCELs study

11.3.1.2 Exclusion Criteria

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment include the following requirements:

- Have a life expectancy of less than 6 months
- Expected to receive heart transplantation or ventricular assist device within 6 months
- Chronic atrial fibrillation
- Presence of another life-threatening, underlying illness separate from their cardiac disorder
- Received MPP pacing prior to enrolment into the MPP sub-study

11.3.2 Specific Testing

This sub-study protocol involves very specific inclusion and exclusion criteria. Therefore, detailed evaluation of all patients before enrollment is important to the success of the trial.

The specific visits that are part of the study are provided below. Specific Procedures are described in more detail in the following sections.

- MPP Enrollment (QP ExCELs 6-Month follow-up or 3-Month follow-up with HF hospitalization)
- 9-Month MPP Follow-up
- 12-Month MPP Follow-up

Subjects enrolled in the QP ExCELs MPP sub-study will be evaluated at the MPP enrollment visit, then 3- and 6-months post MPP enrollment. Subjects enrolled in the MPP sub-study will rejoin the main QP ExCELs study after the 12-Month** Follow-up; however, no further specific MPP related data will be assessed. Subjects with a HF Hospitalization event, as classified by investigator, prior to 90 days post implant may be enrolled into the MPP sub-study at the 3-Month follow-up visit.

11.3.2.1 New York Heart Association (NYHA) Classification

During the course of the study, the NYHA classification will be utilized for evaluation of the specific level of cardiac disease. The NYHA class will be evaluated and reported by the study investigator. The NYHA will be evaluated at all protocol-defined follow-ups. The following bullets provide the definitions for each class:

- Class I: Subjects with cardiac disease, but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II: Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III: Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV: Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

The description for each of the classes was taken from the ACC/AHA Guidelines for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices[8].

11.3.2.2 Patient Global Assessment (PGA)

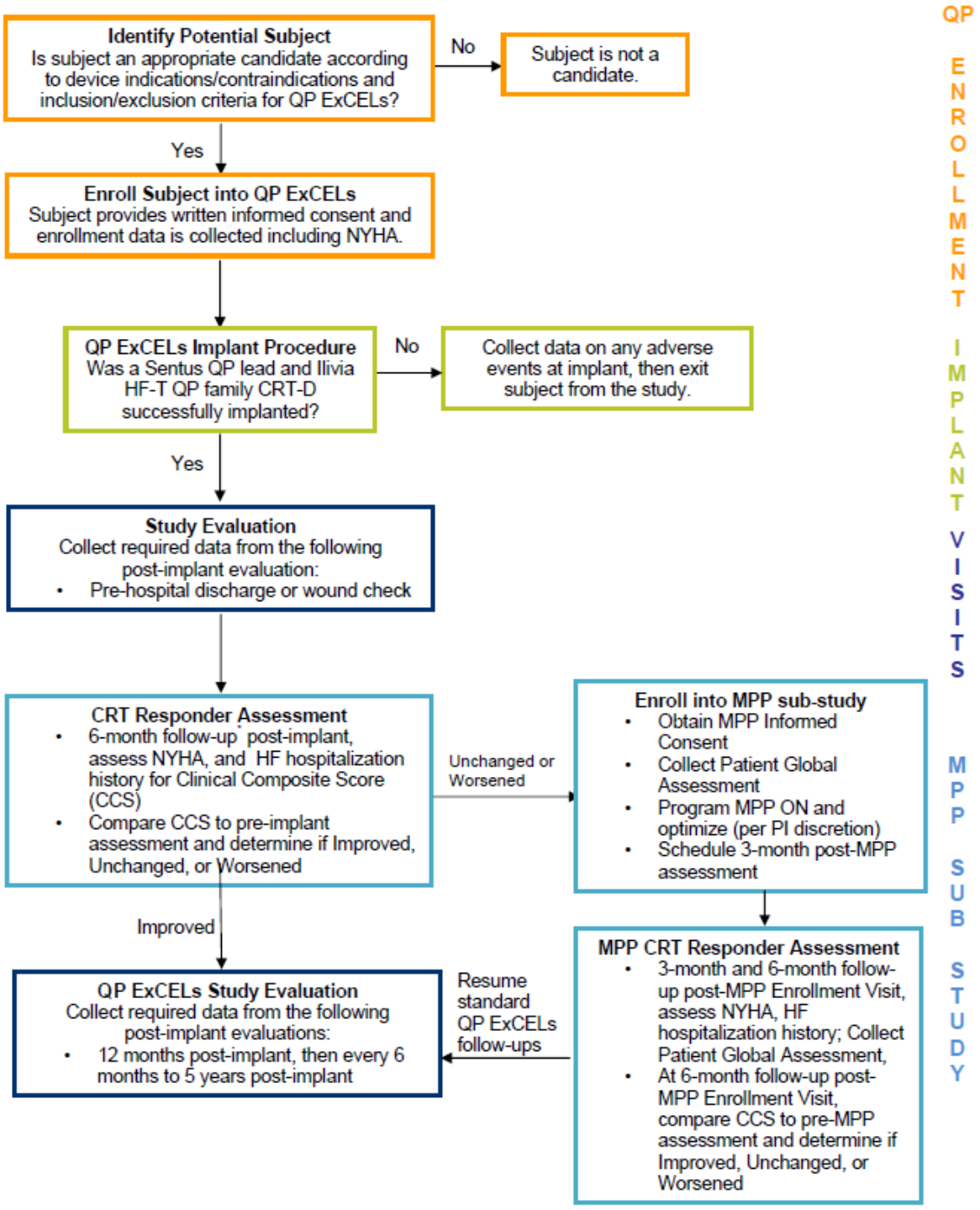
During the course of the study a patient global assessment will be given to assess how the subject's overall status has changed since prior to receiving CRT therapy (markedly better, better, unchanged, worse, markedly worse). It is important to minimize the influence on the respondent by limiting their interaction and verbal exchanges with spouses or other individuals who may affect results while the assessment form is being completed.

