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Clinical Investigation Plan

Benefit of dual-chamber pacing with Closed Loop Stimulation (CLS) in tilt-induced cardio-inhibitory reflex syncope.

A randomized double-blind parallel trial

BIOSync CLS trial

Reference Number BA103

Version 7-0

Date, 20-JUN-2016

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List of principal investigators, investigation sites, and institutions

A current list of participating investigators, investigational sites, and institutions and a detailed list of sponsor contacts are filed in the Trial Master File.

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Signature of the Principal Investigator

Name: _____

Institution: _____

Street: _____

ZIP code/ City: _____

Country: _____

I have read this Clinical Investigation Plan (CIP) and agree to adhere to the requirements described in this study protocol.

I will provide copies of this study protocol and all necessary information about this study to the staff under my supervision.

I will discuss this material with them and ensure they are fully informed about the devices under investigation as well as all aspects concerning the conduct of this study.

_____ _____

City, date Signature of Principal Investigator

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1 LIST OF ABBREVIATIONS

ADE: Adverse Device Effect
AE: Adverse Event
AV: Atrio-Ventricular
BP: Blood Pressure
CA: Competent Authority
CCI: Coordinating Clinical Investigator
CDMS: Clinical Data Management System
CIP: Clinical Investigation Plan
CLS: Closed Loop Stimulation
CRO: Contract Research Organization
CRT: Cardiac Resynchronization Therapy
DD: Device Deficiency
DSMB: Data Safety Monitoring Board
EC: Ethics Committee
ECG: Electrocardiogram
eCRF: electronic Case Report Form
EDC: Electronic Data Capture
ESC: European Society of Cardiology
IB: Investigator Brochure
ICD: Implantable Cardioverter Defibrillator
IEGM: Internal Electrogram
IPG: Implantable Pulse Generator (pacemaker)
IRB/EC: Institutional Review Board/Ethics Committee
ITT: Intention to treat
LVEF: Left Ventricle Ejection Fraction
RCT: Randomized Clinical Trial
SADE: Serious Adverse Device Effect
SAE: Serious Adverse Event
SAV: spontaneous atrio-ventricular interval
SBP: Systolic Blood Pressure
TT: tilt table test

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2 SYNOPSIS

Title:	BIOSync CLS. Benefit of dual-chamber pacing with Closed Loop Stimulation (CLS) in tilt-induced cardio-inhibitory reflex syncope. A randomized double-blind parallel trial
Patient collective:	The study will select 128 patients with a Class IIb indication for cardiac pacing due to tilt-induced cardio-inhibitory response with recurrent frequent unpredictable syncope and age ≥40 years, after alternative therapy has failed.
Design:	Prospective, multi-center, double-blinded, randomized, intention-to-treat, placebo-controlled study
Investigational device(s)	BIOTRONIK Eluna 8, Epyra 8, Etrinsa 8 IPG families. Dual-chamber IPGs only will be included in this investigation.
Objectives	The study has the primary objective of comparing syncopal recurrences between an active group treated with the Closed Loop Stimulation (CLS) in addition to the DDD pacing and a control group of patients with pacemaker programmed in ODO mode (sensing only). The study hypothesis is that DDD pacing with CLS stimulation is able to prevent syncopal recurrence completely or partially by transforming syncope in pre-syncope.
Definitions of end-points	Syncope is defined as a transient complete loss of consciousness characterized by rapid onset, short duration, and spontaneous complete recovery. Pre-syncope is defined as any of the various signs and symptoms which are recognized by the patients as premonitory of imminent syncope but not followed by syncope.
Primary endpoint:	The Primary Endpoint will be the time to the first post randomization recurrence of syncopal episode
Secondary endpoint:	The Secondary endpoint 1 will be the time to the first post randomization recurrence of pre-syncope or syncope, whichever comes first
Inclusion criteria	Patients affected by clinical diagnosis of reflex syncope who meet all the following criteria: • age ≥40 years • significant limitation of social and working life due to unpredictable frequent syncope recurrences, ≥2 within the last year. • type 2B cardio-inhibitory response to TT (according to the VASIS classification). • Alternative therapies have failed or were not feasible. • exclusion of other possible competitive causes of syncope.

Exclusion criteria	• Any other indication to IPG, implantable defibrillator (ICD), cardiac resynchronization therapy (CRT), according to current guidelines
	• Any cardiac dysfunctions possibly leading to loss of consciousness:
	  ○ overt heart failure;
	  ○ ejection fraction (LVEF) <40% (Echo-assessed within

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	3-month prior to study participation); ○ myocardial infarction; ○ diagnosis of hypertrophic or dilated cardiomyopathy; ○ clinically significant valvular disease; ○ sinus bradycardia <50 bpm or sinoatrial block; ○ Mobitz I second-degree atrioventricular block; ○ Mobitz II second or third-degree atrioventricular block; ○ bundle-branch block; ○ rapid paroxysmal supraventricular tachycardia or ventricular tachycardia; ○ preexcited QRS complexes; ○ prolonged QT interval; ○ Brugada syndrome; ○ arrhythmogenic right ventricular cardiomyopathy) • Symptomatic orthostatic hypotension diagnosed by standing BP measurement; • Nonsyncopal loss of consciousness (eg, epilepsy, psychiatric, metabolic, drop-attack, cerebral transient ischemic attack, intoxication, cataplexy). • Symptomatic cardioinhibitory carotid sinus hypersensitivity.
Study duration:	~ Q2 2015 – Q2 2019 Year (~ 48 months)
Number of follow-ups per patient	A maximum of 3 scheduled in-hospital follow-ups.
Follow-up scheme:	In-hospital: 12-, 24-month follow-up Anonymous patient questionnaires quarterly collected by and independent institution
Coordinating Clinical Investigator	Dr. M. Brignole Dr. M. Tomaino
Boards (if applicable)	Steering Committee, Data Safety Monitoring Board, Primary Event Adjudication Board
Sponsor	BIOTRONIK SE & Co. KG Center for Clinical Research Woermannkehre 1 D-12359 Berlin

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3 INTRODUCTION

3.1 Rationale for a large randomized trial

The latest update of the European Society of Cardiology (ESC) guidelines for cardiac pacing has set a Class IIb (evidence B) indication for permanent cardiac pacing in patients with tilt-induced cardio-inhibitory response with recurrent, frequent, unpredictable syncope and age ≥40 years after alternative therapy has failed.[1]

The reason behind the indication is that randomized clinical trials (RCTs) did not lead to a conclusive evidence due to some limitations in study design and controversial results. In particular:

- The SYDIT[2] and VASIS PM[3] trials selected patients with positive cardio-inhibitory (mostly asystolic) response during tilt test. Two-year results were in favor of pacing with a significant reduction of syncopal recurrences in the pacemaker (IPG) arm. However the SYDIT study was early terminated and both SYDIT and VASIS studies were open-label. Particularly, studies on syncope recurrences may be prone to potential bias deriving from a lack of blinding.
- On the other hand, the VPS II[4] and the SYNPACE[5] studies, which included younger patients with both cardio- and non-cardio-inhibitory response to tilt test, failed to demonstrate significant superiority of pacing.
- A recent small sub-study of the International Study on Syncope of Uncertain Etiology 3 (ISSUE-3[6]) showed that syncope still recurred after cardiac pacing in 35% (95% CI, 13–75) of patients at 12 months.

Consequently, the *status quo* is that pacing *may be* considered (Class IIb indication) in patients with a cardio-inhibitory response to Tilt-Test (TT), after any cardiac dysfunction likely leading to loss of consciousness and other non-syncopal causes (including epilepsy, psychiatric, metabolic, drop-attack, etc.) have been excluded.

On the hand, the 2009 ESC guidelines for diagnosis and management of syncope established that cardiac pacing showed higher evidence of benefit and *should be* considered (Class IIa indication) in patients with frequently recurrent reflex syncope, age ≥40 years and spontaneous cardio-inhibitory episodes during long-term monitoring.[7]

Recently, a sub-analysis of the ISSUE-3[6] showed that an asystolic response to TT predicts similar clinical forms of asystolic syncopal events during follow-up with an 86% probability, thus tracing back to a Class IIa indication for cardiac pacing. This is the main reason why pacing is currently preferred in structured Syncope Units and, more generally, in normal medical practice.

In conclusion, the ESC Task Force consider further research is extremely important as it is very likely to have an important impact on recommendations.[1] This is the objective of the BIOSync CLS study.

3.2 Possible benefits from the Closed-Loop Stimulation (CLS)

In all the cited trials, a dual-chamber pacing mode was used with an automatic feature promptly responding to heart rate drops by rapid DDD pacing for a programmed interval. However, few small studies have reported that the DDD-CLS mode may be effective as well.[8]-[12]

During the CLS mode intracardiac impedance curves are collected during systolic phases by injecting subthreshold high frequency current pulses. The waveforms of such rheometric signals are influenced by contractility, and this principle is exploited to adjust the pacing rate in normal rate responsive operation.[13]

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It has been hypothesized that the detection of an increase in contractility in the early stage of a vasovagal syncope could allow the system to activate atrio-ventricular pacing that may anticipate withdrawal of sympathetic tone and counterbalance vagal tone reaction.[8] Therefore CLS would react early during a first sympathetic phase of the reflex, while rate-drop response functions would intervene after the vagal reaction (bradycardia) has been already triggered for a while. Since cardiac output is the result of the product of BP and heart rate, an early heart rate increase achieved by CLS detection during the phase preceding syncope could be able to sustain cardiac output even when BP start falling thus counteracting, at least in part, the vasodepressor reflex and avoiding syncope or at least delaying it. Results appeared amazing so far: no syncope recurrence was reported in the CLS arm by a first randomized study testing CLS against placebo during one-year follow-up[9]; 83% of patients remained free from recurrences after a 3-year period[10]; the number of recurrences of syncope or presyncope were reduced by 87% and 83% respectively, in a within-patient comparison obtained in a 18-month period crossover-designed study[12]; finally, CLS appeared superior even when compared with the rate-drop-response pacing functions, with a 90% relative reduction of the recurrence rate, as reported by a retrospective analysis.[11]

However despite these impressive data, all the studies conducted so far suffered from severe limitations in study population size, design and conduct methods which made conclusions less firmly supported by evidence. Nevertheless these first clues would deserve a rigorous assessment by means of a large randomized double-blinded clinical study testing CLS against placebo in a parallel design.

