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| **Document Title:** | Clinical Investigation Plan for the BIO\|MASTER.Cor Family Study |
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# Clinical Investigation Plan

## for the

# BIO|MASTER.Cor Family Study

| | |
|---|---|
| Reference Number: | TA115 |
| Version: | 1.0 |
| Date of CIP: | 21-Dec-2018 |
| Investigational device: | Acticor/Rivacor ICDs/CRT-Ds (Cor Family) |
| | Plexa ProMRI S DX lead |





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**List of principal investigators, investigation(al) sites, and institutions**

A current list of the principal investigators at each investigational site, the address details for each investigational site, the emergency contact details for the principal investigator at each site and a detailed list of sponsor contacts are filed in the Central File.

## 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

| | |
|---|---|
| ACC | American College of Cardiology |
| aCRT | Adaptive Cardiac Resynchronization Therapy |
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| AF | Atrial Fibrillation |
| AHA | American Heart Association |
| AIMD | Active Implantable Medical Device (Directive 90/385/EEC) |
| ASADE | Anticipated Serious Adverse Device Effect |
| AT | Atrial Tachycardia |
| ATP | Antitachycardia Pacing |
| AV | Atrio-Ventricular |
| AVD | Atrio-Ventricular Delay |
| BiV | Bi-Ventricular |
| BP | Bipolar |
| bpm | Beats Per Minute |
| CA | Competent Authority |
| CCC | Concordance Correlation Coefficient |
| CCR | Center for Clinical Research; BIOTRONIK SE & CO. KG study department |
| CCS | Clinical Composite Score |
| CDMS | Clinical Data Management System |
| CE | CE mark, a stylized "CE" (Conformité Européenne) placed on products to signify conformance with European Union regulations |
| CELESTIAL | Post Approval Registry - Corox OTW, Endocardial, Left VEntricular STeroId LeAd, BipoLar (BIOTRONIK Study) |
| CFR | Code of Federal Regulations in USA (www.gpoaccess.gov/cfr) |
| CHF | Chronic Heart Failure |
| CI | Confidence Interval |
| CI | Coordinating Investigator |
| CIP | Clinical Investigation Plan |
| CIR | Clinical Investigation Report |
| CLEPSYDRA | Clinical Evaluation of the Physiological Diagnosis Function in the PARADYM CRT device Trial |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CRT | Cardiac Resynchronization Therapy |
| CRT-D | Cardiac Resynchronization Therapy Defibrillator |

| | |
|---|---|
| CT | Computed Tomography |
| DATAS | Dual chamber and Atrial Tachyarrhythmias Adverse events Study |
| DD | Device Deficiency |
| DDI | Dual chamber pacing and sensing, but inhibited mode |
| DF-1 | Lead connector standard according to ISO 11318 |
| DF4 | Four-pole lead connector system according to ISO 27186:2010 for implantable cardiac rhythm management devices |
| DFT | Defibrillation-threshold testing |
| DGK | German Cardiac Society (Deutsche Gesellschaft für Kardiologie, www.dgk.org) |
| DM | Data Management |
| DR | Dual chamber and Rate adaptive |
| DR-T | Dual chamber Rate adaptive device with Telemonitoring capabilities |
| DX | Diagnostics Capabilities |
| DXA | Dexamethasone Acetate |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| EchoCRT | Echocardiography Guided Cardiac Resynchronization Therapy Clinical Investigation Echocardiography Guided Cardiac Resynchronization Therapy 8biotronik Study) |
| eCRF | electronic Case Report Form |
| EDC | Electronic Data Capture |
| ESC | European Society of Cardiology |
| FDA | US Food and Drug Administration (www.fda.gov) |
| FPI | First Patient In |
| FSR | „Funktionale Systemrisikoanalyse"; functional system risk analysis (QM-Document) |
| FU | Follow-up visit |
| GALAXY | LonG-Term EvALuAtion of the LinoX Family ICD Leads Registry (BIOTRONIK Study) |
| GDPR | General Data Protection Regulation |
| $H_0$ | Null Hypothesis |
| $H_A$ | Alternative Hypothesis |
| HF | Heart Failure |
| HF-T | Triple chamber ICD with BIOTRONIK Home Monitoring® functionality (automatic remote monitoring system) |
| HIPAA | Health Insurance Portability and Accountability Act |
| HM | Home Monitoring |
| HMSC | Home Monitoring Service Center |
| HR | Hazard Ratio |

| | |
|---|---|
| HRS | Heart Rhythm Society |
| HV | High voltage |
| ICD | Implantable Cardioverter Defibrillator |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (www.ich.org) |
| ICMJE | International Committee of Medical Journal Editors |
| ID | Identification Number |
| IEGM | Intracardiac Electrocardiogram |
| IFU | Instructions For Use (user manual) |
| iMedNet | Web-based electronic data entry (EDC) system for clinical trials provided by MedNet Solutions Inc. |
| IS-1 | Lead connector standard according to ISO 5841-3 |
| ISO14155 | International Organization for Standardization, norm no. 14155 |
| LPI | Last Patient In |
| LPO | Last Patient Out |
| LV | Left Ventricle |
| LVEF | Left Ventricular Ejection Fraction |
| LVVO | Left Ventricular VectorOpt |
| MADIT | Multicenter Automatic Defibrillator Implantation Trial |
| MATRIX | Management and Detection of Atrial TachyarRhythmias in Patients Implanted with BIOTRONIK DX Systems (BIOTRONIK study) |
| MEDDEV | Collection of guidelines of the European Commission for conformity assessment of medical devices |
| MedNet | Supplier of Clinical Trial Software (MedNet Solutions, Inc. www.mednetstudy.com) |
| MIRACLE | Clinical Trial on "Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure" |
| MPP | MultiPole Pacing |
| MR | Magnetic Resonance |
| MRI | Magnetic Resonance Imaging |
| NYHA | New York Heart Association |
| OTW | Over-the-wire |
| PCS | Promotional Claim Specification |
| PHD | Pre-hospital Discharge |
| PI | Principal Investigator |
| PMCF | Post Market Clinical Follow-up |
| PNS | Phrenic Nerve Stimulation |

| | |
|---|---|
| PSA | Pacing System Analyzer |
| PSW | Programmer Software |
| PVC | Premature ventricular contraction |
| PWD | P-wave duration |
| QM | Quality Management |
| QP | Quadripolar |
| QRS | Electrical complex on an ECG related to the depolarization of the ventricles |
| RA | Right Atrium |
| RV | Right Ventricle |
| RVp | Right ventricular pace |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Statistics and Analysis Software produced by SAS Institute Inc. (www.sas.com) |
| SCD | Sudden Cardiac Death |
| SD | Screw Dual Coil |
| SMS | Short Message Service |
| SOP | Standard Operating Procedure |
| SVT | Supra-Ventricular Tachycardia |
| TD | Tines Dual Coil |
| TRUST | The Lumos-T Reduces Routine Office Device Follow-Up Study (BIOTRONIK study) |
| UMTS | Universal Mobile Telecommunications System |
| US | United States |
| USA | United States of America |
| USADE | Unanticipated Serious Adverse Device Effect |
| USB | Universal Serial Bus |
| VF | Ventricular Fibrillation |
| VR | Ventricular single chamber Rate adaptive device |
| VR-T DX | Ventricular single chamber Rate adaptive device with Telemonitoring and atrial Diagnostics capabilities |
| VR-T | Ventricular single chamber Rate adaptive device with Telemonitoring capabilities |
| VT | Ventricular Tachycardia |
| VTA | Ventricular Tachyarrhythmia |
| VTI | Velocity Time Integral |
| ZIP | File compression format |

# 2 SYNOPSIS

| | |
|---|---|
| Title | BIO\|MASTER.Cor Family |
| Patient population | Patients with indication for ICD or CRT-D therapy according to standard clinical guidelines |
| Design | Multicenter, international, prospective, open, non-controlled, non-randomized; 127 patients |
| Investigational device(s) | Acticor, Rivacor ("Cor Family") ICDs and CRT-Ds<br>Plexa ProMRI S DX ICD lead |
| Objectives | To identify and evaluate residual risks associated with the use of the Cor Family ICDs and the Plexa S DX lead that remained unrevealed even after risk analysis, risk mitigation and successful conformity assessment. |
| Primary endpoint | Cor Family-related SADE-free rate until 3-month follow-up |
| Secondary endpoint(s) | • Kaplan-Meier estimate for the Cor Family related SADE-free rate<br>• Automatic LV VectorOpt test (CRT only)<br>• CRT AutoAdapt feature (CRT only) |
| Inclusion criteria | • Standard indication for ICD or CRT-D therapy according to clinical guidelines.<br>• Planned for de novo implantation of an ICD/CRT-D, or upgrade/exchange from existing ICD/CRT-D or pacemaker implant<br>• Able to understand the nature of study and to provide written informed consent.<br>• Willing and able to perform all follow-up visits at the study site.<br>• Willing and able to use the CardioMessenger and accepts the BIOTRONIK Home Monitoring® concept. |
| Exclusion criteria | • Contraindication to ICD and CRT-D therapy.<br>• Planned for implantation of a CRT-DX system.<br>• For VR-T DX devices: permanent atrial tachyarrhythmia.<br>• For VR-T DX devices: patients requiring atrial pacing.<br>• Less than 18 years old.<br>• Pregnant or breast feeding.<br>• Participating in another interventional clinical investigation<br>• Life-expectancy is less than 12 months. |

| | |
|---|---|
| | • Cardiac surgical procedure planned within 12 months after implantation (including interventional procedures like ablation, valve replacement, heart transplant etc.). Procedures to occur during or prior to implantation are not exclusionary. |
| Study duration | ~ March 2019 – December 2020 (~21 months) |
| Sample size | 127 patients |
| Investigational sites | ~14 |
| Number of follow-ups per patient | 5 |
| Follow-up scheme | Enrollment – Implantation – PHD – 3-month – 6 month – 12-month - Termination |
| Coordinating Investigator | [redacted] |
| Boards | none |
| Sponsor | BIOTRONIK SE & Co.KG<br>Woermannkehre 1<br>12359 Berlin, Germany |

# 3 INTRODUCTION

Sudden cardiac death (SCD) is the most common cause of death in western industrialized countries. SCD affects e.g. about 156,000 people in Germany and it adds up to about 15 – 20% of all natural deaths [1–3].