** Subjects enrolled in the MPP sub-study at the 3-Month QP ExCELs follow-up, qualifying with a HF hospitalization event, will rejoin the main QP ExCELs study after the 9-Month Follow-up

11.3.3 Sub-Study Procedures

Figure 13 provides an overview of the MPP sub-study design as part of the QP ExCELs study. Details of subject eligibility requirements and specific study procedures are noted in Section 11.3.1. While participating in the MPP sub-study, all subjects will continue to complete all required QP ExCELs study follow-ups.

Figure 14: MPP Sub-Study Design



* 3 Month follow-up if heart failure hospitalization event occurred.

A subject may qualify as a CRT non-responder and be enrolled at the 3-month follow-up if a HF hospitalization has occurred while receiving standard bi-ventricular pacing.

11.3.3.1 Enrollment into MultiPole Pacing Sub-Study

Prior to enrollment, the patient's background and history must be reviewed in order to ensure that the patient is an appropriate candidate for this sub-study. In addition, as part of the clinical study, informed consent must be obtained from the patient prior to initiating any study-related procedures.

Subjects enrolled in the QP ExCELs study evaluation who reach the 6-month post-implant follow-up with a CRT Responder Assessment as Unchanged or Worsened and meet the sub-study inclusion/exclusion may be enrolled into the sub-study. Subjects at the 3-month QP ExCELs follow-up with a HF hospitalization event since the QP ExCELs implant will be considered worsened and may be enrolled at the 3-month visit. Subjects are considered enrolled in the sub-study once MPP sub-study informed consent is obtained.

MPP optimization may be performed or not performed per investigator discretion at the time of enrollment into the MPP sub-study. The investigator will determine if MPP optimization will be performed for each subject and which method will be used (e.g. QRS width, electrical delay, echocardiography, etc.). MPP programmed parameters may be adjusted as needed during the follow-up period for MPP sub-study subjects.

The following data will be collected at the MPP enrollment visit:

1. Collect all lead testing data for standard QP ExCELs study follow-up
2. Turn MPP ON and collect MPP programmed settings
3. Document MPP optimization method
4. Obtain NYHA classification and HF hospitalization status
5. Obtain Patient Global Assessment
6. Collect device initial and final programmed settings
7. Document any reportable Adverse Events
8. Review and complete the appropriate eCRFs

The MPP feature must be programmed ON from MPP enrollment until the subject exits the sub-study. Subjects who have the MPP feature permanently turned OFF prior to completion of the sub-study will be required to report a protocol violation.

MPP follow-up windows are ± 30 days. Care should be given to ensure scheduling of MPP study visits fall within the corresponding QP ExCELs visit windows (± 45 days).

11.3.3.2 9-Month MPP Follow-up††

At a 9-month follow-up (90 ± 30 days post-MPP enrollment), subjects return to the investigational site for an in-office assessment of their heart failure status and implanted system.

The following data should be collected:

1. Collect MPP programmed settings
2. Obtain NYHA classification and HF hospitalization status
3. Obtain Patient Global Assessment
4. Collect device initial and final programmed settings
5. Document any reportable Adverse Events
6. Review and complete the appropriate eCRFs

11.3.3.3 12-Month MPP Follow-up‡‡

At the QP ExCELs 12-month follow-up (180 ± 30 days post-MPP enrollment), subjects return to the investigational site for an in-office assessment of their heart failure status and implanted system.

1. Collect all lead testing data for standard QP ExCELs study follow-up
2. Collect MPP programmed settings
3. Obtain NYHA classification and HF hospitalization status
4. Obtain Patient Global Assessment
5. Collect device initial and final programmed settings
6. Document any reportable Adverse Events
7. Review and complete the appropriate eCRFs

Following the 12-month follow-up, all subjects may be programmed to MPP or standard BiV pacing, per physician discretion.

11.3.4 Clinical Events Committee – MPP Sub-Study Events

The QP ExCELs Clinical Events Committee (CEC) described in Section 5.1 will adjudicate all adverse events that require additional invasive intervention to resolve which may be related to the MPP feature. These events include any software issues related to MPP programming or any adverse event that occurs while MPP is enabled and that may be attributed to the use of the MPP feature. The CEC will

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†† Subjects enrolled at the 3-Month follow-up due to a prior HF hospitalization event will be followed at 6-months (90 ± 30 days post-MPP enrollment).

‡‡ Subjects enrolled at the 3-Month follow-up due to a prior HF hospitalization event will be seen at 9-months (180 ± 30 days post-MPP enrollment) and join the main QP ExCELs study at the 12-Month visit.

indicate whether the adverse event is related, possibly related, not related, or has an unknown relation to the MPP feature.

In addition, the CEC will adjudicate all deaths reported while participating in the MPP sub-study and classify each death as cardiovascular, vascular, non-cardiovascular/vascular, or unknown.