The BIOSync CLS is a RCT designed to reliably assess the benefit of pacing against placebo, by using the CLS algorithm on top of DDD mode, in patients with frequent syncope recurrences, age ≥40, cardio-inhibitory response to TT, after all competing causes have been excluded.

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4 INVESTIGATIONAL DEVICE

4.1 Summary description of the device and its intended purpose

The investigational devices included in the BIOSync study are the BIOTRONIK Eluna 8, Epyra 8, Etrinsa 8 dual chamber IPG families.

All the mentioned investigational devices provide a function called CLS, developed to provide a physiologic pacing rate modulation. CLS is based on an indirect monitoring of the myocardial contractility, which is a function of the neurovegetative tone. Such monitoring is obtained via a permanent sampling of the intraventricular impedance signal by a high frequency sub-threshold pulse train: an increase of the impedance curve slope, with respect to a reference rest curve, is an indication of an increased activity and it is used by the algorithm to adapt the heart rate. CLS functioning actively interacts with the autonomic regulation process of cardiac output, occurring under any condition of daily life, not only exercise-related stresses.[14]

4.2 Manufacturer

The manufacturer of the Eluna 8, Epyra 8, Etrinsa 8 IPGs is the sponsor of the study:

BIOTRONIK SE & Co. KG
Woermannkehre 1
D – 12359 Berlin
Germany
www.biotronik.com

4.3 Model name including software version and accessories

The following models will be included in the study:

- BIOTRONIK Eluna 8 DR(/-T/ProMRI), software PSW 1303.A and later versions
- BIOTRONIK Epyra 8 DR-T(/ProMRI), software PSW 1303.A and later versions
- BIOTRONIK Etrinsa 8 DR-T(/ProMRI), software PSW 1303.A and later versions

These devices will be used along with any CE-marked bipolar leads. A detailed description of these systems is reported in their product manual and the Investigator Brochure (IB).

4.4 Description of traceability

Device traceability will be obtained by serial numbers.

4.5 Intended purpose of the device in the study

According to IFU, the implantable pacemakers listed in section 4.3 may be implanted for all bradycardia arrhythmia indications. The primary objective of the therapy consists of improving patients' symptoms that can be clinically manifested. The implantation of the pacemaker is a symptomatic therapy with the objective of compensating bradycardia by atrial, ventricular, or AV sequential pacing.

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In order to conduct the BIOSync CLS study, a special function (ODO mode) will be activated in patient randomized to the control group. This function inhibits any pacing functions until reprogramming, as described in section 4.5.1. The activation of this function is therefore an off-label use of the above listed pacemaker models.

4.5.1 Description of the ODO function

Among the programmable pacing modes, the user can activate the ODO mode with the programmer device, by selecting "OFF" in the "Modes" window. During the ODO mode the pacemaker does not deliver any pacing therapy, while it maintains all the sensing and related diagnostic functions to monitor cardiac rhythm. In standard operating conditions, pacing OFF is a temporary function: it is active until the programming head is applied or the radiofrequency telemetry connection (SafeSync®)is enabled. The BIOSync CLS study design requires the pacing OFF condition (ODO mode) to be permanently active (without the programming head or radiofrequency connection) during the patient's participation in the study (that is until the first adjudicated syncope recurrence, follow-up termination or study withdrawal).
In order to activate the OFF mode permanently, a special code is required by the programmer software.

4.6 Intended patient population and indications

The IPG systems used in this study are used for all bradycardia arrhythmia indications, to improve patients' symptoms that can be clinically manifested and compensate bradycardia by atrial, ventricular, or Atrio-Ventricular (AV) sequential pacing.

The patient collective selected for this study have a Class IIb indication for the IPG therapy according to the current European guidelines[(1)]. The investigational devices are therefore used within their indication.

4.7 Summary of training and experience needs

In addition to having basic medical knowledge, the Investigators must be thoroughly familiar with the operation of a device system. Only qualified medical specialists having the special knowledge required for the proper use of implanted devices are permitted to use them. Investigators will be trained.

4.7.1 Description of medical and surgical procedures

The investigational devices will be implanted and followed up according to standard techniques and normal clinical practice. The study protocol does not require any additional procedure during implantation beyond those normally performed in normal clinical practice.

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5 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

As discussed in the Section 3, there are data suggesting that CLS functioning on top of dual-chamber pacing may be beneficial in preventing syncopal recurrences in patients affected by tilt-induced cardio-inhibitory syncope. However a definitive evidence of benefit from pacing, in general, with the addition of the CLS function, in particular, has never been obtained. Therefore, evaluating this benefit (if it exists) by means of a double-blinded, placebo-controlled, randomized trial, is justified.

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6 RISKS AND BENEFITS OF THE DEVICE AND CLINICAL INVESTIGATION

6.1 Anticipated clinical benefits

There are no specific benefits for the individual patient directly deriving from the participation to the study. Nevertheless, the patients included in the study will have a thoroughly monitored medical supervision.

6.2 Anticipated risks

6.2.1 Anticipated adverse device effects

Patients fulfilling the inclusion/exclusion criteria of the BIOSync CLS study have a Class IIb indication to pacemaker implant. The risks related to the implantable pacemaker therapy are reported below in this section. These risks were excluded from the Risk Analysis as they have already been considered for the CE certification of the pacemakers manufactured by BIOTRONIK SE &_Co. KG and used in the BIOSync CLS investigation.

Known adverse events associated with pacemaker therapy are listed below along with probability ranges.

Table 1. Adverse events and probability ranges associated with pacemaker therapy

Adverse Event	***Range of probability (%)***	***References***
Related to venous access		
Pneumothorax	1-10	20-22
Hemothorax	0.1-0.01	20-22
Massive air embolism	1-0.1	23
Air embolism	>10	24-26
Endocarditis	0.06-7	39
Related to leads		
Lead dislodgment	1-10	20-22
Pericardial tamponade	0.1-0.01	20-22
Malposition	unknown	21
Deep vein thrombosis	0.1-1	27
Exit block	unknown	
Insulation failure/conductor fracture	0.1-1	27
Related to pocket		
Hematoma	1-10	27
Infection	1-10	21, 27
Wound dehiscence	unknown	21
Pain	unknown	21
Skin erosion	0.1-1	27
Device migration	unknown	21
Device function issues		
Externally mediated damage	0.1-1	27
Oversensing	0.1-1	28
Undersensing	unknown	21
Crosstalk/far-field sensing	unknown	21
Pacemaker syndrome	unknown	21
Pacemaker-mediated-tachycardia	unknown	21

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Device failure (early battery depletion, advisory, electronic failure, etc.)	13 (of explanted devices)	29

The term "unknown" for the probability range has been used when frequency was not assessable on the basis of recent scientific literature.

Other possible adverse events of unknown frequency are:[21, 30-38] allergic reaction to contrast media or dexamethasone acetate, bleeding, brachial plexus injury, diaphragmatic stimulation, discomfort, failure to insulate set screw, hemoptysis, injury to vagus nerve, lead insulation fracture, lead microdislocation, local tissue reaction, loosing of set screw, muscle stimulation, nerve stimulation (general), myocardial lesion, phrenic nerve stimulation, pocket seroma, subclavian artery puncture, higher x-ray load due to extended fluoroscopy times, injury due to implantation accessories, connector deficiency, chronic nerve damage, fibrotic tissue formation, keloid formation, formation of cysts, sensing of myopotentials, pulse generator failures, device extrusion, vein occlusion, Twiddler's syndrome.

Patients assigned to the treatment group will have the pacemaker CLS function activated. No major complications associated with this function are expected. However, palpitations have been reported in rare cases, eliminated by proper device reprogramming.[8]

Patients assigned to the control group will have the ODO function activated (see section 4.5). This particular operating mode is outside the intended use for pacemaker models included in the study. Anticipated hazards have been analyzed in the Risk Analysis and reported in the IB.

6.2.1.1 Protective measures

The above mentioned adverse device effects will be minimized by the following additional protective measures:

- During pacemaker implant and follow-up, only CE-marked medical devices will be used according to their IFU: pacemaker (except for the ODO mode), leads, programmer, accessories, surgical equipment and external medical devices;
- Only study sites and investigators with proven long-term experience in pacemaker implantation will be included in the BIOSync CLS investigation;
- Only study sites and investigators for whom the pacemaker therapy is routinely practiced in the patient population enrolled in the BIOSync CLS study will be selected

6.2.2 Residual risks associated with the device

The devices used for the treatment group are CE certified and used within the approved intended use.

Patients in the control group will receive the same CE-marked pacemaker model, in which the ODO function will be activated. Residual risks of the ODO mode and their acceptance criteria were analyzed in the Risk Analysis report and reported in the IB.

6.2.3 Risk associated with participation in the study

The implantation of the investigational device systems and the follow-up procedures do not differ from the procedures in routine care with comparable systems.

Patients will undergo a randomization procedure which will assign each of them either to the treatment (pacing ON with CLS) or to the placebo. Placebo will consist of the implantation of the investigational device and subsequent programming with only sensing and diagnostic functions activated (ODO mode). This mode is outside the intended use of the pacemaker models included in the BIOSync CLS study. Risks associated with the ODO mode have been analyzed in the Risk Analysis and reported in the IB.

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Participating patients may optionally undergo a TT examination one month after hospital discharge. TT is a safe procedure and often considered as part of normal clinical practice in the study population, even after pacemaker implant, to predict response to the therapy. There have been no reported deaths nor severe complications during the tests.

6.2.4 Possible interactions with concomitant medical treatments

No interactions are expected with medical treatments.

6.3 Steps to control or mitigate the risks

As reported in the Risk Analysis and in the IB the following measures will be adopted to mitigate the risks associated with the participation in the study.

Clinical Investigation Plan and Study Design shall include:

1) An independent DSMB will be monitoring the study conduct reviewing all available source document related to any death occurring during the study and recommending early study termination, if deemed appropriate.

2) Should a patient in ODO mode study arm die, source document review will be performed immediately, without any undue delay as soon as all relevant documents are available

3) The following procedures have been introduced in the study CIP:

- Subjects terminate study participation at the first adjudicated syncope recurrence

- Three interim analysis are planned to early terminate the study in case of evidence of superiority of the treatment arm

- independent DSMB to periodically monitor the study status and preliminary results, recommending termination in case of unacceptable risk

- Investigators are allowed to take any medical decision deemed appropriate, including pacemaker reprogramming

- Advice the patient to avoid activity which may pose risks in case of transient loss of consciousness

4) The password/code is communicate only to hospital staff involved in the study after appropriate training

5) Resuscitation equipment available during pacemaker setup

6) The following measures must be taken during a TT:

- a pacemaker programmer available in the room and switched on before the test starts

- Adherence to current guidelines

- Use of nitroglycerine

- Resuscitation equipment available during tests

7) Initial training and, if necessary, periodic re-training of the hospital study staff

6.4 Risk-to-benefit rationale

According to the Risk Analysis, considering their probability of occurrence and their severity, the residual risks associated with the study participation are considered acceptable.