Implantable cardioverter defibrillators (ICD) are a common therapy approach to improve the survival of patients at risk of sudden cardiac death[4] by the termination of life-threatening ventricular tachyarrhythmias (VTA).

Antitachycardia pacing in the ventricular fibrillation zone

ICDs terminate VTAs by administration of antitachycardiac pacing (ATP) or high-energy electric shocks. While ATP has a lower conversion rate than shocks, they are not painful. In slower VTAs, which are not immediately life-threatening, several attempts of ATP are typically started before a shock is delivered in case of failure of all ATP attempts. In contrast, for fast VTAs detected in the "ventricular fibrillation" (VF) zone, only one attempt of ATP will be delivered prior to shock delivery, to avoid protracted repeated ATP attempts in this urgent situation.

Atrial sensing

The choice of single vs. dual chamber ICDs varies per country, with a majority of countries (60%) having a preference for single chamber ICDs[5].

In patients implanted with single chamber ICDs, no information about the atrial rhythm is available. Early information about clinical events such as the onset of atrial fibrillation may allow faster medical treatment, which can improve the clinical status of the patientsc[6,7]. Furthermore, inappropriate shocks frequently result from supraventricular tachyarrhythmias such as sinus tachycardia, atrial fibrillation or atrial flutter[8–10], which are difficult to identify in single-chamber devices without atrial sensing. Inappropriate shocks occur significantly more often in patients with single chamber than dual chamber ICDs (24% vs. 8%; $p<0.02$)[8]. The DATAS study could show that implantation of a dual chamber ICD in patients with a conventional single chamber ICD indication, was associated with less clinically significant adverse events[11,12]. The BIOTRONIK DX system allows monitoring of the atrial rhythm in a single chamber ICD and thus potentially allows reduction of inappropriate shocks and fast reaction to atrial fibrillation.

Dual chamber devices are indicated for patients with abnormal sinus node function, atrial arrhythmias, bradycardia, or second/third degree atrio-ventricular block[13].

Cardiac Resynchronization Therapy (CRT)

Patients who receive an ICD for primary prevention will typically have a reduced ejection fraction and a NYHA class of II to III, thus presenting with a mild to moderate chronic heart failure (CHF) of various origin[14]. CHF is a major public health issue with a current prevalence of 2-3% in the total and 10-20% in the aged population[15]. The overall mortality for the population is 50% in the first 4 years. 40% of the patients with HF-related hospitalizations have to be readmitted to hospital or die within one year[16].

Cardiac Resynchronization Therapy (CRT) is used in order to synchronize interventricular and intraventricular contraction patterns of the heart in patients with CHF in whom there is evidence of electrical asynchrony (QRS width ≥130 ms). CRT with defibrillator function (CRT-D) is recommended to reduce morbidity and mortality in ambulatory patients in NYHA II-IV who are symptomatic despite optimal medical therapy and suffer from a reduced left ventricular ejection fraction (LVEF ≤ 35%)[17,18].

Acticor/Rivacor ICDs/CRT-Ds (Cor Family)

BIOTRONIK's new generation of ICDs and CRT-D devices is called Acticor or Rivacor, according to a dual branding strategy. The device family is named 'Cor Family'.

Compared to its predecessors (I3 Family: Ilivia, Intica and Inlexa) the Cor Family is updated at the electro-mechanical as well as software platform level. Besides the thinner shape with rounder edges and an increased number of LV pacing and sensing vectors, the Cor Family provides a range of novel features that will be investigated in the BIO|MASTER.Cor Family study. With Auto LV VectorOpt and CRT AutoAdapt two features address the optimization of CRT response, as it has been shown that the most important settings to achieve an optimal cardiac resynchronization are the pacing mode, the lower and upper rate limits, the capture output, the stimulation vectors configuration, and the AV–VV intervals.

The Plexa ProMRI S DX lead is the latest generation of active-fixation, single-coil ICD leads with a floating atrial dipole for atrial sensing (DX leads). It is equipped with a DF-4/IS-1 connector and can be connected with the DX devices as well as the HF-T/HF-T QP devices of the Cor Family.

Aims of this study

This study is designed to provide post-market data and supporting evidence for the clinical safety and performance of the new ICD family and the Plexa ProMRI S DX ICD lead for regulatory approvals.

Endpoints include the SADE-free rate of the Cor Family ICDs, the automatic LV VectorOpt test for the automatic measurement of LV pacing thresholds, and the CRT AutoAdapt feature that continuously adjusts the AV-delay and ventricular pacing configuration based on periodic automatic measurement of electrical intra-cardiac conduction times.

# 4 INVESTIGATIONAL DEVICE

## 4.1 Summary description of the device and its intended purpose

The investigational devices used in this clinical investigation are the ICDs and CRT-Ds of the Acticor/Rivacor ICD family and the Plexa ProMRI S DX ICD lead.

The ICDs/CRT-Ds of the Acticor/Rivacor family are state-of-the art implantable defibrillators intended for defibrillator therapy in patients with indication for primary or secondary prevention of sudden cardiac death. Triple-chamber devices (CRT-D) are additionally indicated for cardiac resynchronization therapy (CRT) for patients with congestive heart failure with ventricular asynchrony.

The Plexa ProMRI S DX ICD lead is intended for implantation in the right ventricle to deliver ATP and shock therapies during ventricular tachycardia. The lead provides sensing and pacing in the right ventricle, as well as sensing in the right atrium (floating atrial dipole).

Both the Acticor/Rivacor ICD family and the Plexa ProMRI S DX lead are equipped with a DF4 connector.

For better legibility in the following text, the investigational devices listed above are referred to as *Cor Family ICDs* and *Plexa S DX lead*, unless otherwise stated.

## 4.2 Manufacturer

The manufacturer of the Cor Family ICDs and the Plexa S DX ICD lead 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

Except for the CRT-DX models and the Rivacor 3 series, all commercially available Acticor and Rivacor devices and Plexa ProMRI S DX models can be used in this study. The exact device names and catalogue numbers are listed in Table 1 and

Table 2. Participating sites located outside the CE area will only use those devices which received market or study approval by the respective regulatory institution according to the national regulations.

**Table 1: Eligible devices of the Cor Family**

| Device name | Catalogue number |
|---|---|
| Acticor 7 VR-T | [redacted] |
| Acticor 7 VR-T DX | |
| Acticor 7 DR-T | |
| Acticor 7 HF-T | |
| Acticor 7 HF-T QP | |
| Rivacor 7 VR-T | |
| Rivacor 7 VR-T DX | |

| Device name | Catalogue number |
|---|---|
| Rivacor 7 DR-T | [redacted] |
| Rivacor 7 HF-T | [redacted] |
| Rivacor 7 HF-T QP | [redacted] |
| Rivacor 5 VR-T | [redacted] |
| Rivacor 5 VR-T DX | [redacted] |
| Rivacor 5 DR-T | [redacted] |
| Rivacor 5 HF-T | [redacted] |
| Rivacor 5 HF-T QP | [redacted] |

**Table 2: Eligible Plexa S DX leads**

| Device name | Catalogue number |
|---|---|
| Plexa ProMRI S DX 65/15 | [redacted] |
| Plexa ProMRI S DX 65/17 | [redacted] |

During this clinical investigation, the devices under investigation are to be used with the following components:

- Any commercially available bipolar atrial lead providing IS-1 connection, preferably a BIOTRONIK lead (or no atrial lead in case single chamber device system is implanted).
- Any commercially available ICD lead providing a DF4 connector, preferably a BIOTRONIK lead. (For VR-T DX devices the Plexa ProMRI S DX lead is mandatory.)
- For CRT-D: Any commercially available left ventricular lead providing an IS-1 (HF-T) or IS4 (HF-T QP) connector, preferably a BIOTRONIK lead. If a HF-T QP device is implanted, Sentus ProMRI OTW QP lead is recommended.
- BIOTRONIK accessories are recommended, e.g. Selectra catheter
- BIOTRONIK Renamic or successor devices
- BIOTRONIK programmer software PSW 1801.A/4 and subsequent versions
- BIOTRONIK Renamic PSA module, PSA patient cables and patient adapters, e.g. BIOTRONIK IS4/DF4 adapter are recommended
- BIOTRONIK CardioMessenger Smart or successor devices
- BIOTRONIK Home Monitoring Service Center (HMSC) 3 and subsequent versions

Within the frame of this clinical investigation, all used devices carry a CE mark. Participating sites located outside the CE area will only use these devices after market or study approval by the respective regulatory institution according to the national regulations.

## 4.4 Description of traceability

Every ICD/CRT-D and every Plexa S DX lead has an 8-digit serial number. The traceability is assured due to recording of serial numbers and patient ID during the implantation procedure. Moreover, this information is documented on the corresponding electronic case report form (eCRF) and recorded in the clinical data management system (CDMS) enabling to create a list with all used devices within the study.

All devices used in this clinical study carry a CE mark and will be used within their intended use. Therefore special device accountability procedures are not applicable.

Explanted or malfunctioning devices shall be sent back to the manufacturer. The investigator shall contact the respective sales representative in order to organize shipment.

## 4.5 Intended purpose of the device in the study

In this study, all investigational devices will be used within their original intended use as specified in the instructions of use.

The primary objective of ICD therapy is to prevent sudden cardiac death. Furthermore, the devices are capable of treating bradycardia arrhythmias and cardiac resynchronization therapy with multisite ventricular pacing.

ICD implantation as symptomatic therapy has the following objectives:

- Termination of spontaneous ventricular fibrillation (VF) through shock delivery
- Termination of spontaneous ventricular tachycardia (VT) through antitachycardia pacing (ATP); in situations of ineffective ATP or hemodynamically not tolerated VTs, with shock delivery
- Cardiac resynchronization through multisite ventricular pacing (triple-chamber devices)
- Compensation of bradycardia through ventricular (single-chamber devices) or AV sequential pacing (DX, dual- and triple-chamber devices)

In combination with a compatible ICD, this Plexa S DX lead is designed for the following:

- Permanent sensing and pacing in the right ventricle
- Permanent sensing in the right atrium
- Delivery of defibrillation/cardioversion therapies

## 4.6 Intended patient population and indications

### 4.6.1 Intended patient population for Cor Family ICDs

The Cor Family ICDs are indicated for all patients fulfilling the generally accepted indications for implantable defibrillator therapy according to the combined guidelines of the American Congress of Cardiology (ACC), the American Heart Association (AHA), the Heart Rhythm Society (HRS), the German Society of Cardiology (Deutsche Gesellschaft für Kardiologie, Herz- und Kreislaufforschung, DGK), and the European Society of Cardiology (ESC)[19–21].