The CEC will adjudicate all reported protocol-defined hospitalizations while a subject is enrolled in the MPP sub-study. Hospitalization events will be classified as cardiovascular, vascular, non-cardiovascular/vascular, or unknown. Additionally, hospitalizations classified as cardiovascular will be further classified as a HF hospitalization, non-HF hospitalization, or unknown. Hospitalization events reported by the investigator as part of the initial responder classification for enrollment into the MPP sub-study will not be adjudicated by the CEC.

11.4 Benefits and Risks

11.4.1 Potential Benefits

The clinical benefit of the Ilivia HF-T CRT-D is similar to that of standard CRT-Ds. Subjects taking part in this sub-study will receive additional and detailed examinations of their CRT system.

Although the participating study subjects might benefit from the new CRT-D system with MPP feature, currently there is only limited benefit for enrolled study subjects. Studies have shown that multiple point LV pacing via a QP LV lead may be an alternative approach to improve CRT response by delivering multiple LV pacing pulses, simultaneously recruiting a larger volume of myocardium.[2] A recent IDE study showed that quadripolar multiple point LV pacing was non-inferior to standard quadripolar biventricular pacing.[3] The medical community, as well as future subjects, may benefit from these study results, which will enable a better understanding of the safety and efficacy of the MPP feature.

11.4.2 Potential Risks

During the course of this sub-study subjects may experience potential adverse events related to the MPP feature. Although not expected these risks may include excessive battery drain or phrenic nerve stimulation. There is no current data to support superiority of MPP to conventional BiV pacing and it is not known if this feature will turn a non-responder into a responder. Adverse events will be determined by the investigator during subject follow-ups, documented in the subject medical record, and reported in the EDC system. Documentation includes the evaluation of the relation between the adverse event and the MPP feature. The date of the adverse event and resolution must be recorded. When an adverse event is noted in the EDC system, corrective action will also be provided with any supportive documentation available. Corrective actions may include, for example: drug therapy changes, programming changes, lead repositioning, new lead implants, or CRT-D explant.

Study sites may report adverse events through MedWatch, FDA's adverse event reporting tool for market-released devices. As defined in BIOTRONIK's internal procedures, these adverse events may be reported by BIOTRONIK through manufacturer's MedWatch reports.

11.5 Other General Information

11.5.1 Subject Death

Personnel at the investigational site should notify BIOTRONIK as soon as possible concerning any subject death during the investigation. This notification should include a completed study termination eCRF, death certificate, and a copy of the notification of the death sent to the IRB. If a death certificate is not available, a detailed statement (death report) signed by the investigator should be written in addition to the termination eCRF. The death report should include all of the following, if available:

- date and time of death
- place death occurred
- identification of the rhythm at the time of death, if known (include any available documentation)
- immediate cause of death
- any other circumstances surrounding the death
- whether it was device or procedure related

All implanted devices that are involved with the investigational study should be removed and returned to BIOTRONIK.

All deaths occurring while enrolled in the MPP study will be reviewed by the CEC.

11.5.2 Reporting Hospitalizations

To eliminate possible bias at the site level related to possible endpoint events of the MPP sub-study, adverse events requiring hospitalization for any cardiovascular hospitalizations and any other hospitalizations in which cardiovascular symptoms occur will be collected while subjects are enrolled in the MPP sub-study. Each hospitalization will be adjudicated to determine whether it meets the MPP sub-study endpoint criteria as a heart failure hospitalization by the Clinical Events Committee (CEC).

BIOTRONIK will be responsible for verifying completeness of the initial reported event and coordinating with sites to obtain any missing or additional source documentation required by the CEC to adjudicate the case. Additional documentation will be requested from the enrolling site as needed. The hospital report should include the following, if available:

- Discharge summary
- History and physical and admission summary.
- Diagnostic and laboratory test results.
- Chest X-ray, echocardiography, ultrasound or other imaging test results, as appropriate.
- Consultations, operation reports, progress notes and discharge summaries from the subject medical records.
- Investigator description and assessment of the event.

11.5.3 Definition of Heart Failure Hospitalization

Hospitalization for worsening heart failure is defined as a hospitalization that includes increased signs and/or symptoms of worsening heart failure requiring the administration or augmentation of intravenous or oral heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators).

A hospitalization classification will be based on the primary admission diagnosis, not on the development of new events that occur during the hospitalization.

For each hospital admission, the investigator will be requested to state whether or not the subject experienced worsening heart failure at the time of admission or during the admission, and if so, whether or not this was the primary reason for admission or secondary to an obvious precipitating factor such as atrial fibrillation. The investigator will also be asked to state whether or not the subject received an intravenous medication for heart failure including diuretics, vasodilators or inotropic agents or a substantial increase in oral diuretic therapy for heart failure.

11.5.4 Adverse Events

In addition to the adverse events reportable for the main QP ExCELs study, Section 6.2, the investigator shall report to the sponsor by completing the appropriate eCRF, the following type of events specific to the MPP sub-study:

- Any cardiovascular hospitalizations and any other hospitalizations in which cardiovascular symptoms occur on or before the date of the 12-Month follow-up[§§].
- All adverse events that required additional invasive intervention to resolve, specifically related to the MPP feature of the CRT-D. These adverse events include any software issues related to MPP programming for any adverse event that occurs while MPP is enabled and that may be attributed to the use of the MPP feature.