Patients are provided with one of the latest BIOTRONIK IPG systems. They are monitored closely due to regularly scheduled follow-ups. The CLS function may physiologically support

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the heart rate improving exercise and general quality of life, while presumably reducing the risk of a syncopal recurrence. Also, patients in the placebo arm may benefit from the diagnostics features of the implanted device, and from pacing after the first occurrence of a primary endpoint event.

The follow-ups are not expected to last longer than a routine follow-up. The general benefit of the study is the collection of clinical data including the proof of efficacy of CLS in preventing syncopal recurrences.

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7 OBJECTIVES AND HYPOTHESES

The hypothesis of the study is that DDD pacing with CLS stimulation is able to overcome the cardioinhibitory reflex with DDD pacing and to counteract, at least in part, the vasodepressor component of the reflex - which is usually associated in tilt-positive patients- with CLS activation. The study hypothesis is that DDD pacing with CLS stimulation is able to prevent syncopal recurrence completely or partially by transforming syncope in pre-syncope.

7.1 Objectives

7.1.1 Primary objectives

The study has the primary objective of comparing time to first syncopal recurrence between

- active group (CLS): CLS in addition to DDD pacing mode; and
- control group (CTL): sensing only, ODO mode.

Definition. According to the 2009 ESC guidelines[7], a syncopal recurrence is defined as a transient complete loss of consciousness characterized by rapid onset, short duration, and spontaneous complete recovery.

7.1.2 Secondary objectives: clinical outcome

The Secondary endpoint will be the time to the first recurrence of pre-syncope or syncope, whichever comes first, compared between the study groups during follow-up

Definition. Pre-syncope is defined as any of the various signs and symptoms which are recognized by the patients as premonitory of imminent syncope but not followed by syncope.

7.2 Primary hypotheses

7.2.1 Comparison of syncope survival rate during 2-year follow-up

Null: the 2-year survival rate of syncopal recurrence in the treatment arm (S_{CLS}) is equal to the 2-year survival rate of the control arm (S_{CTL}), assuming an exponential distribution with proportional hazard rates.

H_0: $S_{CLS}(t=2 \text{ years}) = S_{CTL}(t=2 \text{ years})$

Alternative: the 2-year survival rate of syncopal recurrence in the treatment arm is different from the 2-year survival rate of the control arm.

H_1: $S_{CLS}(t=2 \text{ years}) \neq S_{CTL}(t=2 \text{ years})$

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7.3 Secondary hypotheses

7.3.1 Comparison of pre-syncope or syncope survival rate during 2-year follow-up

Null: the 2-year survival rate to the combined event of pre-syncope or syncope, $\Sigma(t)$, is equal in both study groups

H_0: $\Sigma_{CLS}(t=2 \text{ years}) = \Sigma_{CTL}(t=2 \text{ years})$

Alternative: the 2-year survival rate to the combined event of pre-syncope or syncope is different in the two study groups.

H_1: $\Sigma_{CLS}(t=2 \text{ years}) \neq \Sigma_{CTL}(t=2 \text{ years})$

7.4 Safety assessments

All Adverse Events (AE) and Adverse Device will be reported and documented and risk analysis will be constantly updated throughout the study.

An independent DSMB will be monitoring the study conduct reviewing all available source document related to any death occurring during the study and recommending early study termination, if deemed appropriate.

Should a patient in ODO mode study arm die, source document review will be performed immediately, without any undue delay as soon as all relevant documents are available

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8 DESIGN OF THE CLINICAL INVESTIGATION

8.1 General considerations

The study is a prospective, multi-center, double-blinded, randomized, intention-to-treat, placebo-controlled study.

8.2 Endpoints

8.2.1 Primary endpoint

The Primary Endpoint will be the time to the first post randomization recurrence of a syncopal episode as defined in Section 7.1.1.

8.2.2 Secondary endpoints

The Secondary endpoint will be the time to the first post randomization recurrence of a pre-syncope or syncope episode (as defined in Section 7.1 and 7.1.2.1), whichever comes first.

8.3 Measures taken to minimize or avoid bias

8.3.1 Randomization

Patients will be randomized to the active group or to placebo immediately after their enrolment and before any subsequent study-related procedure.

- Active group: before post-implant hospital discharge, IPG will programmed in a dual-chamber DDD pacing mode with the CLS function ON, and according to the programming recommendations reported in section 9.4.
- Control group: before post-implant hospital discharge, pacing will be programmed in the ODO mode, according to the programming recommendations reported in section 9.4.

Randomization ratio will be 1:1, therefore the randomization procedure will ensure that each individual patient will have (approximately) 50% chance to be assigned to the active group or to the control.

A centralized block-randomization procedure will be used. Block size will vary from 2 to 4 and investigators will not be aware of randomization block sizes at any time. Randomization will not be stratified.

Randomization will be communicated with an online procedure: investigators will connect to a dedicated webpage of the electronic Case Report Form (eCRF).

8.3.2 Blinding

Patients will be blinded to the treatment assignment until the end of the study or the first endpoint event.

Investigators will not be blinded to the randomizations but they will not assess the primary endpoint events.

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The primary endpoint events will be collected by dedicated patients' self-administered structured questionnaire. Responses to the questionnaire will determine whether or not the event description and the associated symptoms are consistent with a primary endpoint event.

Questionnaires will be anonymous, identified by the patient ID study code, and provided to patients at enrolment. Questionnaires will be prepared upfront in 8 pre-paid envelops (additional backup questionnaires may be provided) addressed to an external contract research organization (CRO), whose personnel will remain blinded both to patients' identity and randomization assignment.

8.3.3 Primary and clinical secondary endpoint assessment

At enrolment, participating subjects will be instructed on how and when to fill in and mail the questionnaires to the CRO.

A questionnaire will be completed by the patient him-/herself at home separately after each single experienced syncope or pre-syncope event. Every 3 months starting from enrolment date patients will mail the collected questionnaires to the CRO using the pre-paid and pre-addressed envelops provided at enrolment. If a patient will not experience any syncopal or pre-syncopal event during a 3-month period, he/she will complete a single questionnaire documenting the absence of any recurrence.

Patients will be instructed to mail only anonymous questionnaires and envelops.

CRO personnel will monitor the timing of questionnaire flow. In case of delays, the CRO staff will inform the investigator, who will contact the patient to solicit the questionnaire or to fix any related problems. The CRO will also inform the investigators about the occurrence of a syncope or pre-syncope event.

Responses to the questionnaire will determine whether or not the event description and the associated symptoms are consistent with a primary or secondary endpoint event.

8.4 Methods

8.4.1 eCRF

All parameters and measurements that are recorded within the study are described in this section and are documented on the appropriate eCRFs.

The corresponding time schedule is described in Section 9.

- Enrollment Form
- Baseline Form
- Implantation Form
- Pre-Hospital Discharge Form
- In-hospital Follow-up Form for 1- (optional), 12-, 24-month follow-up visits, as well as interim visits.
- Patient's self-administered questionnaire
- Adverse Event/Device Deficiency Form
- Study Termination Form

8.5 Equipment to be used for the assessment of variables

Implanted device and related equipments and accessories are described in Section 4.3.

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In addition, at investigator's discretion, selected patients may undergo TT exam before and during study participation (1-month after discharge). This test will require the use of standard CE-marked equipments, such as TT tables and related tools to electronically record continuous data on BP and heart rate.

8.6 Replacement of subjects

The sample size is calculated in consideration of an expected dropout rate. Therefore it is not planned to replace subjects.

However a patient undergoing a surgical implant revision (implying skin incision for pocket and lead position revision) before the 1-month follow-up, will continue his/her study.

8.7 Used devices and comparators

8.7.1 Description of exposure to the investigational device and/or comparator

All patients are exposed to the investigational devices Eluna 8, Epyra 8, Etrinsa 8 IPGs as described in Section 4.3.

8.7.2 Justification of the choice of comparators

The comparator is the same investigational device programmed in the ODO mode. Justification is given in section 3.1.

8.7.3 List of any other medical device and/or medication to be used during the investigation

In addition to the investigational device, the following devices, tools and accessories may be used during device implantation and follow-up:

- Threshold analyzer;
- RENAMIC programmers or later models;
- Implant accessory kits

The remote monitoring system, namely BIOTRONIK Home Monitoring (HM), is recommended during the study. The HM enables automatic daily transmissions from the implant to a patient unit (CardioMessenger) which forwards diagnostic, therapy and device data to Service Center (SC). Data resident in the SC are available to the attending physician by connecting to a secure web page.

As per clinical practice, selected patients will undergo TT exam before and, optionally, at 1-month follow-up during study participation. This test will require the use of standard CE-marked equipments: TT tables and CE-marked devices to electronically record continuous data on blood pressure (BP) and heart rate.

Such devices must be available at the investigational sites before study participation and will not be provided by the Sponsor.

8.7.4 Number of investigational devices to be used and a justification

Within the study, 128 Eluna 8 DR(/-T/ProMRI), Epyra DR-T(/ProMRI), Etrinsa DR-T(/ProMRI) IPGs willl be used.

Justification is given in Section 11.

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8.8 Subjects

8.8.1 Description of patient population

Patient selection adheres to the class IIb indication for cardiac pacing of the guidelines of the European Society of Cardiology[1].

8.8.2 Inclusion criteria

Patients affected by clinical diagnosis of reflex (neurally-mediated) syncope who meet all the following criteria:

- age ≥40 years
- significant limitation of social and working life due to unpredictable frequent syncope recurrences, ≥2 of which within the last year.
- type 2B cardio-inhibitory response (VASIS classification) during TT performed according to the 'Italian protocol'.[7, 17]
- alternative therapies have failed or were not feasible.
- exclusion of other possible competitive causes of syncope.