***Indications:***

Single-chamber and dual-chamber ICDs are indicated for patients with the following risk:

- Sudden cardiac death caused by ventricular arrhythmias

Triple-chamber ICDs are indicated for patients with the following risks:

- Sudden cardiac death caused by ventricular arrhythmias
- Congestive heart failure with ventricular asynchrony

***Contraindications:***

- Tachyarrhythmia caused by temporary or reversible irritation e.g. poisoning, electrolyte imbalance, hypoxia, sepsis or acute myocardial infarction
- Very frequent VT or VF requiring therapy causing disproportionately rapid depletion of the device battery
- VT with infrequent, or lack of, clinically relevant symptoms
- VT or VF treatable by surgery
- Concomitant diseases that would substantially limit a positive prognosis

- Accelerated intrinsic rhythm

#### 4.6.2 Intended patient population for Plexa S DX lead

The indications and contraindications for the Plexa S DX lead are similar to those of the respective ICD. The implanting physician is responsible for choosing the lead type, fixation and Plexa S DX variant. For the indications of an ICD therapy, the respective current guidelines of the American Congress of Cardiology (ACC), the American Heart Association (AHA), the Heart Rhythm Society (HRS), the German Society of Cardiology (Deutsche Gesellschaft für Kardiologie, Herz- und Kreislaufforschung, DGK), and the European Society of Cardiology (ESC) are recommended[19–21].

Plexa S DX leads are intended for single use only. Re-sterilization and re-use are prohibited.

***Indications:***

In combination with a compatible ICD, the Plexa S DX lead is designed for the following (intended use and indication):

- Permanent sensing and pacing in the right ventricle
- Permanent sensing in the right atrium
- Delivery of defibrillation/cardioversion therapies

ICD leads with two dipoles for sensing in both chambers are especially indicated for patients who, in addition to the usual ICD indications, have documented paroxysmal atrial fibrillation.

With its active fixation screw, this lead is especially suitable for patients with degenerated trabeculae in the ventricle for whom passive fixation with silicone or polyurethane tines is not possible.

Size and anatomy of the patient's heart determine the choice of distance between the atrial dipole and the lead tip (15 cm or 17 cm).

This lead is exclusively designed to connect to ICDs which have an atrial sensing channel in addition to the ventricular sensing and pacing channel (e.g., Acticor 7 VR-T DX or Rivacor 7 VR-T DX).

The ICD used has to meet the following requirements:

- The atrial sensing channel can sense signals of 0.25 mV (atrial fibrillation).
- An AV discrimination algorithm can distinguish between ventricular and atrial tachycardia.
- If atrial sensing is insufficient, the ICD can deactivate atrial sensing and continue functioning in single-chamber mode.

***Contraindications:***

Implantation of the Plexa S DX lead is contraindicated in the following cases:

- Patients with mechanical tricuspid valve prostheses or severe tricuspid valve diseases
- Patients with a dexamethasone acetate intolerance
- Patients with a sick sinus syndrome
- Patients with an unsuitable atrium anatomy (e.g., following partial resection of the atrium)

## 4.7 Description of the investigational device

#### 4.7.1 Cor Family ICDs

The Cor Family ICDs include the following devices:

- Acticor 7 VR-T, VR-T DX, DR-T, HF-T and HF-T QP
- Rivacor 7 VR-T, VR-T DX, DR-T, HF-T and HF-T QP

- Rivacor 5 VR-T, VR-T DX, DR-T, HF-T and HF-T QP

Further models are commercially available, but must not be used in this investigation. All devices are available as ProMRI versions only.

Single chamber devices have the suffix "VR-T", single chamber devices with additional atrial diagnostics have the suffix "VR-T DX", dual chamber devices have the suffix "DR-T", triple chamber devices that support IS-1 standard for LV lead have the suffix "HF-T", and triple chamber devices that support the IS4 standard for the LV lead will have the suffix "HF-T QP". The "-T" always indicates that a device is providing BIOTRONIK Home Monitoring®. The Cor Family offers devices with DF4 and with IS-1 and IS4 connectors, and the connector is therefore compatible with the respective leads (see Figure 1).


**Figure 1: Device types of the Cor ICD family (exemplary shown for Acticor)**

The Cor Family ICDs come with a new electro-mechanical platform, different at dimensions and with less thickness compared to the predecessor devices, larger edge radii and less weight. This leads to a further miniaturization (decrease in dimension, less volume), which should increase the wearing comfort for the patient.

The Cor Family ICDs consist of a housing and a device header. The housing contains the battery, the hybrid circuit and the HV capacitors and is made of biocompatible titanium, welded from outside and thus hermetically sealed. The ellipsoid device shape facilitates implantation in the pectoral muscle area. The device header contains the connections to contact the necessary transvenous or epicardial leads to the system. Thus the connections for bipolar pacing and sensing (and unipolar or quadripolar connections for the triple-chamber device) as well as for shock delivery are found in the device header. The device housing serves as a potential antipole during shock delivery or in the case of unipolar lead configuration.

Materials in contact with body tissue:

- Housing: titanium
- Header: epoxy resin, polysulfone
- DF4 seal: Silastic
- Silicone plugs and blind plugs (if applicable): Silopren or Silastic

#### 4.7.1.1 LV pacing and sensing configurations (HF-T QP only)

With the HF-T QP variants the Cor Family offers the option to connect a quadripolar LV lead with an IS4 connector at the device and therefore more options in pacing and sensing configurations for the LV channel as the conventional HF-T devices. The additional LV pacing vectors offered by the quadripolar lead allows the user to choose the best pacing vector to improve hemodynamic response and to overcome technical issues such as high pacing thresholds and phrenic nerve stimulation (PNS). Quadripolar leads have been shown to be associated with lower rates or LV lead-related problems and improved acute hemodynamic CRT response[22–24].

The HF-T QP devices of the Cor Family provide in total 20 LV pacing and 7 LV sensing configurations (see Figure 2 and Figure 3), compared to 12 LV pacing and 7 LV sensing vectors in the predecessor device. The vectors are built between a cathode electrode and an anode electrode. Beside the four consecutively numbered LV electrodes of the quadripolar LV lead

(LV1 tip, LV2 ring, LV3 ring, LV 4 ring) the distal shock coil of the RV lead (RV) or the ICD housing (ICD) can be used additionally as anode electrodes for the LV pacing configuration.

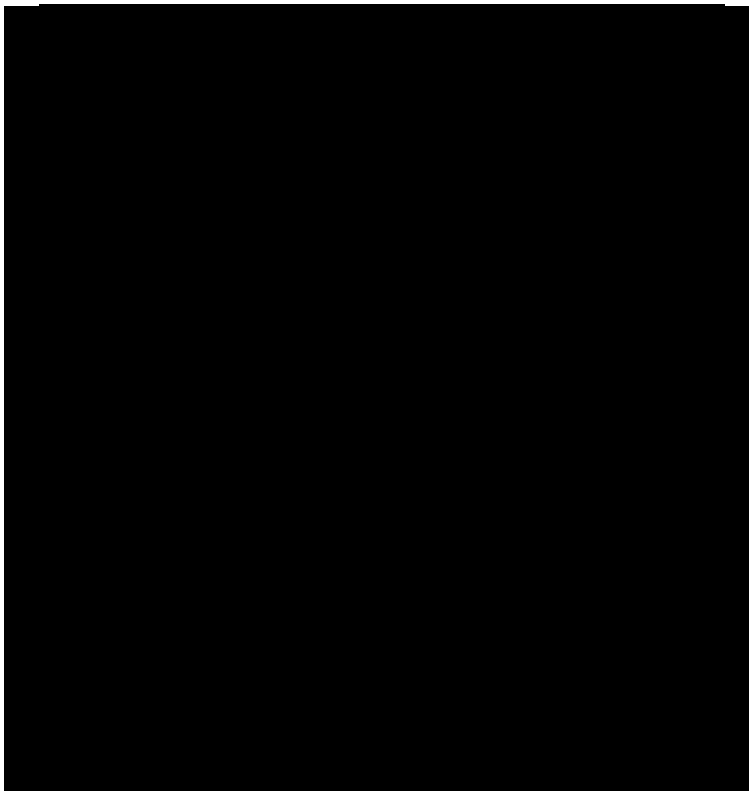

**Figure 2: LV pacing vectors for the Cor Family**

**Figure 3: LV sensing vectors for the Cor Family**

4.7.1.2 Auto LV VectorOpt test (CRT only)

Along with the increased number of LV pacing polarities, Cor Family ICDs offer Auto LV VectorOpt (LVVO), a feature that allows automatic measurement of the LV thresholds (Figure 4).

**Figure 4: User-Interface of Auto LV VectoOpt**

By pre-selecting the LV polarities that are to be measured and the automatic measurement of the responding threshold, the test is now more effective and faster than in its previous version. In addition, the preselection of manual threshold measurements has been separated from PNS threshold measurements in order to store the specific test parameter for these threshold measurements and thus to accelerate the workflow.

In addition, the RV-LV conduction time measurement, another discriminator for finding an optimal LV polarity for CRT patients, has been extended to RVp or RVs to LVs measurement. Thus, the real intrinsic conduction time from the right to the left ventricle in addition to the RVp-forced conduction time is measured.

#### 4.7.1.3 CRT AutoAdapt (CRT only)

The hemodynamic benefit of CRT depends on the setting of an AV-delay that allows the full atrial contribution for optimal filling of the ventricles and the setting of a ventricular pacing configuration that ensures ventricular synchronization for optimal ejection. Observational studies have identified suboptimal programming of the AV and VV delays as determinant factor of a poor response to CRT[25]. Since physiologic conditions change over the day and also on a longer scale with cardiac remodeling, the settings need frequent adaptation to ensure optimal benefit of CRT. Therefore, the adaptive CRT AutoAdapt algorithm (see Figure 5) can be used to adjust the AV-delay and set the ventricular pacing configuration to BiV or LV, based on periodic automatic measurement of electrical intra-cardiac conduction times (see Table 3). (*Ventricular pacing configuration 'LV'* is sometimes called *'LV only' pacing configuration*.)