[§§] 9-month follow-up for subjects enrolled at the 3-month follow-up.

11.5.5 Adverse Events for Secondary Endpoint Analysis

The AE-free rate calculated for secondary endpoint 1 will be based on the total number of subjects with at least one MPP related adverse event requiring additional invasive intervention to resolve. For the secondary endpoint analysis, the AE classification, category, resolution, and relation to the MPP feature for each individual event will be determined by the Clinical Events Committee (Section 11.3.4)

All adverse events which the CEC determines the event is related or possibly related to the MPP feature will be included in the secondary endpoint event analysis. Adverse events with a final CEC adjudicated relation of not related or unknown will not contribute to or be included in the evaluation of the secondary endpoint.

11.5.6 Consent Materials (MPP Sub-Study)

Prior to the patient's participation in the sub-study, informed patient consent is required from all patients. Informed consent should be obtained in accordance with the FDA regulations (21CFR, Part 50). The investigator is required to inform BIOTRONIK and the reviewing IRB within 5 days if any patient was not appropriately consented to participate in the study. BIOTRONIK is then required to report any failure to obtain patient consent to the FDA within 5 working days of learning of such an event. In order to assist with the consent process, BIOTRONIK will provide a template patient consent form to investigational sites participating in the study.

11.5.7 IRB Approval

Institutional Review Board (IRB) approval is required from each institution prior to participation in this clinical investigation (sub-study). Patient enrollment may not begin until the IRB and BIOTRONIK have granted approval for the investigational site. IRB approval is also required throughout the duration of this clinical investigation. If IRB approval is withdrawn, BIOTRONIK must be notified within 5 working days.

11.5.8 MPP Sub-Study References

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12. JUSTIFICATION FOR THE DESIGN OF THE PRE-MARKET CLINICAL INVESTIGATION

The Sentus QP leads are 4.8 French (F) quadripolar left ventricular leads designed for use with biventricular pacing systems. Sentus QP is the successor of the Corox OTW bipolar (BP) LV leads. The Corox LV leads are market approved in the U.S. and internationally. They have been extensively studied in the ongoing CELESTIAL Post Approval Registry (NCT#00810264). Quadripolar LV leads are relatively new to the market. In the U.S., the first quadripolar LV lead received market approval November 2011 and is currently undergoing evaluation in a post-approval study. A second quadripolar LV lead more recently received approval for the U.S. market.

The results of CELESTIAL, summarized below, along with data collected during the EchoCRT study and available results from competitive quadripolar lead studies were used to support the expected performance goals and design for the pre-market endpoints of this clinical study.

Several clinical investigations conducted by BIOTRONIK Inc. or BIOTRONIK SE & Co. KG were relevant for the design of this clinical investigation:

- EveresT
- CELESTIAL Post Approval Registry
- EchoCRT
- Eluna Family/Sentus BP Master Study
- Iperia Family / Sentus QP Master Study

12.1 EveresT

The clinical study everesT was conducted by BIOTRONIK SE & Co. KG to assess the clinical safety and efficacy of the Corox OTW BP steroid polyurethane coated bipolar left ventricular lead and of Lumax HF-T 300/340 CRT-D devices. Two different fixation types of the Corox BP were investigated: a three dimensional pre-shaped helical tip to achieve a stable position in larger veins (Corox OTW BP) and a straight tip ‘wedge position’ (Corox OTW-S BP) for placement in smaller veins.

148 subjects in 25 sites from Austria, Germany, Italy, Israel, Switzerland and United Kingdom were enrolled in this prospective, non-randomized investigation. The first implantation was conducted on August 2, 2006 and the analysis consists of clinical data until September 30, 2007.

Summary of results:

- Corox LV lead implantation was attempted in 144 of 148 study subjects (97%)
- 131 of the attempted Corox implants were successful (91%)
- Implantation efficacy of Corox OTW BP helix was 91.5% (89/97)

- Implantation efficacy of Corox OTW-S BP straight was 89.5% (30/34)
- Out of 131 study subjects with a successful Corox implantation, a total of 2 Corox BP LV lead related complications were seen in 2 subjects within 90 days post implantation
- 1.5% of the study subjects with a successful Corox BP implantation experienced an LV lead related complication at 3 months post implantation (lead dislodgement, loss of capture)
- One Lumax HF-T device related complication occurred due to a pocket infection
- Corox BP LV lead measurements demonstrated good results in known ranges at implantation, pre-hospital discharge/wound check, and 1-, 3- and 6- month follow-up visits

Table 9 lists the reasons for the 13 unsuccessful Corox BP lead implantations:

Table 12: Reasons for Corox BP Implantation Failure

Reasons for implant failure	$N_{Failure}$*
Inability to find stable position	6 (46%)
Anatomical difficulties	5 (38%)
Inability to advance the lead	4 (31%)
Lead dislodged while removing guide catheter	4 (31%)
High threshold	3 (23%)
Dissection of coronary sinus	1 (8%)
Phrenic nerve stimulation	1 (8%)
No reason given	1 (8%)
Total Corox BP implant failures	13

*Percentages total over 100% because multiple answers could be given for reason of implant failure.

The data received and analyzed during the everesT clinical study demonstrate the safety and efficacy of the Lumax HF-T CRT-D device and Corox OTW (-S) BP Steroid.