8.8.3 Exclusion criteria

- Any classified indication to pacemaker different from reflex syncope with positive Tilt Test response
- Any classified indication implantable defibrillator (ICD), cardiac resynchronization therapy (CRT), according to current guidelines
- Any cardiac dysfunctions likely leading to loss of consciousness:
  - overt heart failure;
  - ejection fraction (LVEF) <40% (Echo-assessed within 3-month prior to study participation);
  - myocardial infarction;
  - diagnosis of hypertrophic or dilated cardiomyopathy;
  - clinically significant valvular disease;
  - sinus bradycardia <50 bpm or sinoatrial block;
  - Mobitz I second degree atrioventricular block;
  - Mobitz II second or third-degree atrioventricular block;
  - bundle-branch block;
  - rapid paroxysmal supraventricular tachycardia or ventricular tachycardia;
  - pre-excited QRS complexes;
  - prolonged QT interval;
  - Brugada syndrome;
  - arrhythmogenic right ventricular cardiomyopathy;
- Symptomatic orthostatic hypotension diagnosed by standing BP measurement;
- Nonsyncopal loss of consciousness (eg, epilepsy, psychiatric, metabolic, drop-attack, cerebral transient ischemic attack, intoxication, cataplexy).
- Symptomatic cardio-inhibitory carotid sinus hypersensitivity.

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8.8.4 Screening failure

Screening will be based on patient's medical history and documented type 2B (cardio-inhibitory) response of the the VASIS classification[3] during baseline TT, according to the Italian protocol. [7]

Type 2B TT response is defined as asystole occurring for more than 3 sec irrespective of BP fall.

Patients who will not meet these requirements in addition to the inclusion/exclusion criteria cannot be enrolled in the study. Screening will be documented in the Screening Log Sheet.

8.8.5 Drop-out criteria

8.8.5.1 Withdrawal of patient consent

Informed patient consent is voluntary and required from all patients. The patient can withdraw her or his consent at any time. If a patient withdraws her or his consent, the investigator should try to ascertain the reasons of withdrawal while fully respecting patient's rights.

If the health status of the patient does not allow further participation in the study the investigator will decide on early study termination. An early study termination or withdrawal will not affect the patient's future medical care in any way.

8.8.6 Point of enrolment and study termination

A subject is considered enrolled in the BIOSync CLS Study upon the signature of the Informed Consent Form.

Patients will terminate their study participation at the 24-month in-hospital follow-up or at the assessment of a primary endpoint event occurrence, whichever comes first.

8.8.7 Timelines

The study is planned to start in the second quarter of 2015 and will be probably completed in 2019. The enrolment period is expected to last 24 months and the planned duration of subject's participation is 2 years.

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9 STUDY PROCEDURES

9.1 Overview

This section describes all the study-related procedures.

At enrolment, patients will receive anonymous syncope and pre-syncope assessment questionnaires to be self-administered upon each primary and secondary endpoint event experienced and mailed (by ordinary mail) to an external CRO every 3 months after discharge by using anonymous pre-paid and pre-addressed envelops.

Furthermore, subsequent to the IPG implant and hospital discharge, patients will be visited in hospital at 12-, and 24-months. More frequent scheduled visits are optional and can be performed according to the site clinical practice. However, any scheduled or unscheduled in-hospital visit must be documented in the appropriate eCRF. Optionally, a 1-month (±14 days) in-hospital visit may be performed to repeat the TT.

The follow-ups should take place within a certain time frame as listed in Table 1. This schedule should be followed as closely as possible. If circumstances prevent the presence of the patient at the follow-up visit, the reason for the missed follow-up has to be indicated on the eCRF.

9.1.1 Remote monitoring

Home Monitoring is highly recommended for remote control in order to optimize patient retention and reduce loss. It may be activated at any time throughout the study. It does not replace in-hospital visits for the purpose of this study.

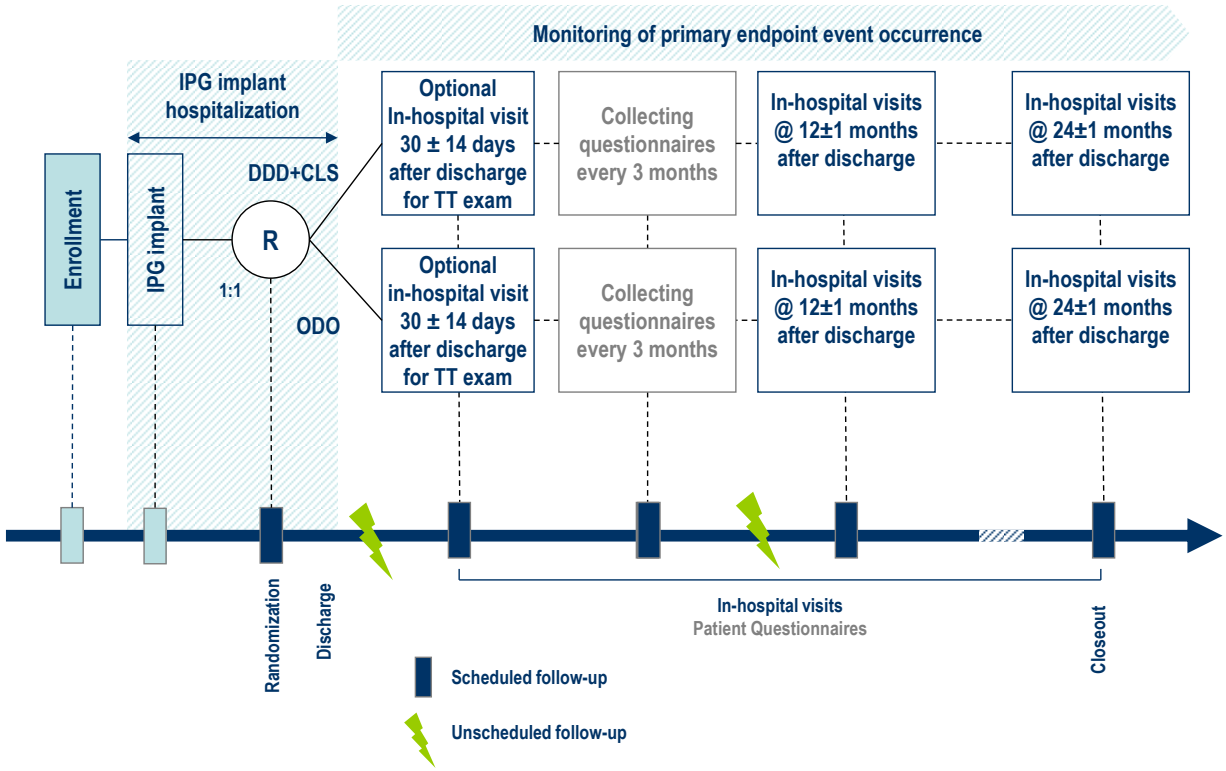

Figure 1. Study flow-chart

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Table 2. Investigation schedule

Investigations	Enrollment	Implantation /Discharge Month 0	Month 1 ± 14 days in-hospital (optional)	Month 3 PSAQ* collection	Month 6 PSAQ collection	Month 9 PSAQ collection	Month 12 PSAQ collection; ±30 days in-hospital	Month 15 PSAQ collection	Month 18 PSAQ collection	Month 21 PSAQ collection	Month 24 PSAQ collection; ±30 days in-hospital
Patient informed consent	x										
Verification of in- and exclusion criteria	x										
Demographic data	x										
ECG	x										
Echo data (not older than 3 months)	x										
Medical history	x										
Co-morbidities	x										
Cardiovascular medication	x						x				x
Tilt table test	x		x								
IPG implantation		x									
Randomization		x									
Device programming settings and diagnostics		x	x				x				x
Primary endpoint assessment (syncope) by independent agency				x	x	x	x	x	x	x	x
Pre-syncope assessment by independent agency				x	x	x	x	x	x	x	x
Other secondary endpoint assessment			x								
(S)AE, (S)ADE, DD		x	x	x	x	x	x	x	x	x	x

PSAQ= Patient self-administered questionnaire

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9.2 Enrolment

If the patient meets all the inclusion criteria and no exclusion criterion, he/she will be asked to read and sign an Informed Consent Form. This will allow a detailed recording of data being evaluated during the study. The consenting process is described in detail in Section 17. A subject is considered enrolled in the BIOSync CLS Study upon signing the Informed Consent Form. The patient will be advised to avoid activities which may pose risks in case of transient loss of consciousness.

The baseline data may be collected the same day the consenting procedures are completed.

For baseline evaluation, the investigator collects the following data on an eCRF:

- Demographic characteristics
- Device therapy indication
- ECG diagnosis
- Number and type of previous ineffective therapies for reflex syncope
- Comorbidities
- Cardiomyopathies
- Arrhythmias
- Cardiovascular medication
- Baseline TT response which includes time of onset of pre-syncope (first symptoms), BP value at the time of onset of pre-syncope, occurrence and time of onset of syncope, type and duration of asystole, minimum BP.

Enrolments take place before IPG implantation.

9.3 Implantation

IPG implantation will be performed according to standard technique and will be conducted so as to ensure optimal pacemaker functioning with acceptable pacing, sensing, impedance values.

9.4 Pre-hospital discharge

After implant and prior to hospital discharge, the investigator shall query and obtain the patient randomization by accessing the dedicated web site. The IPGs will be programmed accordingly.

Programming details are reported in the following Table 3. Parameters which are not listed have to be intended freely selectable.

Table 3. Device programming recommendations

Parameter	Active group	Control group
Mode	DDD-CLS	OFF*
Basic rate Day/Night	50 bpm/OFF	---

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Maximum CLS rate**	120 bpm	---
CLS response**	Medium	
CLS Resting rate control**	OFF	---
Mode switching	OFF	---
AV Delay	Low; 150-120ms	---
AV hysteresis mode	IRSplus	
Atrial Overdrive Pacing	OFF	---
PMT protection	ON	---
IEGM recordings		
High atrial rate	AT	AT
High ventricular rate	ON	ON
Patient triggering	OFF	OFF
Rates for statistics		
HAR limit	200 bpm	200 bpm
HVR limit	180 bpm	180 bpm
HVR counter	8 events	8 events
Home Monitoring**	ON	ON
Time of transmission***	01:00 am	01:00 am
Periodic IEGM***	30 days	30 days
High Atrial Rate***	AT	AT
Ongoing Atrial Episode***	12 h	12 h
High Ventricular Rate***	ON	ON

* In the investigational devices, the pacing OFF mode can be normally programmed only temporarily for diagnosis purpose. However it can be made permanent in this study by releasing a special code in the programming software.