The pre-conditions for CRT AutoAdapt activation or continuation are an atrial heart rate below 100 bpm and an AV conduction time after pace of less than 250 ms. Switching to *LV only pacing* is only allowed if LV Capture Control is enabled. This is to ensure that the LV only mode cannot be activated if the LV pacing threshold is not sufficient.

If the measurements of conduction times indicate that the condition for starting/continuing CRT AutoAdapt are not fulfilled (see Figure 5), the algorithm switches back to the BiV pacing settings that the physician programmed before activating CRT AutoAdapt.

**Figure 5: CRT AutoAdapt flowchart**

Once per minute, CRT AutoAdapt measures AV conduction times on the right (A-RV) and the left (A-LV) side of the heart. Based on the differences between these conduction times, the algorithm decides on the automatic adaptions (see Table 3).

| Intrinsic AV conduction | AV delay (CRT AutoAdapt) | Ventricular Pacing configuration |
|---|---|---|
| A-RV < A-LV | Minimum of<br>• A-RV-40 ms or<br>• A-RV*0.7 | LV |
| A-RV = A-LV | Minimum of<br>• A-RV-40 ms or<br>• A-RV*0.7 | BiV |
| A-RV > A-LV | Fixed AV delay | BiV |

**Table 3: Adaptations of CRT AutoAdapt based on the comparison between AV conduction on the right side (A-RV) and on the left side (A-LV).**

Possible effects of erroneous measurements, i.e. due to a premature ventricular contraction (PVC), are minimized by using averages of three measurements. In case of an AV conduction block, frequent occurrence of unphysiologically long AV delays during intrinsic conduction measurements, are avoided by a gradual prolongation of the measurement interval from 1 minute up to 16 hours at maximum. However, patients with chronic AV block III° are generally not indicated for CRT AutoAdapt activation.

#### 4.7.1.4 MultiPole Pacing (MPP) (HF-T QP only)

The IS4 connector standard allows the usage of LV leads that offer 4 separate electrodes which results in an increased number of effectively different pacing vectors (see also 4.7.1.1). Along with the quadripolar LV leads comes the possibility of stimulating more than one left ventricular pacing site within one cardiac cycle. MPP has been shown to improve CRT response[26].

MultiPole Pacing (MPP) makes the HF-T QP devices capable to deliver 2 LV paces in the left ventricle and one pace in the right ventricle. The pacing sequence can be delivered sequentially or synchronously. In addition to activate capture control for the 1st LV polarity, the HF-T QP devices of the Cor Family also offer this option for the 2nd LV polarity.

MPP offers the following options:

- 2 LV paces (requires different LV polarities) during each cardiac cycle
- 1 RV pace during each cardiac cycle
- Simultaneous or delayed pacing; 0 – 50 ms delay between (1st) LV and 2nd LV pacing sites
- Two MPP sequences are possible:
    - LV → 2ndLV → RV
    - RV → LV → 2ndLV

#### 4.7.1.5 AV delay Optimization (AV Opt)

The AV Optimization Test facilitates the tuning of AV delay (AVD) settings such that neither premature nor excessively delayed atrio-ventricular coordination dominate. The test is designed to be performed on the programmer during in-office follow-up sessions.

The AV Optimization Test determines patient-specific AV delay settings by combining a measured P-wave duration with an additive offset of 50 ms (Δ) (see Figure 6).

**Figure 6: AV delay calculation by AV Opt test**

This test is enabled as a follow-up measurement utilizing the temporary program mechanism. Within this context, the test can be terminated at any time. The programmer seeks measurable P-wave durations (PWD) from within the IEGM and displays the AV delay recommendations on the programmer screen.

The PWD is measured from the intracardiac far field signal (collected between RA ring and RV ring). For each test-affiliated cardiac cycle, atrial event markers (paced or sensed) establish the onset of the represented P-waves. The termination of each P-wave is found by using an algorithm which considers amplitude threshold, the slope threshold of each P-wave and a consistency criterion.

The AV Optimization Test is partitioned into two distinct segments, one for determining the AV delay following intrinsic atrial events and another for measuring AV delays that follow paced atrial events.

The results obtained via the AV Optimization Test are not automatically applied to the permanent program of the implant. They simply are displayed within the test page's results section and are used to update related parameters found on the dynamic AV delay screen.

#### 4.7.1.6 Statistics for ATP optimization

The ATP optimization algorithm counts for a successful ATP attempt, one up, and for each failed one, one down, starting with the same count for all ATP attempts at initial ATP programming. Thus the device filters out the most successful ATP for this patient automatically over the time. In this matter the programmed ATP sequence will be reorganized according to the success rate of the delivered ATP attempts and thus statistically optimized. Furthermore accelerating ATP attempts will be withhold/blocked until next in-office follow-up.

New in the Cor Family ICDs is a statistics for this ATP sequence adaptation. The statistics informs the user about the changed ATP sequences and the blocked ATP attempts since the last in-office follow-up. The blocked ATP sequences can be reactivated easily on the new ATP statistics tab by the physician (see Figure 7).

**Figure 7: New ATP optimization statistics in the Cor Family ICDs.**

#### 4.7.1.7 RV/LV CC at permanent DDI mode

Capture control (CC) algorithms are used in all channels to automatically monitor pacing thresholds and adapt the pacing amplitudes accordingly. Thus it is possible to ensure that the stimulation amplitude always is set to small but effective values but also never falls below the minimum value required for the patient. Temporal threshold changes are thus reflected in a safe and effective manner.

The pacemaker modes for RV/LV CC could not be combined with DDI(R) mode in the previous ICD families. However, nowadays DDI(R) mode is used more frequently as permanent mode in patients with persistent or paroxysmal AT/AF heart rhythm, than in the past. Thus the Cor Family ICDs will complete the pacemaker modes by DDI(R) mode in combination with RV/LV CC.

#### 4.7.1.8 BIOTRONIK Home Monitoring®

BIOTRONIK ICDs have the ability to transmit and receive data over a distance of several meters using bi-directional long-range telemetry, i.e. without the need of a programmer head.

The data is transmitted to a patient device (CardioMessenger) that is placed a few meters away from the patient.

Through mobile phone network, the CardioMessenger forwards the data to the BIOTRONIK Home Monitoring Service Center (HMSC). The data received by the Service Center are arranged in graphs and tables in the form of a Cardio Report and can be viewed by the physician on a secure internet platform. The physician is also automatically informed via SMS or email in case of pre-specified data deviating from the normal range, which might require an in-office follow-up of the patient (e.g. electrode problems, inappropriate or appropriate ICD therapies) (see Figure 8).

The idea behind the Home Monitoring systems is the support of device check and early detection of events.

**Figure 8: BIOTRONIK Home Monitoring® data transmission scheme**

The integrated Home Monitoring component is able to provide information about rhythm disturbances and delivered therapies close to real time by IEGM Online HD®. Furthermore, statistical data about the patient's condition as well as information about the integrity status of the device itself can be sent on a daily basis.

Data collected during in-office follow-ups on the programmer can also be uploaded to the HMSC using the ReportShare function of the programmer. For this purpose the investigator triggers the submission of measurement data collected onsite to the BIOTRONIK Home Monitoring Service Center after each study procedure.

During the course of the study the sponsor will have access to patient data transmitted via Home Monitoring and/or ReportShare in a pseudonymized form. The transmitted data will be used for evaluation and publication of the BIO|MASTER.Cor Family study, if applicable. Patients will be informed accordingly in the patient information and will sign patient informed consent prior to use of the data by the sponsor.

#### 4.7.1.9 QuickCheck

In addition to the current functionality of BIOTRONIK Home Monitoring®, the physician also has the possibility to use the "QuickCheck"-feature, which extends the BIOTRONIK Home Monitoring® service by a "real-time" report due to remote interrogation of the device on demand.

QuickCheck allows the clinician to request transmission of fresh data from the patient's device. The data, including an IEGM, typically arrives within a few minutes, provided that the patient is in the proximity of his/her CardioMessenger Smart.

This new feature enables clinicians to be more responsive to patient's needs. Immediate clarification and re-assurance of the patient may be possible via a phone call, reducing the need for spontaneous hospital visits. This is even of more importance if the patient lives in a rural area, making it very cumbersome for him/her to visit the hospital or doctor´s practice. On the basis of the transmitted data, the physician can advise the patient on the next steps.

### 4.7.2 Plexa S DX lead

The Plexa S DX lead is based on the Plexa ICD lead family, especially its predecessor, the Plexa DF-1 S DX. While the basic structure and functionality of the Plexa S DX is identical to its predecessor Plexa DF-1 S DX, the main new feature is the DF4 connector in combination with an IS-1 connector (see Figure 9).

All Plexa ProMRI leads are equipped with a modified fixation mechanism for an improved retention force of the screw and an approved white suture sleeve for better visibility. In addition, the peripheral cables feeding the ventricular ring and the shock coil are designed in a helical manner along the longitudinal axis. This helical design is intended to reduce the mechanical stress acting on the cables and the lead body. The helical design already known from the Plexa DF-1 S DX (and the rest of the Plexa ICD lead family) is introduced in Plexa S DX in the region between the IS-1 connector and the yoke. It is intended to expand the benefits of reduced mechanical stress acting on the lead body and cables in the pocket area to the new DF4/IS-1 connector combination.

Additionally, the white label tubing already known from DF4 connectors and stand-alone IS-1 connectors was used for the IS-1 connector of the Plexa S DX as well. Located at the distal end, the Plexa S DX leads have one tip electrode and one ring electrode for bipolar sensing and stimulation. As their predecessor leads, Plexa S DX leads are equipped with one ventricular shock coil and an atrial dipole for bipolar sensing. The atrial dipole senses the natural signals generated in the atrium. The atrial dipole is connected to the additional IS-1 connector at the proximal end of the lead. Fixation of the lead in the right ventricle is accomplished by means of an electrically active extendable and retractable screw, which also forms the distal tip electrode.