12.2 CELESTIAL Study: Clinical Experience with Corox LV Lead

BIOTRONIK, Inc. is currently conducting the CELESTIAL post-approval study (P070008) to confirm the long-term safety and reliability of the Corox OTW BP LV leads. This multi-center, prospective, non-randomized registry has been ongoing since December 2008 with enrollment of 2,499 subjects completed on October 16, 2013. As of the May 2014 bi-annual report, the cumulative follow-up duration was 5,741 years (mean duration 2.3 years).

Data from the May 2014 bi-annual report is summarized below. In one column, results from all three Corox LV lead models included in the CELESTIAL Study (OTW, OTW-S, and OTW-L) are provided, as the materials and lead body design are similar to Sentus QP. In a separate column, data from the Corox OTW-L and OTW-S leads are presented as these lead tip shapes are similar to those leads included in this study.

The CELESTIAL Study permits enrollment up to 180 days post-implant and the visit schedule permits 3, 4, or 6 month visit intervals depending on the investigator's standard of care for CRT subjects. The complication-free rate at 6 months was calculated using the implant date and any qualifying adverse events occurring within 6 months post-implant. Lead measurements are from the actual 3 month evaluation; therefore, the number of subjects is less than the total study population.

Table 13: CELESTIAL Study Supporting Data

	All Corox models	Corox OTW-L and Corox OTW-S
Data supporting safety endpoint		
Subjects with safety data through 6 months post-implant, n	2,128	1,520
Corox related complication-free rate at 6 months post-implant*	97.4%	97.6%
Total subjects with Corox related complication, n (%)	56 (2.6%)	37 (2.4%)
Lead dislodgement	35 (1.6%)	21 (1.4%)
Diaphragmatic/pectoral stimulation	13 (0.6%)	10 (0.7%)
High pacing threshold/intermittent or no capture	7 (0.3%)	5 (0.3%)
Lead impedance out of range. Potential conductor fracture.	1 (0.0%)	1 (0.1%)
Procedure-related events	0 (0.0%)	0 (0.0%)
Data supporting efficacy endpoint		
Subjects with efficacy data at 3 months post-implant, n	1,475	1,095
Elevated threshold† free rate at 3 months post-implant	93.2%	93.0%
Total subjects with elevated threshold, n (%)	101 (6.8%)	77 (7.0%)
Corox lead performance at 3 months post-implant		
R-wave sensing, mean (±SD) in mV	13.6 (±7.3)	13.5 (±7.3)
Pacing threshold, mean at 0.5 ms (±SD) in V	1.4 (±1.1)	1.4 (±1.1)
Impedance, mean (±SD) in ohms	732 (±251)	730 (±248)

*Includes all Corox related events resolved with an invasive action or for which the lead was abandoned, continued to be used despite a known clinical performance issue, or when polarity or mode reprogramming was utilized for suspected lead failures. In addition, procedure-related events

(such as cardiac perforation, pneumothorax, and coronary sinus dissection) that were directly caused by the LV lead were included.

†Elevated threshold is defined as an LV pacing threshold > 3.5 V in any standard bipolar pacing vector.

12.3 Complication-free Rate in the EchoCRT Trial

To further refine the expected complication-free rate, adverse events collected as part of the EchoCRT trial (IDE# G080067) were evaluated. The EchoCRT trial was a randomized control trial conducted at 115 sites in 17 different countries conducted by BIOTRONIK, Inc. At study termination, 821 narrow QRS subjects had been implanted with a CRT-D system (mean implant duration of 1.7 years). Though the LV leads implanted in EchoCRT were not exclusively manufactured by BIOTRONIK, the data is informative because subjects were consented prior to implant, which limits subject selection bias and ensures reporting of all adverse events that occur at or immediately after device implant.

Table 14: EchoCRT Supporting Data

Data supporting safety endpoint	All LV leads
Subjects with safety data through 6 months post-randomization, n	670
LV lead related complication-free rate at 6 months post-randomization*	94.5%
Total subjects with LV lead related complication, n (%)	37 (5.5%)
Lead dislodgement	24 (4.3%)
Diaphragmatic/pectoral stimulation	4 (0.6%)
High pacing threshold/intermittent or no capture	2 (0.3%)
Procedure-related events	2 (0.3%)

*Includes all LV lead related events resolved with an invasive action or for which the lead was abandoned, continued to be used despite a known clinical performance issue, or when polarity or mode reprogramming was utilized for suspected lead failures, or events in which these actions would have been taken if subject had been randomized to CRT ON treatment arm. In addition, procedure-related events (such as cardiac perforation, pneumothorax, and coronary sinus dissection) that were directly caused by the LV lead were included.

12.4 Eluna Family /Sentus BP Master Study

This Master Study is performed by BIOTRONIK SE & Co. KG to confirm the safety and efficacy of the Eluna pacemaker family and the Sentus BP left ventricular lead. The Sentus BP left ventricular lead is the bipolar model of the Sentus leads and is similar in design to the quadripolar QP lead variants. After implantation of the Sentus BP lead, 2 in-hospital follow-ups are part of the study (pre-hospital discharge and 3 months after implantation). The data will be used to support the regulatory process in Japan. The study has enrolled 166 subjects and is currently in the follow-up phase.