** Recommended value. The parameter can be modified if necessary. Different settings are not considered protocol deviations.

*** If HM is activated.

9.4.1 ODO mode programming

The ODO mode can be activated by selecting "OFF" in the "Modes" window. In standard operating conditions, pacing OFF is a temporary function: it is active until the programming head is applied or the radiofrequency telemetry connection (SafeSync®)is enabled. This is indicated by a "Conflict" symbol and explained by the text "*The OFF mode is only intended for diagnostic purposes during follow-up. Therefore it can only be temporarily programmed*", appearing on the programmer display when clicking on the "Conflict" button, once the OFF program is enabled. When the programming head is removed or the SafeSync® telemetry is disabled, the OFF program is cancelled and the latest pacing mode is restored.

In order to activate the OFF mode permanently, a special code will be required by the programmer software. To release the code the user must access the "Release" tab under the "More" menu of the programming device. The password/code is communicated only to hospital staff involved in the study after appropriate training.

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A "Conflict" symbol will still be displayed on the programmer screen. The OFF program will then be permanently active even after the programming head removal or the radiofrequency connection interruption.

9.4.2 AV Delay programming

The AV Delay programming should favor the intrinsic conduction as much as possible.

In addition, in patients in the active group (DDD-CLS) the AV Delay should be programmed to ensure that both during spontaneous and paced atrial rhythms, the intrinsic AV conduction always occurs at least 80 ms earlier that the programmed ventricular pace.

9.4.3 Patient's Questionnaire

At enrolment or at post-implant hospital discharge, enrolled patients will be provided with a questionnaire for self-reporting of syncopal recurrences and syncope/pre-syncope-related symptoms.

Patients must be thoroughly instructed on the scope of the diary and when and how it must be filled in.

9.5 In-hospital follow-up visits

9.5.1 1-month in-hospital visit (optional)

A 1-month follow-up may take place 30 ± 14 days after post-implant hospital discharge, in order to repeat a TT and assess the effect of pacing therapy on TT response. This additional visit is optional and the decision on whether or not to perform it, is left to Investigator's discretion. If preformed, the procedures described below should be followed.

Before performing the TT, the following procedures should be performed, in order to assess the correct functioning of the pacing system:

- Interrogate the IPG and document (print or save electronically) all the manually or automatically measured results of the P/R-wave amplitude, threshold, impedance tests.
- Document and assess any spontaneous high atrial or ventricular rate episode, by electronically saving or printing the relative IEGM (whenever available) occurred since the last interrogation.
- Check the activation of required and recommended parameter settings (see Table 3). In case the CLS function is not active in a subject randomized to the Active group, immediately activate the CLS and do not perform the TT immediately. Reschedule another appointment 24 hours later or as soon as possible thereafter.
- Report any adverse event or device deficiency. In case of a serious adverse event, please provide the information immediately to BIOTRONIK, and inform the ethical committee and competent authority, if required.
- Interrogate and store the final programmed parameters.
- Perform the TT as reported in next subsection.
- Schedule the next in-hospital visit within the allowed time windows.
- Complete the appropriate eCRF. Store IPG data of the programmer (Renamic) on USB flash drive and send it via email to the project management.

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9.5.2 Tilt Test procedure at 1-month in-hospital follow-up (optional)

The same device programming assigned by the randomization must be maintained throughout the TT: patients randomized to the Active arm will perform TT in DDD-CLS mode and patients randomized to the Control arm will perform TT in ODO mode.

A pacemaker programmer must be available in the room and switched on before the test starts. TT will be performed according to the Italian protocol[7]. Electrocardiogram and systolic and diastolic BP will be continuously monitored and recorded using an external device (see Section 4.3). After 10 min of supine rest, the patients will be tilted to 70° using an electronically operating tilt-table with a footboard. If syncope will not occur after 20 min, 300 mg of nitroglycerin will be administered sublingually, and the test continued for a further 20 min or until syncope occurrence.

TT response includes: time of onset of DDD pacing and its duration, BP value at the time of onset of DDD pacing, time of onset of pre-syncope (as defined in the section 7.1.2.1), BP value at the time of onset of pre-syncope, occurrence and time of onset of syncope, type and duration of asystole, minimum BP. ECG strip of the event must be collected.

In case of device interrogation, the following procedures should be performed:

- During the device interrogation an emergency equipment for resuscitation must be kept at hand and properly certified staff must be available.
- Continuously monitor the patient's hemodynamics during the entire device interrogation using at least one of the following parameters: blood oxygen saturation, blood pressure or ECG.

9.5.3 In hospital follow-ups at 12 and 24 months

Routine in-hospital follow-up visits will occur 12 and 24 months after post-implant hospital discharge, within a ±30 days interval, in order to check for the correct functioning of the pacing system. More frequent visits should be documented.

The following procedures should be performed:

- During the device interrogation an emergency equipment for resuscitation must be kept at hand and properly certified staff must be available.
- Continuously monitor the patient's hemodynamics during the entire device interrogation using at least one of the following parameters: blood oxygen saturation, blood pressure or ECG.
- Interrogate the IPG and document (print or save electronically) all the manually or automatically measured results of the P/R-wave amplitude, threshold, impedance tests.
- Document and assess any spontaneous high atrial or ventricular rate episode, by electronically saving or printing the relative IEGM (whenever available) occurred since the last interrogation.
- Check the activation of required and recommended parameter settings (see Table 3).
- Report any adverse event or device deficiency. In case of a serious adverse event, please provide the information immediately to BIOTRONIK, and inform the ethical committee and competent authority, if required.
- Interrogate and store the final programmed parameters.
- Schedule the next in-hospital visit within the allowed time windows.
- Complete the appropriate eCRF. Store IPG data of the programmer (Renamic) on USB flash drive and send it via email to the project management.

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9.5.4 Interim follow-up

Unscheduled interim follow-up may occur anytime during the course of the study. No specific study procedures are required for interim follow-up.

If any adverse events or device deficiencies occurred, they must be documented on the respective eCRFs.

In case of device interrogation, the following procedures should be performed:

- During the device interrogation an emergency equipment for resuscitation must be kept at hand and properly certified staff must be available.
- Continuously monitor the patient's hemodynamics during the entire device interrogation using at least one of the following parameters: blood oxygen saturation, blood pressure or ECG.

9.5.5 Study termination

Should the dropout criterion (section 8.8.5) or a termination criterion (section 8.8.6) be met for a patient, a follow-up must be performed. This follow-up can coincide with one of the scheduled study follow-ups. If the patient's pacemaker was programmed in ODO mode, this must be deactivated (see section 9.5.5.1) and a different pacing mode must be programmed. The physician is responsible for the correctness and appropriateness of the pacemaker programming after this follow-up. The programmer printout of the follow-up must be filed in the Investigator Site File for source data verification.

9.5.5.1 ODO mode disabling

As any other pacing mode, the OFF program may be disabled by applying the programming head (or enabling the SafeSync® telemetry), interrogating the device with the programmer and selecting and transmitting a different pacing mode.

9.6 Primary endpoint collection

Self-administered anonymous patient questionnaires will be collected every 3 months after post-implant hospital discharge (within a ±14 day interval) by independent personnel of a CRO as described in section 8.3.3.

Syncope and pre-syncope assessment will be exclusively based on what patients will refer by self-administering the questionnaire, at home, separately for each event.

Despite patients will be instructed to fill in the study questionnaire, they might react differently to a syncope recurrence during the study. The following Table 4 reports the most awaited situations and illustrates the subsequent steps accordingly.

Table 4. After a syncopal and pre-syncopal recurrence

Situation:	The patient fills in the questionnaire	The patient shows up for a medical examination
1 step	The CRO quarterly collects patient questionnaires	The investigator recommends the patient to mail the questionnaire to the CRO in due time and reports any AE
2 step	If an AE occurred, the CRO informs the investigator	

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Any change of the programmed pacing mode not justified by a primary endpoint (even when a-posteriori assessed), will be considered as a crossover, but analyzed according to the Intention-To-Treat (ITT) principle, see Section 11)

9.7 Description of the activities performed by sponsor representative

Sponsor representatives may support the investigator by conducting lead and device based measurements at IPG implant or in-hospital visits. They might also support the investigator for IPG programming.

During follow-up procedures, sponsor's representatives might support the interrogation of the IPG or memory dump download as needed. Monitoring will be performed by Sponsor representatives or delegated CRO personnel according to the monitoring plan.

9.8 Responsibilities of the coordinating clinical investigator and the Steering Committee

The BIOSync CLS clinical study is coordinated by:

Dr. med. Michele Brignole

Arrhythmologic Centre

Department of Cardiology

Ospedali del Tigullio

Via Don Bobbio, 25

16033 Lavagna (GE)

Italy

Dr. med. Marco Tomaino will co-chair the Steering Committee.

The Steering Committee will consist of a local study coordinator in participating country with a sufficient number of active investigational sites.

The CCI (M. Brignole) and the co-CCI (M. Tomaino) will be supported in the following activities by the Steering Committee.

The responsibilities of the CCI and the Steering Committee are:

- Development and review of the clinical investigation plan
- Procurement of the central vote of an ethics committee (CCI)
- Performance and progress control of the study
- Continuous assessment of the risk/benefit ratio
- If necessary, decision on premature study termination in consultation with the sponsor
- Contribution to coordination of publication and presentations of study results
- Advising all investigators in medical questions related to the study or study conduction
- Evaluation of potential unexpected adverse events
- Discussion of possible interim results
- Cooperation in writing of the final clinical report

The CCI and the Steering Committee are supported by the clinical study manager and other members of the sponsor.

In addition, the CCI and the Steering Committee members have the same rights and duties as other investigators which are described in the Investigator Agreement.

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9.9 Primary and clinical secondary endpoint Adjudication Board

All the unclassified syncope or pre-syncope episodes (see section 8.3.3) will be adjudicated by an Adjudication Board of at least 3 members. The members will be selected among experienced physicians with documented expertise in syncope. The members will not participate in the study as Investigators

The Adjudication Board will review unclassified endpoint events according to a charter provided in a separate document.

The members will remain blinded to the randomization, even if they will have access to the electronic CRF.

The adjudication process will be requested by the study Project Manager after the required number of primary endpoint events for the interim analyses has exceeded the predefined levels (see section 11.6).

The interim analyses will be performed only with the events collected at the times of the call for the adjudication from the Project Manager. Further events possibly occurring thereafter will not be included.