Plexa S DX has a silicone lead body with a SilGlide surface treatment to enhance the lead body's gliding properties (already known from the all other members of the Plexa ICD lead family). The active surface of the leads shows a fractal iridium coating. The steroid collar is made of silicone and 0.93mg dexamethasone acetate (DXA).

The leads are available in a length of 65 cm with different distance-to-tip lengths for the atrial dipole (150 or 170 mm).

**Figure 9: Schematic representation of Plexa ProMRI S DX**

## 4.8 Summary of training and experience needs

The devices of the Cor Family and the Plexa S DX lead are medical implants intended for physicians who are familiar with the implantation of an ICD or CRT-D device and its leads. The handling and implantation instructions are described in the respective Technical Manuals. The physician must be familiar with the associated risks and complications. The interrogation and programming of the ICD or CRT-D device shall only be done by appropriately trained personnel using the BIOTRONIK programmer.

All study procedures, including implantation and follow-up procedures, must be performed by a physician who is appropriately trained on the study.

All (co-)investigators must dispose of adequate research training and experience. Training on ISO 14155 and/or several years of experience in conducting clinical trials are generally required.

### 4.8.1 Description of medical and surgical procedures

The devices of the Cor Family and the Plexa S DX lead have to be implanted by a physician according to the standard implantation procedure. Specific information pertaining to procedures is provided in the respective Technical Manuals. The ICD and CRT-D measurements should be regularly observed via Home Monitoring by the investigator. During the onsite visits, the measurements will be performed via the BIOTRONIK programmer.

# 5 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

## 5.1 Pre-clinical data

No pre-clinical data are available that contradict the design of the clinical investigation.

## 5.2 Clinical data

For the ICDs, the following four BIOTRONIK sponsored clinical studies contribute to the evaluation of clinical data:

- DF4 Master Study (first use of the DF4 connector with the Ilesto/Iforia ICD family) (NCT01790841),
- BIO|Master.Ilivia Family/Plexa Study (predecessor of the Cor Family ICD in combination with the Plexa DF-1 lead variants (S, SD and S DX) and DF4 lead variants (S and SD) (NCT 02774616)
- BIO|Master.Edora Family Study (first use of the AV Opt test and first use of the predecessor for Auto LV VectorOpt ) (NCT 03091322)
- AV Optimization Study (AV Opt Study) (assessment of the AV Opt algorithm) (NCT03049722)

For the Plexa S DX ICD lead, the following BIOTRONIK sponsored studies are taken into consideration:

- LinoxSmart S DX Master Study (NCT0109041)
- Lumax DX/Linox DX Evaluation (NCT01486836)
- MATRIX (Management and Detection of Atrial TachyarRhythmias in Patients Implanted with BIOTRONIK DX Systems)(NCT01774357)
- BIO|Master.Ilivia Family/Plexa Study (see above) (NCT 02774616)

In the following, the above mentioned studies are described in more detail:

### 5.2.1 DF4 Master Study (Ilesto/Iforia ICD family)[27]

The objective of this study was to prove the safety and efficacy of the BIOTRONIK ICD/CRT-D family Ilesto/Iforia and the Protego SD/TD ICD lead. The study focused on the safety and efficacy of the new DF4 connection.

The study was conducted as a prospective, multicenter, and international clinical investigation. 240 patients were enrolled in 20 investigational sites worldwide. All participating patients received an ICD or CRT-D device of the Ilesto/Iforia product family. The ICD/CRT-D devices with DF4 connection were used with the Linox$^{smart}$ DF4 or Protego ICD lead. Both names refer to the same lead which was renamed while the study was conducted. Patients were enrolled prior to implantation. Implantation, pre-hospital discharge (PHD) and 1-, 3-, 6-, 12- and 24-month follow-up were part of the study. A Home Monitoring follow-up was conducted 20 days after PHD and 18 months after implantation.

Safety was assessed by evaluating the SADEs related to the investigational devices. Acute and chronic lead parameters for sensing, pacing threshold, pacing and shock impedance were evaluated for all leads, including right atrial and right and left ventricular leads.

***Results:***

Enrollment started on February 12, 2013 and was completed on April 02, 2014. The last patient finished participation on April 07, 2016 (last 24-month follow-up). The contingent of premature terminations was 25%, including 24 patient deaths.

- 239 Ilesto/Iforia ICDs/CRT-Ds were implanted successfully:
    - 173 with DF4 connection (66 VR-T, 42 DR-T, 65 HF-T)
    - 66 with DF-1 connection (21 VR-T, 10 VR-T DX, 15 DR-T, 20 HF-T)
- 171 (98.8%) out of 173 DF4 ICD leads were placed successfully during initial study implantation. All implanted leads had a fixation screw (SD).
- In total 520 adverse events (364 serious, 156 non-serious) were reported.

Primary endpoints

- One SADE related to the DF4 ICD family was reported, resulting in an SADE rate of 0.58 % (95%-CI: [0.000, 0.032]). It was concluded that the SADE rate for the DF4 ICD family is statistically significant lower than 10%. The endpoint was met.
- 9 SADEs related to the right ventricular ICD DF4 lead occurred in 173 patients from implantation to 3-month follow-up which results in an SADE rate of 5.2% (95%-CI: [0.024, 0.097]). It was concluded that the SADE rate related to the DF4 leads is statistically significant lower than 10%. The endpoint was met.
- The painless shock impedance was used as a surrogate parameter for the integrity of the DF4 connector system. No shift of the painless shock impedance greater than 20Ω was reported between 3- and 6-month follow-up in 150 evaluable patients. A confidence interval of the shift rate was calculated to [0.000, 0.024]. The endpoint was met.
- The RV pacing thresholds of the DF4 and DF-1 systems were compared. A non-inferiority test with a non-inferiority limit of 0.2 V was applied. The Wilcoxon test delivered a p-value of <0.001. The endpoint was met.

Secondary endpoints

- Due to the new right atrial threshold monitoring feature in the Ilesto family, the manual and the triggered automatic atrial threshold measurements were compared. Equality was shown within the specified range of [-0.2V, 0.2V]. The endpoint was met.
- The right ventricular sensing of the DF4 ICD leads was investigated at the 3-month follow-up. The rate of appropriate sensing was calculated to 99.35% (95%-CI: [0.965, 1.000]). The rate is statistically significant higher than 93%. The endpoint was met.
- The right ventricular pacing of the DF4 ICD leads was investigated at the 3-month follow-up. The rate of appropriate pacing was calculated to 100% (95%-CI: [0.977, 1.000]). The rate is statistically significant higher than 93%. The endpoint was met.
- The conversion of ventricular tachycardia and fibrillation of induced and spontaneous episodes were investigated in the patients with DF4 devices. 156 patients experienced an induced or spontaneous VT or VF. In all cases the fast ventricular rhythm was converted successfully to sinus or paced rhythm. The success rate of VT/VF conversion was 100% (95%-CI: [0.977, 1.000]). The endpoint was met.
- One SADE related to the DF-1 ICD family was reported, resulting in an SADE rate of 1.52 % (95%-CI: [0.000, 0.082]). It was concluded that the SADE rate for the DF-1 ICD family is statistically significant lower than 10%. The endpoint was met.
- 2 SADEs related to the right ventricular ICD DF-1 lead occurred in 66 patients from implantation to 3-month follow-up. This results in a SADE rate of 3.03% (95%-CI: [0.004, 0.105]). The upper confidence interval exceeds the defined limit of 0.1 - but statistical significance was not expected due to the low sample size of the DF-1 devices.
- The success-rate of the triggered automatic pacing threshold tests between DF4 and DF-1 devices was investigated. The success rate of both systems is 100%. The difference of the success rates between the DF4 and the DF-1 system was calculated to 0% (95%-CI: -0.032, 0.014), indicating non-inferiority of the DF4 system with respect to DF-1 system. The endpoint was met.

***Conclusion:***

The results demonstrate that the Ilesto/Iforia 5/7 ICDs in combination with the Protego ICD leads are safe and efficacious.

### 5.2.2 BIO|MASTER.Ilivia Family/Plexa Study[28]

This study was designed as prospective, and multicenter PMCF study with the CE-marked ICD/CRT-D devices of the Ilivia, Intinca and Inlexa family ('Group A'), the direct predecessors of the Cor Family, and the Plexa DF-1 lead variants (S, SD and S DX) and DF4 lead variants (S and SD) ('Group B') to identify and evaluate residual risks associated with the use of the Ilivia ICD family devices and the Plexa ICD leads that remained unrevealed even after risk analysis, risk mitigation and successful conformity assessment.

BIOTRONIK's Ilivia/Intica/Inlexa ICD/CRT-D Family introduced several new features and enhancements such as MultiPole Pacing (MPP), MRI AutoDetect, DX functionality in CRT devices and measures for the reduction of unnecessary therapies and lead monitoring.

Safety was assessed by calculating the Ilivia/Intica/Inlexa- and the Plexa-related SADE free rate from SADEs occurring between implantation and the 3-month follow-up. The efficacy of the Ilivia/Intica/Inlexa Family was assessed by determining the percentage of patients with successful conversion of a fast ventricular arrhythmia by the 'ATP One Shot' function (Anti-Tachycardia-Pacing therapy programmed with 8 pulses delivered with 88% of the fast ventricular tachycardia's cycle) at the 6-month follow-up. The efficacy of the Plexa ICD lead was confirmed by assessing the appropriateness of pacing and sensing at the 3-month follow-up. After pre-hospital discharge, patients underwent a 3-month follow-up as well as a 6-month follow-up at the investigational site, after which their study participation was terminated.

***Results:***

Enrollment started on June 14, 2016 and the last patient was included on July 17, 2017. The last patients of group A and B concluded the study on June 27, 2017, and on March 09, 2018, respectively.

Overall, 292 patients were enrolled in 25 sites worldwide. 111 patients were enrolled in group A, 183 patients in group B, and 16 patients were enrolled in both, group A and B; they are also counted in the 111 patients of group A and in the 183 patients of group B. In total 14 patients did not receive a study device.