12.5 Iperia Family / Sentus QP Master Study

This Master Study is performed by BIOTRONIK SE & Co. KG to confirm the safety and efficacy of the Iperia ICD family. The CRT-D devices of the Iperia Family are implanted in combination with the Sentus QP left ventricular lead. After implantation of the device system, 2 in-hospital follow-ups are part of the study (pre-hospital discharge and 3 months after implantation). The data will be used to support the regulatory process in Japan. The study has enrolled 152 subjects and is currently in the follow-up phase.

12.6 Published Results for Competitive Quadripolar Leads

Tomassoni et al., 2013 evaluated the safety and efficacy of the St. Jude Medical Promote® Q device system (Promote® Q CRT-D and Quartet® LV lead) in a clinical investigation. The CRT-D device is equipped with an IS4 connector to facilitate the implantation of the corresponding LV lead. The Quartet® LV lead is a quadripolar lead and has an over-the-wire design. In total 178 subjects were enrolled in the study. The device system was implanted successfully in 170 subjects (95.5%). The primary safety endpoint was designed to show the freedom from LV lead related complications from implantation to the 3-month post-implantation visit. The complication free rate was calculated to 96%. The 97.5% lower confidence interval of 93% is greater than the success criterion of 85%. The LV capture thresholds and pacing impedances in all 10 vectors remained stable during follow-up. LV lead dislodgment occurred in 6 subjects and phrenic nerve stimulation (PNS) was observed in 23 subjects. PNS was resolved non-invasively in all cases by reprogramming of the device.

Performance criteria and results from this IDE study are presented in Table 15.

Table 15: Competitive Quadripolar LV Lead Performance

	Safety	**Efficacy**
Performance criteria	85%	75%
Outcome	96% (97.5% LCB = 93%)	79.7% (97.5% LCB = 73%)

Source: Review Memo for P030054-S173 from FDA.gov. Efficacy is from the per protocol analysis (percentage of subjects with threshold < 2.5 V in Vector 1 and at least one nonstandard vector).

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14. APPENDIX A: DEFINITION OF TERMS

Abnormal Defibrillation Impedance – Defibrillation impedance is typically considered abnormal if a measurement is < 25 Ω or > 150 Ω (based on lead model and measurement range of the device). Includes high or low shock impedance when attempting to deliver a shock.

Abnormal Pacing Impedance – Pacing impedance is typically considered abnormal if a measurement is <200 Ω or >3000 Ω (based on lead model and measurement range of the device).

Cardiac Perforation associated with a lead – Penetration of the lead tip through the myocardium (including microperforation), clinically suspected and confirmed by chest x-ray, fluoroscopy, echocardiogram, intracardiac electrogram and/or visually.

Clinical Lead Failure – Inability of the lead to correctly sense or pace in the heart, not attributable to a mechanical or electrical failure of the lead or pulse generator and that remains unresolved despite reprogramming and/or repositioning.

Coronary Sinus Dissection – A tear that occurs in the wall of the coronary sinus.

Electrical Lead Failure – Confirmed or suspected lead issue that is due to an electrical failure of the lead, such as electrical noise not attributable to other causes, and that leads to loss of pacing and/or sensing. Specific types of confirmed or suspected electrical lead failures, such as high impedance values, no capture, and loss of sensing, are separate adverse event categories and should only be reported once. Confirmed or suspected electrical lead failures caused by induced malfunctions, such as lead damage caused during a procedure, are excluded.

Elevated Pacing Threshold – Either of the following is considered an elevated pacing threshold for the Sentus QP lead:

- At implant: pacing threshold > 3.0 V at 0.4 ms or 0.5 ms
- At routine evaluation: pacing threshold > 2.5 V at 0.4 ms or 0.5 ms

These thresholds are less than half of the maximum output in BIOTRONIK CRT devices and allow for an adequate safety margin.

Extracardiac Stimulation – Clinical observation of inadvertent nerve/muscle stimulation other than cardiac muscle, such as phrenic nerve stimulation.

Failure to Capture or Intermittent Capture – Intermittent or complete failure to achieve cardiac stimulation at programmed output delivered outside of the cardiac refractory period. This will be considered an AE if invasive intervention is taken. In absence of invasive intervention, this will only be considered an AE if there is failure to capture at the permanently programmed output with a minimum 2:1 safety margin. Sudden and significant increase in the pacing threshold value (elevated threshold compared to previous measured value) at which 2:1 safety margin can no longer be achieved.

Failure to Sense or Undersensing – Intermittent or complete loss of sensing or failure to detect intended intrinsic cardiac signals (atrial or ventricular) during non-refractory periods at programmed sensitivity settings. In absence of additional invasive intervention, this will only be considered an AE if the loss of sensing is not due to a medical reason and cannot be resolved with reprogramming.

Hematoma – A localized collection of extravasated blood, usually clotted, in an organ, space, or tissue. A hematoma is not considered a protocol defined AE unless it is a major hematoma related to the implant procedure. See major hematoma.

High Pacing Threshold – High lead pacing threshold resulting in invasive intervention. In absence of invasive intervention, at follow-up, lead threshold that has increased two fold from the chronic threshold value, and is unable to achieve a 2:1 safety margin.

Incorrect Lead/Header Connection – Lead connector pin connected to wrong header port, such as swapping leads or reversing connector pins, that is not identified and corrected prior to the end of the implant/revision procedure.

Infection – An invasion and multiplication of microorganisms in body tissues causing local cellular injury and requiring intravenous antibiotics and or system removal/extraction.

Lead Conductor Fracture – A mechanical break within the lead conductor (includes connectors, coils and / or electrodes) observed visually, electrically, or radiographically.