9.10 Possible influencing factors on outcome or interpretation of results

No factors that could influence the outcome or interpretation of the results are known at time of protocol drafting.

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10 MONITORING PLAN

The responsibility of BIOTRONIK as sponsor is to ensure protocol and regulatory compliance through proper monitoring of the study. BIOTRONIK is 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 study in accordance with the signed clinical investigation agreement, the study protocol, applicable laws, and FDA and/or local regulations (e.g. CFR 21, parts 50, 54, 56, and 812, ISO 14155, Declaration of Helsinki) and any conditions of approval imposed by the reviewing IRB/EC.

The entries in the eCRF will be reviewed and source data verified at the investigational site by monitors (authorized BIOTRONIK personnel, Clinical Research Associates-CRAs, or by authorized BIOTRONIK designees) to ensure that the investigator and the clinical investigation team conducts the clinical investigation in accordance with the CIP, The Declaration of Helsinki, ISO 14155, 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.

A monitor will visit the study site periodically during the study. All participating sites will be monitored during the course of the study with visits occurring as frequently as deemed necessary to ascertain adherence to the protocol procedures, as well as maintenance of the highest quality data. A detailed monitoring plan developed by BIOTRONIK will be followed.

Periodic monitoring visits will assure, amongst others, that the facilities are still acceptable; that the CIP is being followed, that the EC/IRB/CA has been informed about approved CIP changes as required, that records on study conduct and data collection are complete and present, that appropriate and timely reports have been made to the sponsor and the authorities, and that the investigator is carrying out all agreed activities.

Periodic monitoring visits, assessments of the study site will include but will not be limited to the following:

1. Availability and correctness of the signed patient informed consent
2. Completion and submission of the required case report forms and other applicable study documentation
3. Continued acceptability of the facilities
4. Adherence to the clinical investigation plan
5. Adherence to current version of ISO 14155 and applicable FDA and local regulations and laws

If a monitor becomes aware that an investigator is not complying with the requirements mentioned above, the monitor is obliged to notify BIOTRONIK study management. BIOTRONIK will evaluate the non-compliance and issue corrective actions, discontinue enrollment or as a last measure close the clinical investigation site.

A monitoring plan will be prepared as additional document. It provides detailed information about frequency and extent of monitoring.

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11 STATISTICAL CONSIDERATIONS

11.1 Statistical design, method and analytical procedures

Standard summary statistics will be calculated for all patients and study outcome variables. Categorical data will be summarized via distributions of absolute and relative frequencies. For all relevant parameters 95% confidence intervals will be calculated.

For the analysis of the primary endpoint and the secondary endpoint the Kaplan-Meier plots will be generated and the estimated survival functions of the study groups tested with the two-sided log-rank test. Dependence of survival on major baseline predictors will be studied with proportional hazard Cox models. Hazard ratios and relative 95% confidence intervals for each predictor will be calculated, respectively. Data will be censored at the date of last patient contact. The ITT principle will be applied.

Statistical calculations will be carried out by using STATA 11.1 ®, SAS 9.3 © or R.

11.2 Sample size calculation

The study sample size calculation is based on the minimum relative difference in the 2-year incidence of syncopal recurrences as compared with placebo (pacemaker OFF).

The 2-year incidence of the primary endpoint in the control group will be assumed equal to the incidence observed in the control arm of the ISSUE 3 trial:[16] this was reported as high as 57%. The ISSUE 3 trial was considered as it selected a large population, had very similar inclusion/exclusion criteria, was recently published.

The BIOSync CLS study is designed to detect a 40% relative reduction of the 2-years incidence of syncopal recurrences (from 57% to 34%) with a statistical Type I and II errors of 0.05 (bilateral) and 0.20, respectively.

Further assumptions:

- Exponential distribution of times to first recurrence
- Accrual time: 2 years
- Total study time: 4 years
- Randomization ratio: 1:1
- Loss incidence: 10% (both arms)

With these assumptions a sample size of 62 patients per study arm (124 in total) is required. This estimate must be further increased by 2%, due to the slight power loss induced by the interim analyses (see section 11.6).

In summary, 128 subjects (64 per study arm) are necessary to reach the study primary objective with the required power.

11.2.1 Required number of primary endpoint events

The required number of primary endpoint events is 62, as calculated with the formula:

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$$events = \frac{\left(z_{\alpha/2} + z_{\beta}\right)^2}{0.25\log(HR)}$$

where $z_{\alpha/2}$ and z_{β} are the standard normal percentiles (α=0.05, β=0.20), HR is the expected hazard ratio. A HR of about 0.49 was calculated assuming an exponential model of the survival functions with proportional hazard rates.

11.3 Level of significance and the power of the study

Target study power: 80%

Significance level: 0.05 (bilateral)

11.4 Expected drop-out rate

Loss incidence: 10% (both arms)

11.5 Pass/fail criteria

The clinical investigation is deemed to be passed if the alternative hypothesis of the primary endpoint is reached.

11.6 Provision for interim analyses

Interim analyses will be performed at t = 0.4 and 0.7 of the required primary endpoint events or, equivalently, after 25 and 43 endpoint events will be collected.

The final analysis will be performed after the study database has been closed out.

In order to keep the overall type I error at the level of 0.05, two-sided, symmetric O'Brien–Fleming boundaries generated with the Lan–DeMets spending function approach to group-sequential testing will be assumed as early stopping rules for efficacy.

t	0.40	0.70	1.00
No. endpoint events	25	43	62
Z_{up}	3.3569	2.4445	2.0005
Z_{low}	-3.3569	-2.4445	-2.0005
p	0.0008	0.015	0.05

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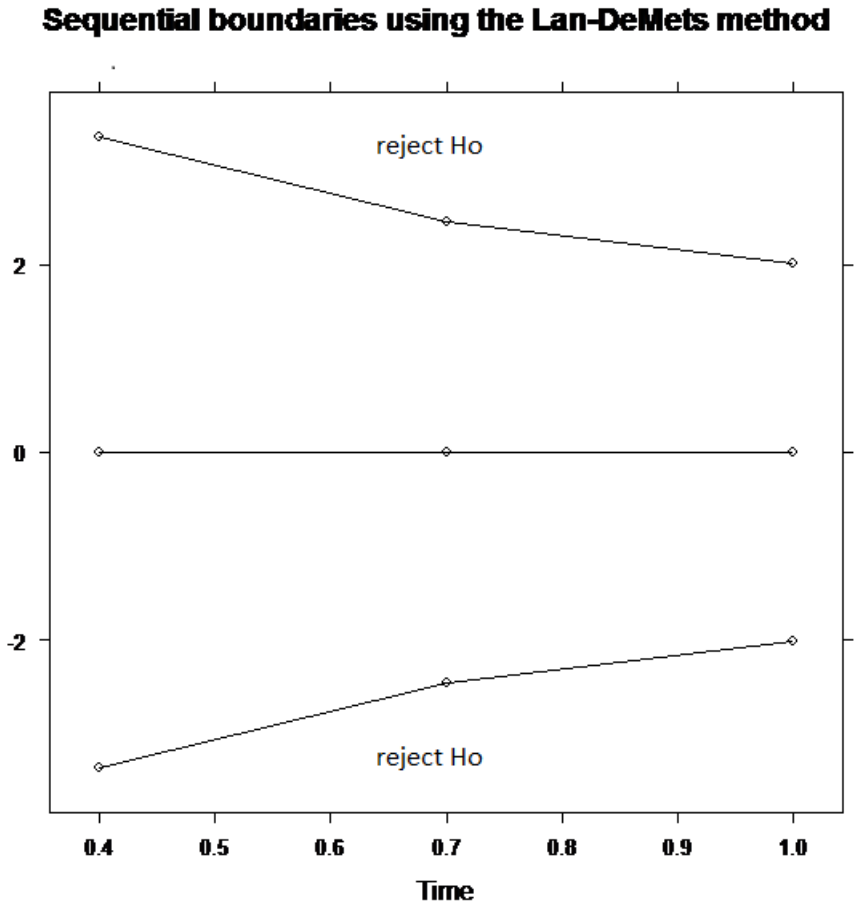

Figure 2. Sequential boundaries during interim analyses. R Software version 3.1.0 (2014-04-10).

11.7 Termination criteria

With a **sequential study design** the study will stop when a total of 62 primary endpoint events will be collected by the independent agency. The following stopping rules will be used.

11.7.1 Stopping Rules

1. The CCI will be informed monthly by the CRO about the total number of patients who will experience a syncope recurrence (primary endpoint event).
2. When the number of events will reach[1] the predefined limits for interim analyses (40% and 70% of the expected number of events), open queries will be resolved and on site monitoring visits for source data verification will be performed.
3. Unclassified primary endpoint events will be adjudicated (see section 9.9). If available primary endpoint events will be less than the predefined limits for interim analyses after the adjudication process, endpoint point event collection will continue until the required number will be reached.
4. When data set will be cleaned the clinical project manager of the study will inform the appointed independent statistician.
5. The independent statistician will analyze the data according to the Statistical Analysis Plan (SAP). The results will be communicated to the CCI and the sponsor of the study. If the

[1] The number of events may exceed the programmed limit whenever 2 or more events occur at the same time.

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primary objective is reached the study stops immediately. The stop date of the study is the date of insertion in the database of the last syncopal recurrence. If the primary objective is not reached the independent statistician will recommend to continue the study until 62 events will be collected. Investigators will not be informed of the results of the interim analyses.

6. After study closure investigators shall complete missing data (apart from the primary events) and close open queries within the following 2 months. Events occurring after the stop date shall not be considered either for primary or for secondary endpoints.

11.8 Procedures for reporting of deviations to the statistical plan

Deviations from the statistical plan are documented accordingly.

11.9 Specification of subgroups

No subgroups are pre-specified.

11.10 Procedure for accounting of all data for analysis

The required strict adherence to the monitoring plans of the respective reference studies will ensure acquisition of all data.

11.11 Handling of missing, unused and spurious data

Missing or spurious data is not substituted; all data – as far as correctly measured – is analyzed.

11.12 Exclusion of data from confirmatory data analysis

In some cases, particular clinical data is excluded from analysis. The following reasons

are possible:

- Data is not measured as described in this clinical investigation plan.
- Data is evaluated beyond the required follow-up schedule.
- Patient has to be excluded because she/he does not fulfill the exclusion/inclusion criteria.
- Patient requires that all recorded data has to be deleted.
- There is no valid patient consent form available.