- 111 patients of group A were successfully implanted with a device of the Ilivia ICD family, thereof 26 patients (23%) with single chamber devices, 26 patients (23%) with dual chamber devices and 59 patients (53%) with triple-chamber devices.
- 183 patients of group B were successfully implanted with a Plexa ICD lead: 37 DF-1 types (20%) and 146 DF4 types (80%).
- In total 300 adverse events (151 (50%) serious, 149 (50%) non-serious) were reported, of which 36 (12%) were device related (20 (56%) serious and 16 (44%) non-serious).
- Of all group A patients, 104 contributed to the primary endpoint 1. Of all serious adverse events, 82 were forwarded to the internal endpoint adjudication board. One event was evaluated as primary endpoint for group A. Hence the SADE free-rate related to the Ilivia ICD family is 99.0% (95% CI 94.0% - 100.0%). These results allow the rejection of the primary null hypotheses 1 of a rate ≤ 90% (2-sided $P < 0.001$).
- Of all group B patients, 175 contributed to the primary endpoint 2. For the primary endpoint 2, 79 serious adverse events were forwarded to the internal endpoint adjudication board for evaluation. Of those, 6 events in 6 patients were evaluated as primary endpoint for group B. Hence, the SADE free-rate related to the Plexa ICD lead is 96.6% (95% CI 92.1 – 98.9%). These results allow the rejection of the primary null hypotheses 2 of a rate ≤ 90% (2-sided $P = 0.002$).

- In group A, fast ventricular tachyarrhythmia conversion by ATP one-shot with the protocol-specified programming was attempted in 5 patients. It was successful in one, thus the percentage of patients with successful conversion is 20%.
- In group B, 145 of 145 (100%) patients showed appropriate sensing and 150 of 150 (100%) patients showed appropriate pacing of the RV lead at the 3-month follow-up. Thus the rate of appropriate sensing is 100% (95% CI 97.5 – 100%) and the rate of appropriate pacing is 100% (95% CI 97.6% - 100.0%). These results allow rejection of both secondary null hypotheses of a rate ≤ 93% (2-sided P < 0.0001).

Thus, all primary and secondary endpoints were met.

***Conclusion:***

In summary, the study has been executed and evaluated as planned. All pre-defined hypotheses have been confirmed with statistical significance. No unexpected safety relevant issues or performance deficiencies have been identified in the study devices. Thus, the results support safety and efficacy of the Ilivia ICD family and the Plexa ICD lead.

### 5.2.3 BIO|MASTER.Edora Family Study[29]

This study was designed as post market clinical follow-up study with the Edora family pacemakers (CE-marked products) to evaluate the new features AV Opt and LV VectorOpt under clinical routine conditions. Furthermore, Adverse Events were evaluated to identify residual risks associated with the use of the study product.

One hundred and twenty patients with standard indication for their respective device were enrolled. Initially, follow-up evaluations were planned before discharge, and at 1 and 6 months after implantation. Following an amendment, patients were asked to agree to an extension of the study period until 18 months after implantation.

Beyond clinically routine device follow-up, the AV Opt and LV Vector Opt features were to be tested in appropriate devices at discharge or at the 1 month FU.

No hypotheses have been defined.

***Interim Results:***

AV Opt

The first study endpoint was related to the new "AV Opt" feature, which was designed to support the selection of appropriate AV delay values. The algorithm suggested AV delay values in 69 of 74 patients (93.2%) with appropriate devices. The investigators used the AV delay values suggested by the algorithm, or considered them at least clinically acceptable, in 66 of 69 patients (95.7%) contributing to this endpoint.

LV Vector Opt

The second study endpoint was related to the new "LV Vector Opt" feature, which was designed to simplify the programming of LV stimulation vectors. The feature was used in 32 patients. The investigators considered the automatic conduction time measurement helpful in 25 of 32 cases (78.1%).

Safety

No serious adverse events have been observed which were related to the study pacemaker.

***Conclusion:***

So far, the study has been executed and evaluated as planned. No unexpected safety relevant issues or performance deficiencies have been identified in the study devices. Thus, the results support safety and efficacy of the EDORA pacemaker family. The final report will include also results of the extension period of the study and is expected in the end of 2019.

### 5.2.4 AV Optimization Study (AV Opt Study)[30]

The AV Optimization (AV Opt) Study was conducted between November 2015 and June 2016 to assess the ability of the AV Opt algorithm to determine P-wave durations (PWD), as well as assess hemodynamic output at the algorithm determined optimal AV delay (AVD). The goal was to evaluate the AV delay optimization algorithm by collecting far-field IEGMs. Additionally, hemodynamic data at various heart rates and AVD settings in an acute clinical setting were assessed.

***Results:***

A total of thirty subjects were recruited for the study. Of the 30 recruited, 26 were successfully enrolled and comprised the study sample used for PWD analysis. Twenty-five subjects comprised the study sample used for VTI analysis, because in addition to the four subjects excluded from the study, echo was not performed on one patient due to refusal to participate in the echo and pacing phase.

Although the study cohort was small, a comparison with the larger Evia HF-T study could show a good match concerning the representativeness to a balanced pacemaker population. All characteristics were found to be comparable between the two studies. The AV Opt population is considered to be representative of the general pacemaker population.

P-wave duration measurements

P-wave durations for the atrial sense-encouraged rhythms were on average 114.5 ms with a standard deviation of 15.3 ms. The paced atrial rhythms resulted in average P-wave durations of 157.8 ms with a standard deviation of 20.4 ms. The results demonstrate that the feature could successfully measure a PWD in every case with just one of the two phases, and measured a PWD in both phases a majority of the time. Furthermore, by using the sense compensation relationship between paced and sense-encouraged rhythms, the overall PWD measurement was successful for all patients. As a result, the primary study endpoint of successfully measuring the PWD in at least 75% of patients was met with 100% success.

Clinical assessment of hemodynamic output

Across the n = 17 patients with valid sense-encouraged data, the mean echo-determined optimal velocity time integral (VTI) was found to be 21.4 ± 5.4 (mean ± std) cm, while the mean VTI at the AV Opt-suggested AVDs was 21.1 ± 5.6 cm. Across the n = 22 patients with valid paced data the mean echo-determined optimal VTI was 19.4 ± 5.2 cm, compared to a mean VTI of 19.0 ± 5.1 cm with AV Opt. Most importantly, the echo-optimal and AV Opt VTI population means were found to be not statistically different (two-sample t-test, alpha = 0.05) for either sense-encouraged or paced rhythms. Furthermore, the concordance correlation coefficient (CCC) between the echo-optimal and AV Opt VTIs for the sense-encouraged and paced rhythms were 0.996 and 0.992, respectively, demonstrating that the AV Opt VTI was comparable to the echo optimal value. The echo determined optimal VTI and AV Opt VTI were compared using CCC to evaluate the clinical appropriateness of the AV Opt-suggested AVD, in the same manner as Baker et al[31].

***Conclusion:***

The study results demonstrate that AV Opt was successful for measuring P-wave durations and providing AV delay suggestions in 100% of patients, thereby meeting the primary endpoint of the study. To establish the appropriateness of these measurements, the VTIs (a measure of hemodynamic response) at the suggested AV delays were compared to the patient's maximum VTIs evaluated by echocardiography (i.e. the echo-optimal VTIs). The findings show that the algorithm's AV delays resulted in VTIs equivalent to the maximum VTIs obtained by echocardiography, thereby demonstrating equivalent clinical benefit in terms of cardiac output between the AV Opt and conventional echo-guided methods. Consequently AV Opt was confirmed to be a reliable approach to provide clinically relevant AVD suggestions compared to echocardiography in a routine follow-up setting.

### 5.2.5 Linox$^{Smart}$ S DX Master Study[32]

This clinical study was designed to demonstrate the clinical efficacy and safety of the Linox$^{smart}$ S DX ICD lead with DF-1 connector in a controlled clinical study with the Lumax DX ICD. A total of 116 patients were enrolled in 25 centers in 7 countries and were observed over 6 months. The period of investigation was March 2010 to June 2011. The assessment of the efficacy of the Linox$^{smart}$ S DX ICD lead was supported by the collection of standard pacing and defibrillation measurements and the investigator's assessment of the pacing and defibrillation system performance. The assessment of safety of the ICD lead was based on the recording and evaluation of all adverse events.

The clinical investigation was designed to evaluate the rate of appropriate atrial sensing, freedom from complications and tachyarrhythmia conversion efficacy.

***Results:***

- The primary endpoint of the rate of appropriate atrial sensing of the Linox DX lead was 93.8% [95% CI 91.4% – 96.2%].
- The secondary endpoint of freedom from complications of the Linox DX lead was 94.8% [95% CI 88.9% - 97.8%].
- The ICD conversion rate was found to be 100 % (144 episodes).

***Conclusion:***

The Linox$^{Smart}$ S DX Master Study has shown that the Linox$^{Smart}$ S DX lead is safe and efficacious.

### 5.2.6 Lumax DX/Linox DX Evaluation[33]

The goal of the clinical investigation was to collect clinical data for the regulatory support in the USA. The evaluation of efficacy of the DX system with the Lumax DX ICD and the Linox DX lead with DF-1 connector was supported by the collection and the assessment of atrial sensing system tests and successfully terminated tachyarrhythmia episodes. The assessment of safety was based on recording and evaluation of all adverse events. The planned and actual sample size was 38 patients which were enrolled at 5 sites in Germany and Hungary. Enrollment started on December 06, 2011 (FPI) and the last patient out was on August 31, 2012. The planned study duration was 3 months per patient.

***Results:***

- Mean p-wave amplitude of 4.3 mV in all four body positions (lying dorsal; sitting position; sitting postion, palms together; sitting position, Jendrassiks manoeuvre) during implantation and follow-up visits (implantation, PHD, 1-month and 2-month follow-up).
- 415 out of 430 atrial sensing assessments result in rate of appropriate atrial performance of 96.5%.
- In 16 out of 17 assessable Holter ECG recordings, appropriate atrial sensing function of the ICD system was demonstrated. One patient Holter ECG recording presented undersensing which was also confirmed by the assessments of the investigator performing atrial sensing tests during the follow-up visits.
- There were no lead repositionings within the study. The SADE free–rate was 100%.

***Conclusion:***

The results of the final analysis demonstrate that the Lumax DX/Linox DX system is safe and efficient.