Lead Dislodgment – Radiographic, electrical or electrocardiographic evidence of electrode displacement from the original implant site or electrode displacement that adversely affects pacing, and/or lead performance.

Lead Explant – Surgical removal of a lead either by simple traction (such as occurs during the acute implant stage) or using manipulation and tools (as can be required for chronically implanted leads).

Lead Insulation Breach or Insulation Break – A disruption or break in lead insulation observed visually, electrically, or radiographically.

Loose Set Screw – Header set screw not properly tightened prior to end of implant/revision procedure.

Major Hematoma – Hematoma requiring evacuation, drainage, blood transfusion, hospitalization or extension of hospital stay to treat hematoma.

Mechanical Failure – Malfunction of the lead through a break in the conductor, insulation, or connector pin leading to loss of pacing / sensing observed visually, electrically, or radiographically. Confirmed or suspected mechanical failures induced by intervention, such as lead damage caused during a procedure, are not protocol defined adverse events.

New York Heart Association (NYHA) Functional Classification – A recognized system of classifying the extent of heart failure.

NYHA Class	Symptoms
I	Subjects with cardiac disease, but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Non-healing Pocket Dehiscence – Separation of wound edges around the pocket of the implanted pulse generator that have not healed.

Pneumothorax – Air or fluid in the pleural space surrounding the lung leading to collapse or partial collapse of the lung requiring observation or chest tube placement

Premature Battery Depletion – Reaching elective replacement indicator (ERI) before the predicted date.

Pulmonary Embolism – Blockage of the main artery of the lung or one of its branches by a substance that has travelled from elsewhere in the body through the bloodstream.

Pulse Generator Failure – Confirmed or suspected pulse generator issue that is due to a mechanical failure or electrical malfunction, such as inability to communicate with pulse generator, electrical circuit failure, or inability to deliver therapy, that is not attributable to another component of the system or caused by an external source.

Skin Erosion – Deterioration of tissue over an implanted device or the movement of a lead toward or through the skin.

Tamponade – Compression of the heart caused by blood accumulation in the space between the myocardium and the pericardium.

Thrombosis – The development of a blood clot in a vein or artery that leads to the obstruction of blood flow.

Twiddler's Syndrome – A condition where the pulse generator leads are dislodged by the subject unwittingly rotating or otherwise moving the subcutaneous pulse generator.

Venous Occlusion – Blockage of a vein causing a reduction of blood supply and associated symptoms.

15. APPENDIX B: PREVIOUSLY IDENTIFIED ADVERSE EVENTS

Based on literature research, the following adverse events may possibly occur as medical complications of a cardiac rhythm management system implant. The most common adverse events related to the implantation procedure are listed in Table 16a. Expected adverse events related to the left ventricular pacing threshold test in the novel vectors are listed in Table 16d. All references used for this chapter refer to the list at the end of this section.

Adverse events listed below are considered expected unless not previously identified in nature, severity or degree of incidence.

Table 16a: Expected Perioperative Events

Frequency	Percentage (%)	Risk
Very frequent >1 out of 10 patients	7-19[45]	LV lead exchange due to unsuccessful positioning
	3-27[32]	Atelectasis (when thoracotomy necessary)
	3-27[32]	Pleural effusion (when thoracotomy necessary)
	3-27[32]	Pneumonia (when thoracotomy necessary)
	Up to 17[32]	VT/VF exacerbation[8,32]
Frequent 1 to 10 patients out of 100	1-7[32]	Infection (general)
	5.2[55,56] - 6[32]	Lead perforation
	3-4[32]	Pericarditis (when patch lead placement necessary)
	Up to 3[32]	Embolism
	Up to 3[49]	Phrenic nerve stimulation
	0.6 – 2.0[49]	Infection requiring reoperation
	0.07*-3[32,54]	Pericardial tamponade (2-3% during patch lead placement)
	0.93[31]-10.6[2,49]	Lead dislodgement
	0.12[31]–3.4[49]	Coronary sinus dissection
Occasionally 1 to 10 patients out of 1.000	0.93[31]	Hematoma
	0.7[54]	Loosening of set screw
	0.02[31] -1[30]	Myocardial infarction
	0.06[31]-2[32]	Cerebrovascular accident, stroke (1-2% during thoracotomy)
	0.6[30]	Lead dysfunction
	0.5[30] – 0.7[57]	Mortality
	0.5[30]	Severe pocket hematoma
	0.5[54]	Pericardial tamponade (2-3% during patch lead placement)
	0.42[31] -1[30]	Pneumothorax
	0.3[31] – 0.4[49]	Cardiac arrest
	0.2[30]	Arrhythmia
	0.2 – 0.3[49]	Respiratory arrest
	0.2[49]	Tamponade