11.13 Minimum and maximum number of patients per site

It may be expected that every 100 over-40 subjects undergoing a head up tilt test and reporting 3 or more syncopal episodes, about 50 of them would be positive, 12 would be eligible with a type 2B cardio-inhibitory response[18], 6 would accept to implant a pacemaker and about 3 to participate to the study, undergoing the randomization[19]. Therefore only centers performing a high number of tilt test examinations per year (≥200 per year) may participate in the trial to effectively contribute to enrolment in a reasonable time period. Each

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center should enroll at least 5 patients in the course of the study, in a competitive enrolment process.

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12 DATA MANAGEMENT

The established Clinical Data Management System (CDMS) is "iMedNet" of the vendor MedNet Solutions, Inc. As a pure internet-based application that is used with the current versions of most internet browsers, there is no specific local software to support (cloud based "Software as a Service" SaaS). iMedNet supports industry standards (FDA 21CFR11, HIPAA and Safe Harbor).

12.1 Procedures used for data review, database cleaning, and issuing and resolving data queries

After data entry into the CDMS, the clinical data is automatically checked with programmed quality checks. Errors, discrepancies, missing data, and entries out of range are resolved by automatically (CDMS) and manually (clinical monitor, data manager) generating data queries.

The system supports detailed tracking of the query process. Corrections to eCRF can only be done by the designated site personnel and need to be signed by the investigator. All changes are automatically recorded in the system's audit-trail.

12.2 Procedures for verification, validation and securing of electronic data systems

The Clinical Data Management System (CDMS) is hosted on a dedicated database server at the vendor MedNet Solutions, Inc. Only authorized users with fixed roles have access to the clinical database. The access is controlled and maintained by the Clinical Data Management. Every access is automatically logged and changes of the clinical data are stored in independent audit trails. The CDMS is verified and validated accordingly. The user interface and the internal business logic of the clinical database is validated accordingly and verified during the study related development and before release for data entry.

An authenticated user account is created and maintained by BIOTRONIK for each authorized user once the user has completed appropriate training. Users are obligated to keep their password confidential.

Depending on their role within the investigational study, users are limited to "read only" or may be given permits to enter or update data, provide resolutions to queries and apply electronic signatures. Only investigators are allowed to sign the entries.

12.3 Procedures for data retention

All study related electronic documents are stored in the archive of BIOTRONIK which provides storage conditions free from risk of fire, flood, theft and vermin. The access to the files is controlled.

After database closure, all eCRF data and the audit trail and other relevant database content are exported and stored electronically on the archive server.

12.4 Specified retention period

All electronic documents and exported data from relevant databases are stored for at least 15 years. At the end of this period, requirements from laws and other regulations will be reconsidered in order to decide whether the retention period must be extended or data must be deleted.

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13 AMENDMENT PROCEDURES

If throughout the course of the study changes to the Clinical Investigation Plan (CIP) are deemed to be necessary, a change justification has to be prepared which includes the rationale and content of the adjustment. The modification of the CIP can either be summarized in a separate document as an attachment to the current applicable version of the CIP or result in a new version of the CIP.

If the changes have impact on study related procedures or data analysis they are substantial by definition.

New versions of the CIP or substantial amendments have to be reviewed and confirmed by the Coordinating Clinical Investigator. All investigators have to acknowledge the receipt of an amendment by signing an amendment agreement form.

Before implementation of any changes, substantial amendments have to be approved by the Ethics Committee (EC) and – if applicable – by the Competent Authority (CA). Non substantial amendments are submitted for notification only.

The investigator should not implement any deviation from or changes to the CIP without agreement of the sponsor and prior review and documented approval from the EC (and CA if required). The only exception is the necessity to eliminate an immediate hazard to the subjects, or when the change involves only logistical or administrative aspects of the study.

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14 DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

14.1 13.1 CIP compliance and exceptions

All sponsor personnel, all investigational site personnel as well as other third parties, who are involved in tasks covered by this CIP, are generally obliged to comply with this CIP.

A **deviation** is any failure to follow, intentionally or unintentionally, the requirements of the CIP, including laws, guidelines and other regulation as far as required by the CIP, as well as applicable amendments. Deviations that are likely to seriously affect or that actually have seriously affected the rights or safety or wellbeing of subjects or the scientific integrity of the clinical investigation are **major** deviations. Otherwise they are **minor** deviations.

Erroneous, spurious or missing data in a CRF is not a deviation in itself and is handled according to the query processes described in the data management section of this CIP. However, the underlying reason might be a deviation.

Under **emergency** circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the ethics committee.

14.2 Recording, reporting and analyzing deviations

14.2.1 Site specific deviations

Investigational sites inform the monitor immediately about any deviation as they become aware of it. In addition, compliance to the CIP is verified by the sponsor through monitoring visits. Each site specific deviation is recorded by monitors in the respective site deviation log and assessed for the need of corrective or preventive actions. Additional information on the type of deviation, actions taken and outcome may be recorded in the **monitoring visit reports**. All information from site deviation logs is consolidated by the sponsor in one overall **study deviation log**.

14.2.2 Other deviations

Deviations by sponsor personnel or third parties are reported immediately to the sponsor by anyone who becomes aware of it. They are recorded in the **study deviation log** and assessed for the need of corrective or preventive actions.

14.2.3 Reporting

Deviations are reported in the interim and final clinical investigation reports.

14.3 Notification requirements and timelines

The sponsor records specific notification requirements of the involved ethics committees and competent authorities and assures that the required timelines are respected.

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14.4 Corrective and preventive actions and disqualification criteria

Corrective actions are taken in order to repair or to avoid any negative consequences caused by a deviation. **Preventive** actions are taken to avoid that the same sort of deviation reappears.

Every individual deviation is assessed by the sponsor for the need of appropriate action. In addition, the sponsor regularly evaluates the overall study deviation log to identify the need of general preventive actions.

All persons involved in a deviation have to co-operate with the sponsor in identifying and implementing the appropriate actions. Performance and implementation of these actions are documented by the sponsor and filed in the **central file** and, in the case of site specific deviations, in the respective **investigator site file**.

Disqualification of study personnel or investigational sites is the ultimate escalation step of preventive actions. This means that in case of major deviations that seriously affect the safety and well-being of subjects or that bear a high risk of refusal of the clinical data and mistrust to the results of the study and that are likely to reappear despite other actions, the responsible person or investigational site is excluded from further conduct of the study, unless this action would jeopardize the rights, safety or welfare of the patients.

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15 DEVICE ACCOUNTABILITY

Investigational devices which are not approved for an overall market release are labeled "Exclusively for clinical investigations" and have to be stored under special conditions.

The sponsor keeps records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until usage, disposal or return. An electronic central device accountability log is used for the documentation of the whole process.

Access to investigational devices is controlled and the devices are used in the clinical investigation only and according to the CIP.

The principal investigator or an authorized designee shall keep records documenting the receipt, usage, return and disposal of the investigational devices. A site device accountability log is used for the site specific documentation.

The responsible field CRA checks the storage, usage and documentation and verifies the completeness of the site device accountability log with the entries in iMedNet, the source data and the electronic central device accountability log regularly during his/her visits.

The information of the site device accountability log will be incorporated in the central device accountability log by the responsible BIOTRONIK personnel. After the closure of the study, the summary of this log will be used for the final report.

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16 STATEMENT OF COMPLIANCE

16.1 Applicable ethical standards

The study will be conducted in compliance with the principles that have their origin in the Declaration of Helsinki (current version).

The study will be registered at the publicly accessible database ClinicalTrials.gov.

16.2 Applicable international and national standards

The study will be conducted in compliance with:

- the international standard ISO 14155 (current version) "Clinical investigation of medical devices for human subjects – Good clinical practice".
- the international standard ISO 14971 (current version) "Application of risk management to medical devices".

The study will also be conducted according to the applicable national legal requirements of the participating investigation sites.

16.3 Ethics committee and competent authority

The study will not begin at an investigation site until favorable opinion of the responsible ethics committee has been obtained for that site and approval of the competent authority (if applicable) has been granted for the conduct of the study in the respective country.

16.4 Statement of adherence to additional requirements

If any additional requirements will be imposed by an ethics committee or a competent authority, these requirements will be followed, if appropriate.

16.5 Statement on subject insurance

All participants of this clinical study are insured against study related injury according to applicable provisions of law.

The insurance of the sponsor does not relieve the investigator and the collaborators of any obligation to maintain their own liability policy.

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17 INFORMED CONSENT PROCESS

A patient information form including the informed consent form has been prepared by the Project Manager. The content of this document needs to be reviewed and approved by the ethics committee, and suggested changes need to be implemented.

17.1 General considerations

The informed consent procedure is performed by the Principal Investigator or any investigator designated for this task as recorded in the delegation of duties log. The investigator has to fully inform the patient of all pertinent aspects of the clinical investigation in language and terms she/he is able to understand. When the patient agrees in the study participation the written informed consent form shall be personally dated and signed by the patient and by the investigator who performed the informed consent discussion. The result of the informed consent process is documented in the patients hospital chart by the investigator. A copy of the signed and dated written informed consent form is provided to the patient.

The investigator ensures that no subjects are included in this clinical study who are unable to give informed consent by selecting patients with age ≥ 18 years, who understand the nature of the procedure.

By signing the informed consent form, the patient is included in the study. Only after that procedure any study specific procedure is performed. Pre-screening of the patient chart in respect to the inclusion and exclusion criteria is not a study specific procedure.

If during the course of the clinical investigation new information emerges, the investigator informs the patient accordingly. If this information concerns safety aspects or other aspects that could influence the decision of the patient to continue participating in the study, the patient shall be informed immediately.

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18 ADVERSE EVENTS AND DEVICE DEFICIENCIES

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

The investigator shall document all events on the respective CRF pages provided within the EDC system. The indicated timelines for reporting of initial cases and possible update reports shall be strictly followed.

According to ISO 14155:2011 events will be classified on the basis of the definitions below.

18.1 Definition of adverse events

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.

It is worth specifying that syncope, pre-syncope, heart rate and blood pressure drop during the 1-month TT which do not result in any consequence of a SAE shall not be reported as adverse events, as intended events and part of the test itself. If these events will result in any consequence of a SAE, then they will be definitively reported.

*see ISO14155 3.2

18.2 Definition of adverse device effects

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.