### 5.2.7 MATRIX[34]

The MATRIX study (Management and Detection of Atrial TachyarRhythmias in Patients Implanted with BIOTRONIK DX Systems) is currently in the closure phase and was designed as

a non-randomized, multicenter study that primarily aims to explore the impact which the enhanced features and capabilities of the BIOTRONIK DX system might have on detection and management of atrial fibrillation (AF). Therefore, MATRIX has enrolled 2054 patients with a primary or secondary prophylactic indication for the implantation of a single-chamber ICD that are implanted with a BIOTRONIK DX system. Objectives are to explore the impact of enhanced features and capabilities of the BIOTRONIK DX system on detection and management of AF in an unselected real-life setting, and to assess rate and nature of complications surrounding the implantation procedure; To assess disease management aspects related to the DX system; To contribute to open questions in current AF research by use of device-related data available from Home Monitoring and programmer downloads.

Patients were enrolled within 90 days after ICD implantation. Implantation data were collected retrospectively. Routine follow-up visits without study specific procedures were performed after 12±2 and 24±2 months, if possible in accordance with hospital routine. Device data were continuously collected via HMSC and via programmer downloads during the course of the study. Furthermore, events of special interest and (S)A(D)Es were continuously collected and reported.

***Interim results:***

Data from 1950 patients enrolled between January 2013 and March 2016 were available for the 2nd interim analysis. Data analysis was restricted to data recorded at enrollment.

The following results regarding the pre-specified secondary endpoints were obtained:

- Early complications surrounding the implantation were reported for 63 patients (3.3%).
- At implantation, ventricular pacing threshold and signal amplitude were rated "sufficient" in 98% and 97% of cases, respectively.
- At implantation, mean (median) ventricular pacing threshold measured with the external analyzer was 0.7 ± 0.3 V (0.6 V) (n=811).
- Values measured with the implanted device were slightly lower (0.5 ± 0.3 V, median 0.5 V, n=919).
- Signal quality at enrollment:
- At implantation, the investigators rated the quality of atrial sensing amplitude as "sufficient" in 97% of cases.
- At enrollment, atrial signal quality and the atrial signal detection were rated "excellent" in 66% and 65% of cases, respectively. Both parameters were rated "poor" in only 1% of cases.
- The mean (median) atrial signal amplitude measured during implantation with the external analyzer and with the implanted device was 3.1 ± 3.0 mV (2.3 mV) and 7.5 ± 5.2 mV, (6.4 mV), respectively.
- The mean (median) ventricular signal amplitude measured with the external analyser and with implanted device was 14.0 ± 5.8 mV (13.1 mV) and 14.9 ± 6.0 mV (14.1 mV), respectively.
- The atrial rhythm had an obvious impact on the atrial sensing amplitude with lower values in patients with atrial fibrillation/atrial flutter compared to patients in sinus rhythm ($p<0.001$, Mann-Whitney-U test). There was no impact, however, on the ventricular sensing amplitude. Atrial signal quality and atrial signal detection were rated worse in patients with atrial fibrillation compared to patients in sinus rhythm ($p<0.001$ for signal quality, $p<0.01$ for signal detection, Mann-Whitney-U test).

***Conclusion:***

The data of the second interim analysis show a very good safety and efficacy profile of the Lumax DX ICD system at implantation with low complication rates, good electrical lead parameters and a high level of satisfaction of the investigators regarding handling and performance of the device.

The study is terminated by now (last patient out on June 28, 2018); Final results are expected in January 2019.

## 5.3 Justification

The above mentioned studies indicate the safety and efficacy of the predecessor devices of the Cor Family ICDs and the Plexa S DX lead, as well as the safety and efficacy of the DX system.

The devices of the Cor Family and the Plexa S DX lead have obtained the CE mark based on technical documentation and a clinical evaluation, according to European regulations (Directive 90/385/EEC on Active Medical Devices (AIMDD)). In addition, according to MEDDEV[1], the manufacturer is obliged to perform a Post Market Clinical Follow-up (PMCF) study in order to identify and evaluate residual unknown risks associated with the use of the devices that remained unrevealed even after risk analysis, risk mitigation and successful conformity assessment. This request is based on the corresponding European guidelines whereby a PMCF study should be considered where CE marking was based on equivalence[2]. This includes the application of new technology in medical devices.

The BIO|MASTER.Cor Family Study design is very similar to that of the BIO|MASTER.Ilivia Family/Plexa study and the BIO|MASTER.Edora study regarding endpoints and general design, given that the devices share a number of features.

In order to provide further supporting clinical evidence with regard to Acticor/Rivacor ICD's/CRT-D's safety and efficacy, and the identification of possible residual risks, one primary endpoint and three secondary endpoints were defined.

The primary endpoint assesses the safety of the Cor Family. For the safety endpoint the SADE-d free rate is calculated based on all SADEs related to the Acticor/Rivacor ICDs/CRT-Ds occurring until 3 months post implantation. The threshold for the respective hypothesis is set to 90% SADE-free rate, which allows for comparison with preceding studies, such as the DF4 Master Study, the Iperia/Sentus QP Master Study and the BIO|MASTER.Ilivia Family/Plexa study, which have used the same value, and which is known to be accepted by authorities outside of Europe who might also be provided with results from this study in the course of regulatory approval submissions. The safety endpoint will be evaluated using the data collected at implantation until the 3-month follow-up-, as the majority of, for example pocket infections, is found within this early postoperative phase [3,35].

Three secondary endpoints were defined:

1. A Kaplan-Meier estimate for the SADE-free rate at 3 and 12 months will be performed as a sensitivity analysis for the primary endpoint.
2. The Automatic LV VectorOpt test will be evaluated with regard to time savings, usability and acceptance criteria. This test was chosen as endpoint because it is a new feature that consists in a further development of the already known manual LV VectorOpt test which was investigated in the BIO|MASTER.Edora Family study.
3. The CRT AutoAdapt feature will be evaluated with regard to its programming, the behavior of the algorithm, usability and acceptance criteria. While CRT AutoAdapt aims at improving hemodynamics, it is not expected that significant effects on hemodynamics can be detected due to the small sample size and relatively short duration of this investigation. However, data on the functionality and acceptance of the feature contribute to this secondary endpoint that was chosen in order to gain more insight in the clinical use of this new feature.

[1] MEDDEV 2.7/1 Rev. 4

[2] MEDDEV.2.12/2 rev.2: 2012 Guidelines on Post Market Clinical Follow-up

Automatic LV VectorOpt and CRT AutoAdapt are new features that were implemented for the first time in BIOTRONIk devices and therefore chosen as secondary endpoints.

Another focus of the study is the data collection for the Plexa S DX lead with DF4 connection. For this reason data of interest are recorded to assess the atrial sensing performance and lead related adverse events but also the handling assessment during the implantation.

The product design of the DF4 variant of Plexa S DX is identical to the Plexa S DX DF-1 lead, except for the connector. In the BIO|MASTER.Ilivia Family/Plexa study, 27 Plexa S DX DF-1 leads were analyzed and already provided enough clinical data for the safety and efficacy of the DX lead variants[28]. Therefore, 30 Plexa S DX leads with DF4 connection are considered to be sufficient for the evaluation in this study.

The decision to include the Plexa S DX lead into the Master Study for the Cor Family devices is based on the fact that Acticor/Rivacor VR-T DX is the only device on the market that is compatible with this new DX lead with DF4 connection. Thus, the requirements for a PMCF for both devices were combined in one study.

The sample size is based on the sample size calculation for the primary endpoint (see section 11.2). The distribution of the device types was chosen in such a way that all device types are covered and thus contribute to the safety endpoint, while setting a focus on the DX system for the evaluation of the Plexa S DX lead (see above), and another focus on HF-T QP devices in order to collect an appreciable dataset for the evaluation of CRT-related features, some of which were defined as secondary endpoints (e.g. CRT AutoAdapt, Auto LV VectorOpt).

Due to suggestions of the notified body to cover a large proportion of the life-time of the devices, the follow-up duration for the study was extended to 12 months as compared to 6 months. However, the study duration does not cover the entire life-time of the devices and therefore, additional measures will be taken to comply with the active PMCF requirements for e.g. Post-Market Surveillance activities.

The BIO|MASTER.Cor Family study is designed as a multicenter and international study. The number of sites and the maximum number of patients per site will be chosen to ensure the multicentric character of this study, i.e. a reduction of investigator- or site-related bias.

Therefore the The BIO|MASTER.Cor Family trial is designed to identify and evaluate residual risks associated with the use of the Cor Family ICDs and the Plexa S DX lead that remained unrevealed even after risk analysis, risk mitigation and successful conformity assessment in a study patient population.

# 6 RISKS AND BENEFITS OF THE DEVICE AND CLINICAL INVESTIGATION

## 6.1 Anticipated clinical benefits

With the participation in this clinical investigation, the patient receives a modern device with many potential clinical benefits. Furthermore, the clinical status of the patient will be intensively supervised during study participation.

The DX functionality, in combination with the Plexa S DX lead, allows right atrial sensing via an atrial dipole on the right ventricular lead. The use of the DX functionality allows reduction of the number of implanted leads in patients who do not require atrial pacing and thus potentially reduces the risks of lead related complications[36–40].

For CRT-D patients, the Cor Family devices provide a range of features that might potentially increase the response to CRT, e.g. by offering a wider range of pacing configurations.

The available approach to extend the pacing vectors due to the use of a quadripolar LV lead has shown in several studies the superiority over a standard bipolar system. The multiple pacing options are the key to overcome, in the most cases, high pacing thresholds and PNS at implantation and at follow-up. Very important in the system are the options to avoid lead repositioning in case of distal phrenic nerve stimulation (PNS) and to have more options to avoid pacing from within scar areas by selecting a near-site stimulation. The latter feature can be selected by evaluating sensing and impedance values of the sites.[41] In general, the risk associated with a quadripolar lead is conservatively considered the same as with bipolar leads. Optimistically considered, quadripolar systems are favorable against bipolar systems concerning stable lead positions, reliable pacing thresholds and non-invasive options to resolve PNS situations at implantation and at follow-up. In one recent study[42] it was shown that the overall mortality was significantly lower in the group with quadripolar leads. Therefore, the number of patient-risky and costly re-intervention procedures can be reduced with these systems.