	0.1 - 0.4[51]	Allergic reaction to ionic contrast material
	0.14[50]	Air embolism
	0.1[49]	Lead fracture/ insulation failure
	0.1[59]	Ventricular fibrillation
Rare 1 to 10 patients out of 10.000	0.09[31]	Drug reaction
	0.08[31]	Hemothorax
	0.07[31]	Cardiac perforation
	0.04[31]	Phlebitis, superficial
	0.03[31]	Conduction block
	0.03[31]	Infection related to device
	0.03[31]	Peripheral embolus
	0.02[52]– 0.04[53]	Allergic reaction to non-ionic contrast material
	0.02[31]	Phlebitis, deep
	0.02[31]	Transient ischemic attack
Very rare <1 patient out of 10.000	<0.01[31]	Cardiac valve injury
	<0.01[31]	Peripheral nerve injury
	<0.01[31]	AV-fistula
Not known Frequency not assessable on the basis of the available data		Allergic reaction to dexamethasone acetate, bleeding[32], brachial plexus injury[32], device migration[30,41], diaphragmatic stimulation[32], discomfort, erosion, exit block[32], failure to insulate set screw[32], hemoptysis[32], injury to vagus nerve[32], lead malpositioning[32], lead microdislocation[32], local tissue reaction[30], muscle stimulation[30], nerve stimulation (general) [30], myocardial lesion[30], pocket seroma[32], subclavian artery puncture[32], higher x-ray load due to extended fluoroscopy times[34], failing of shock test[40], injury due to implantation accessories[42,44]

Table 16b: Expected Postoperative Events

Frequency	**Percentage** (%)	**Risk**
	9.7[20] -37[23]	Lead failure[20,22,23]
Very frequent >1 out of 10 patients	2.9[7]–25.4[24]	Inappropriate shocks[7,24,25,54]
	Up to 13[29]	Device explantation (manufacturers` advisory: 4%[29], electronic failure: 2%[29], housing defects: 1%[29])
	0.3[1] – 13.6[4]	Phrenic nerve stimulation
	12[6,21]	Lead dysfunction
	1.2[19] –10.6[2]	Lead dislodgement
Frequent 1 to 10 patients out of 100	1.7[2] – 9.5[2]	Formation of clinical significant hematomas
	7.6[15] – 9.5[1]	Hematoma[1,3,15,16,17]
	7[46]	Subclavian vein occlusion ≥ 75%
	0.1[5] - 7[1]	Infections[1,5,14] (CRT-D related: 1.9[1,4,13] - 1.9%[1,4]; in-hospital infections: 0.7%[12]; infections after replacement: 1.9%[13])
	0.1 – 4.2[60]	Lead fracture
	1.6[7] – 3.9[4]	Elevated pacing threshold/ loss of capture/ failure to capture
	2.4[30]	Aggregate perforation

	3.4[30]	Pocket erosion
	0[2] – 1.5[7]	Mortality within 30 days after implant (0.4% related to implant procedure[7])
	1.5[30]	Premature depletion of battery
	1.4[7]	Diaphragmatic muscular stimulation
	0.3[2] – 1.3[5]	Lead perforation
	1.3[1]	Pericarditis requiring anti-inflammatory agents
	0.05[7] –1,2[12,57,61]	Pneumothorax
	0.9[1]	High LV threshold
	0.7[5]	Oversensing
	0.6[7]	Discomfort
	0.6[7]	Pain at device pocket
	0.6[1]	Pericardial effusion requiring intervention
	0.6[7]	Seroma
	0.6[7]	Shoulder pain
	0.5[4]	Lead conductor fracture
	0.5[30]	M. pectoralis tremor
	0.3[5] – 0.5[18]	Post-operative perforation
	0.7[54]	Thrombosis of brachial, subclavian or jugular veins
	0.3[12]	Acute renal failure requiring hemodialysis
	0.3[1]	Ipsilateral venous thrombosis
	0.3[7]	System- or lead-related arrhythmia
	0.2[4]	Elevated lead impedance
	0.2[63]	Site pain
	0.2[54]	Thrombosis of deep femoral vein
Rare 1 to 10 patients out of 10.000	0.09[35]	Fluid accumulation due to heart perforation
	0.1[7]	Cardiac/ cardiac vein/ coronary sinus dissection
	0.1[7]	Hypotension
	0.07[39]	Twiddlers syndrome
Not known Frequency not assessable on the basis of the available data		Farfield sensing or crosstalk leading to pacemaker malfunction[30], Pacemaker Mediated Tachycardia[30], isolation deficiency[30], connector deficiency[30], undersensing[30], chronic nerve damage[30], fibrotic tissue formation[30], keloid formation[30], formation of cysts[30], sensing of myopotentials[30], pulse generator failures[26], device extrusion[36, 43], vein occlusion[37], occlusion of coronary sinus[38]

Table 16c: Expected Psychological Events

Frequency	**Percentage** (%)	**Risk**
Very frequent >1 out of 10 patients	25[9,10] - 50[9]	Anxiety or depression[9,10,11,27]
Occasionally	Up to 1[6]	Psychological intolerance

1 to 10 patients out of 1.000		Psychosomatic impairment
Not known Frequency not assessable on the basis of the available data		Decreased energy levels[28], sleep disturbances[28], loss of libido[28], fatigue[28], reduced physical capacity[28], change in body perception[28], decreased activity level[28], sense of impending danger and uncertainty about the future[28], sensation of losing control[28], sensation of isolation[28], cognitive impairment[28], decline in social interaction[28], fear of shock delivery[28], fear of death[28], fear of device malfunction[28], alteration of social relationships[28], obsessive thinking about shocks[28]

Tale 16d: Expected Events due to Pacing Threshold Test of the LV Lead

Frequency	**Percentage** (%)	**Risk**
Very frequent >1 out of 10 patients	32[47]- 41[48]	Phrenic nerve stimulation in 1 or more pacing vectors
Not known Frequency not assessable on the basis of the available data		palpitations

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