*see ISO14155 3.1

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18.2.1 Causality Assessment

The relationship between the use of the investigational device (including the medical-surgical procedure) and the occurrence of each adverse event shall be assessed and categorized, considering the presence of confounding factors, such as concomitant medication and treatment, the natural history of the underlying disease, other concurrent illness or risk factors.

Each SAE will be classified according to five different levels of causality. As defined in the Meddev 2.7/3 rev 3, the investigator will use the following definitions to assess the relationship of the serious adverse event to the investigational medical device or procedures:

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Not related: the relationship to the device or procedures can be excluded

Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt.

The investigators will distinguish between the serious adverse events related to the investigational device and those related to the device procedures (any procedure specific to the investigational device). Procedure related events refer to the procedure related to the application of the investigational medical device only and therefore not to any other procedure for other devices and not to any other procedures or treatments applied later throughout the clinical investigation, for instance to treat (serious) adverse events. In case of a replacement of the investigational device in response to an adverse event (e.g. pacemaker replacement due to battery depletion or malfunction), the replacement will be considered like an initial application of a new investigational device and shall be assessed accordingly.

An adverse event can be related both to the procedure and the investigational device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use or application. For example, in the active arm of this clinical investigation, a cardiac perforation with the right ventricular lead will not be considered as related to the procedure of investigational device use since the right ventricular lead is not specific for the use of the investigational pacemaker.

18.3 Definition of device deficiency

Device deficiency (DD)* is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, including malfunctions, use errors and inadequate labeling.

*see ISO14155 3.15

DDs of the investigational device shall be documented throughout the study. DDs which caused an adverse event are reported on the respective adverse event form. In case the DD did not cause an adverse event the provided DD form shall be used to document this "non-medical" event.

If a DD could have led to a SADE,

- if either suitable action had not been taken,
- if intervention had not been made, or
- if circumstances had been less fortunate,

the DD is classified as an DD with an SADE potential.

18.4 Definition of serious adverse events

AEs are classified as serious* if one or more of the following consequences are fulfilled:

- led to death

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- 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 CIP, without serious deterioration in health, is not considered a serious adverse event.

*see ISO14155 3.37

In-patient hospitalization is defined as at least one overnight stay (change of date) in a hospital. In case, a patient is only for some hours in the hospital (without change of date), this event will not be documented as serious, unless one or more of the other seriousness criteria are fulfilled.

18.5 Definition of serious adverse device effect

An ADE* that resulted in any of the consequences characteristic of a serious adverse event is considered serious.

*see ISO14155 3.6

18.6 Definition of unanticipated serious adverse device effects

SADEs* are defined as unanticipated if by their nature, incidence, severity or outcome they have not been identified in the current version of the risk analysis report.

*see ISO14155 3.42

These events must be reported to the sponsor immediately.

A root-cause analysis will be performed and the possibility of reoccurrence will be evaluated immediately.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

18.7 Anticipated adverse events

See Section 6.2.1.

18.8 Reporting responsibilities

18.8.1 Reporting responsibilities of the investigator to sponsor

The investigator shall document all events on the respective CRF pages provided within the EDC system. The indicated timelines for reporting of initial cases and possible update reports shall be strictly followed.

All Serious Adverse Events (SAE) and Serious Adverse Device Effects (SADEs) shall be reported together with an assessment by completing the SAE-CRF in accordance with ISO 14155:2011.

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For device deficiencies of the investigational device, a DD-CRF shall be completed.

The reports shall be done with all information available, even if this results in an incomplete report. The investigator has to follow-up ongoing (S)A(D)Es either as long as the patient participates in the study, 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 diagnose. The primary diagnose 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 CRF.

Multiple events may occur simultaneously in one subject. For each medically independent event with a primary diagnose 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 study, 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.

18.8.2 Reporting responsibilities of the investigator to other parties, if applicable

According to national and international regulations some of the involved competent authorities (CAs) and ethics committees request reporting of SAEs and DDs with SADE potential during the course of the study. Investigators have to ensure, that they fulfill the reporting obligations of their local competent authorities and EC/IRBs.

Table 5. Event reporting line and time line

Event	Report to	Timeline
Adverse Event (AE) / Adverse Device Effect (ADE)	CCR BIOTRONIK SE & Co. KG: Documentation in the AE CRF	Within 2 weeks
Serious Adverse Event (SAE) / Serious Adverse Device Effect (SADE)	CCR BIOTRONIK SE & Co. KG: Documentation in AE-CRF	Immediately, latest 24h after detection
Unanticipated Serious Adverse Device Effect (USADE)	CCR BIOTRONIK SE & Co. KG: Documentation in AE-CRF	Immediately, latest 24h after detection Immediately
Device Deficiencies	CCR BIOTRONIK SE & Co. KG: Documentation in the DD-CRF	Within 14 days
Device Deficiency with SADE potential	CCR BIOTRONIK SE & Co. KG: Documentation in DD-CRF	Within 24 hours

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18.8.3 Reporting responsibilities of the sponsor, if applicable

BIOTRONIK SE & Co. KG will report all serious Adverse Events (SAEs)/Serious Adverse Device Effects (SADE) and all Device Deficiencies with a SADE potential to the competent authorities depending on the local regulatory requirements.

Furthermore, BIOTRONIK SE & Co. KG ensures that Safety Reports are forwarded to the investigational sites and the Ethics committees depending on the local requirements.

BIOTRONIK SE & Co. KG will inform the investigators about all reported SAEs and DDs that could have led to a SADE on a regular basis. As a proposal, regular listings may be provided quarterly and unanticipated serious adverse device effects (USADEs) shall be reported immediately.

18.9 Reporting timelines

18.10 Emergency contact

A contact address for patients in case of emergency will be provided in the individual patient informed consent forms.

In case technical support is needed the service hotline of BIOTRONIK is available 24 hours a day. Phone: +49 (0) 30 68905-1133.

18.11 Data safety monitoring committee

The Data Safety Monitoring board will consist of the same members of the Endpoint Adjudication Board (see section 9.9).

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19 VULNERABLE POPULATION

No vulnerable population is expected to be consented for this clinical investigation.

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20 SUSPENSION

20.1 Criteria and procedures

Suspension or premature study termination may occur due to several reasons:

- On behalf of the sponsor
- On behalf of the investigator/Steering Committee
- On behalf of the IRB/EC

The sponsor is authorized to terminate the clinical study prematurely due to relevant medical/ organizational reasons.

A consultation of all parties involved prior to study termination is preferable. Reasons for premature study termination should be documented in an adequate way.

The sponsor has the right for premature study termination of the whole study, of single study phases, or to exclude single investigational sites from further study participation.

Reasons for termination may be:

- Occurrence of severe Adverse Events that result in a non-acceptable risk for further study participation.
- The number of premature study terminations exceeds the tolerable percentage of drop-outs so that proper completion of the study cannot be expected anymore.
- Insufficient enrollment rates so that proper completion of the study cannot be expected anymore.
- Results from other clinical trials indicate a non-tolerable risk for further conduction of this study.
- Attempted fraud or fraud that may be evidenced.
- Poor data quality
- Missing compliance of the respective investigator or study site (e.g. protocol violations).

In case the study sponsor decides to suspend or prematurely terminate the study, the sponsor is required to promptly notify the investigator(s) to whom the decision applies. The investigator will inform the IRB/EC of this decision. The investigator will also promptly inform all patients enrolled at the investigational site and are still actively participating. Patients that already left the study shall be informed if they might be affected by safety aspects.

In case of any reasonable ethical concern of the investigator regarding a further study conduct in the respective investigational site, the sponsor shall be informed immediately.

If the investigator decides to suspend or prematurely terminate the study at his/her site he/she will promptly inform the study sponsor, the IRB/EC and all enrolled patients of this decision.

If the IRB/EC decides to suspend or prematurely terminate the study, the investigator will promptly inform the study sponsor (or vice versa, as applicable) and all enrolled patients of this decision.

The eCRF for “Study Termination” has to be completed in all of the above cases.

All open eCRFs have to be completed as far as possible by the investigational site.

Whatever the reason for early or natural study termination, the final dataset will be available to the CCI and the Steering Committee for analysis and publishing. A final study report will be generated.

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20.2 Un-blinding procedures

The subjects enrolled in this study and the CRO personnel collecting self-administered patients' questionnaires will be blinded to the treatment assigned by the randomization procedure throughout the study course, until a termination criterion occurs (see section 8.8.6)

The investigators and study site staff may not be blinded, however they should not disclose the assignment both to patients and CRO personnel during study-related procedures, until the patient study termination (see Section 8.8.6). As the ITT principle will be used, investigators should not disclose the IPG pacing mode programmed even in case of crossover.

20.3 Requirements for subject follow-up

In case of a study suspension no new patients will be enrolled until the suspension has been lifted. During the suspension, follow-up and data collection will continue as per CIP. If the suspension is due to an MEC/IRB decision, additional requirements from the MEC/IRB with respect to follow-up and data collection may apply.

Ongoing SADEs and SAEs of the patient will be followed in a time period of 6 weeks after premature or regular study termination of the individual patient in order to follow the outcome, clarify open questions or for collection of missing information concerning the respective SADE or SAE. Ongoing SADEs related to the investigational device will be followed over a maximum period of 6 months after study termination of the respective patient if not resolved before.

Patients will be informed on this procedure in written form in the patient informed consent form.

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21 PUBLICATION POLICY

The first author of the primary publications will be Dr. Brignole, CCI and chairman of the Steering Committee of the BIOSync CLS trial. Dr Brignole will be responsible for the preparation of the final study report and of the manuscript of the main paper which must be approved by the Steering Committee before submission for publication

The authors of the primary publication will be 10 investigators (or more, depending on the journal requirements) with the highest scores. A minimum of 5 members of the Steering Committee is warranted. All the members of the Steering Committee will always be cited in any publication of study results.

Each Investigator will receive:

- 1 point for each enrolled subject
- 1 point for each enrolled subject with complete and compliant data set (by source data verification)
- +0.25 points for each compliant and fully reported scheduled in-hospital follow-up
- -0.25 points for each unreported or incompliant (e.g., out of window) scheduled follow-up visit
- -1 point for each underreported or delayed reported Serious Adverse Event, and (Serious) Adverse Device Effect.

The study design may be submitted for publication and the authors of this publication will be the members of the SC. Case reports cannot be submitted for publication by the investigators before the paper on the study design has been published.

Publication of sub-analysis will be submitted after the first main publication and the proposing center will have 2 or more authors. Sub-analysis must be approved by the Steering Committee.

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