Regarding the CRT AutoAdapt feature, the available clinical data show beneficial effects of continuous automatic, ambulatory CRT optimization over standard echo-guided optimization at implant. Ambulatory CRT optimization was associated with a higher proportion of patients receiving effective CRT, an improved Clinical Composite Score (CCS), a reduction in HF hospitalization, the reduced occurrence of AF and death. Since AdaptivCRT (aCRT, a competitive algorithm) and the functionally similar CRT AutoAdapt require intact AV node, right bundle conduction, and absence of atrial tachycardia, patients fulfilling these criteria were shown to benefit more than the overall collective patients with CRT indication. Furthermore, LV-only pacing, i.e. withholding right ventricular pacing when intrinsic electrical conduction to the right ventricle is normal, was shown to result in similar or superior LV function and was also associated with improved RV function vs. BiV pacing [43–46]. It was criticized that the entirety of findings regarding clinical outcomes of aCRT is based on only one prospective trial and associated retrospective subgroup analyses. However, based on available data, aCRT and most probably also CRT AutoAdapt offer clinicians and patients enhanced options to improve response to CRT.

The use of Home Monitoring functionality offers the physicians the possibility to monitor their patients remotely whenever it is deemed necessary. The automatic early detection of arrhythmia and device anomalies allows earlier medical intervention as compared to conventional in-office follow-ups. The results of the TRUST clinical study demonstrated the safety and effectiveness of the remote monitoring[47]. In the Cor Family ICDs, the QuickCheck feature offers the additional advantage of providing a "real-time" report including a current periodic IEGM typically within 3-4 minutes of triggering it, e.g. if the patient experiences symptoms.

Finally, the new design of the Cor Family devices is expected to provide greater patient comfort and a better cosmetic outcome.

The individual benefit of study participation for the patient is an intensified medical supervision of his clinical status. In CRT-D patients the chance of responding to CRT-D therapy might be increased due to the increased number of LV pacing vectors, MultiPole Pacing and CRT AutoAdapt.

## 6.2 Anticipated risks

### 6.2.1 Anticipated adverse device effects

Adverse device effects anticipated for patients with ICD or CRT-D implantation are described in section 18.7 of the clinical investigation plan.

### 6.2.2 Residual risks associated with the device

The overall residual risk of the devices was assessed in the 'Functional System Risk Analysis' (FSR) with the following results: The risk control measures identified in the Risk Analysis in consideration of the acceptance justification for individual risks according to the risk acceptance criteria represent appropriate design input requirements so that the product's residual risk is "Acceptable" when all risk control measures have been implemented.

This assessment includes the evaluation of a potentially increased overall residual risk from the consideration of combined individual residual risks leading to higher values of probability of occurrence and severity. All identified individual risks have been found independent of each other so that the overall residual risk is determined by the maximum individual residual risk.

For the Plexa leads the 'Functional System Risk Analysis' states: The risk control measures identified in the Risk Analysis in consideration of the justification of acceptance for individual risks of risk classification level 2 ("Acceptable") represent design input requirements so that the residual risk of the product is acceptable when all risk control measures have been implemented.

For each remaining risk an assessment has been made if other hazardous situations may occur simultaneously that contribute to an increased risk beyond the acceptable range. The evaluation of such simultaneously hazardous conditions based on the Risk Analysis resulted in no identification of increased risks to patient, user, and environment.

### 6.2.3 Risk associated with participation in the study

Implantation of the Cor Family ICDs and the Plexa S DX lead does not differ from the procedures applicable for comparable systems. Thus, no additional risks or burdens concerning device implantation derive from participation in the study.

Risks associated with VR-T DX systems

The use of VR-T DX systems is indicated for patients who do not require atrial pacing, for example patients in atrial fibrillation or patients with normal sinus node function. However, in a proportion of patients an atrial lead might have to be added due to a change of the electrical pattern in the atrium.

Furthermore, the atrial sensing of the ICD connected to a DX lead might be inferior to a standard atrial lead, despite mostly positive clinical experiences[48,49]. This might lead to asynchronous pacing or inadequate shocks.

As the decision to implant a VR-T DX system is based on the physicians' judgment in regard to the medical condition of the respective patient, independently from the study, the risks associated with the use of the VR-T DX cannot be regarded as additional risks of the study participation, compared to routine use of a VR-T DX system.

Risks associated with CRT AutoAdapt

The occurrence of inappropriate CRT settings and an increased battery drain due to the algorithm were mentioned as potential risks of AdaptivCRT (aCRT, a competitive algorithm). Similarly, CRT AutoAdapt calculates CRT settings based on intra-cardiac conduction times. The aCRT trial showed that aCRT did not result in inappropriate device settings, i.e. a high short term variety in computed AV/VV delays. Regarding CRT AutoAdapt, possible effects of erroneous measurements, i.e. due to premature ventricular contractions (PVCs), are minimized by always using averages of three measurements. The aCRT algorithm itself was shown to have only a very small impact on battery life that may be compensated, when LV only pacing is possible.

A potential risk that was not mentioned in any publication is the minute-by-minute measurement of intrinsic intracardiac conduction that could cause repeated un-physiological long AV times in case of AV block or impaired right ventricular conduction. Patients with chronic AV block are generally not indicated for aCRT or CRT AutoAdapt activation. However, the potential risk is avoided in CRT AutoAdapt by a gradual prolongation of the measurement interval from 1 minute to 16 hours at maximum, in case of intermittent occurrence of impaired AV conduction.

The risks associated with CRT AutoAdapt are the same within the study as if the feature is activated in routine care. However, they account as study-specific, as the activation of this feature is mandatory for the respective devices in this study.

Further Risks

In the course of the study, event-triggered or physician-triggered (QuickCheck) IEGMs will be transmitted via BIOTRONIK Home Monitoring®. The transfer of these data will result in a reduction of battery lifetime. The use of QuickCheck is assumed to reduce the battery lifetime by 1-2 weeks per year. However, these transmissions are not expected to be more frequent than in routine care using Home Monitoring, and they provide physicians with more information on patient status and might therefore be beneficial for the treatment of the patient. The benefit of Home Monitoring has been shown in different trials[7,47,50] and has led to a wide acceptance of remote patient monitoring in clinical routine. Thus, physicians might choose these options for their patients even if not participating in the study.

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

Unauthorized access to the patient data or inadequate data protection (e.g. submission of non-pseudonymized data to sponsor representatives) are possible risks associated with the participation. BIOTRONIK undertakes technical and organizational measures to protect patient's data privacy and adheres to applicable European data protection laws.

#### 6.2.4 Possible interactions with concomitant medical treatments

For ICD and CRT therapy, no interactions with concomitant medication or medical treatment are expected.

### 6.3 Steps to control or mitigate the risks

All used investigational devices in this clinical investigation will be implanted after CE-certification. In countries located outside the CE area, devices will only be implanted after market or study approval of the responsible regulatory institution. The investigational devices meet the current state of medical science and technology and are used according to their intended use.

The risks can be minimized through the utilization of strict aseptic technique, compliance with the technical manual, compliance with this clinical investigation plan and technical procedures, adhering to the guidelines for selection of patients, close monitoring of the patient's

physiologic status during the procedures, and by promptly supplying BIOTRONIK with all pertinent information required by this clinical investigation plan.

## 6.4 Risk-to-benefit rationale

Patients in this study are provided with the newest available BIOTRONIK CRT-D or ICD technology. Only CE approved devices and leads will be used in this clinical investigation. The implantation procedure does not differ from other comparable CRT-D/ICD system implantations, thus resulting in no additional risk for the patient.

The Plexa S DX lead is the DF4 variant of the Plexa S DX DF-1 lead that was already investigated in the BIO|MASTER.Ilivia Family/Plexa study. Both leads differ only in the connector system and are part of the well-proven Plexa ICD lead family.

The Cor Family ICDs are based technically and functionally on the predecessor and well-established Ilivia family. Furthermore most of the new features are based on already market approved and proved BIOTRONIK pacemaker and ICDs.

The use of the Cor Family ICDs and CRT-D devices (within their intended use, indication, contraindication in the intended patient group) is beneficial and desirable to the patient group from a clinical standpoint. The possible risks do not exceed the amount generally accepted and are outweighed by the possible therapeutic and diagnostic benefit. Therefore, according to current knowledge/state of the art in the medical fields concerned and according to available medical alternatives, the Cor Family devices show a favourable benefit/risk profile.

The use of a VR-T DX system carries the risk of possible re-implantation of an additional atrial lead, if required. However, implantation of an atrial lead in the beginning, if not needed, might increase the lead burden, e.g. the risk of lead-related complications. Furthermore, atrial undersensing might occur that could lead to asynchronous pacing or inadequate therapies. As the decision to use a VR-T DX system is based on the physicians' discretion independently from the study these risks cannot be accounted for as additional risk of the study.

The literature assessment showed that frequent, automatic, ambulatory optimization of CRT settings associates with an improved clinical outcome. The evaluated aCRT algorithm that works functionally similarly to CRT AutoAdapt was shown to be safe and effective. It is therefore recommended to provide CRT AutoAdapt, as expected benefits outweigh the potential risks.

The mandatory use of Home Monitoring, the transmission of IEGMs and the potential use of QuickCheck decrease battery lifetime. On the other hand, HM-related battery consumption has been shown to be counterbalanced by battery savings due to a lower number of delivered shocks in the HM group of the ECOST trial[51]. Furthermore, the transmitted data provide physicians with more information on patient status and might therefore be beneficial for the treatment of the patient. Thus, physician might choose these options for their patients also if not participating in the study, as recommended by current guidelines[52].

In summary, the potential benefits of the study participation for the patient exceed the potential risks. Taking risks and benefits into account it can be stated that study participation of the individual patient can be regarded as justified.

# 7 OBJECTIVES AND HYPOTHESES

## 7.1 Objectives

This study is designed as post market clinical follow-up study to identify and evaluate residual risks associated with the use of the Cor Family ICDs and the Plexa S DX lead that remained unrevealed even after risk analysis, risk mitigation and successful conformity assessment. Moreover, the study aims at providing additional data, as required by regulatory authorities outside the CE-region. Furthermore, the performance and efficacy of the Cor Family devices and their features, as well as of the Plexa S DX lead shall be assessed. The results will be used for updating the clinical evaluation.

The primary objective of the clinical investigation is to confirm the clinical safety of the Cor Family ICDs by the analysis of the Cor Family-related SADEs until the 3-month follow-up.

Secondary objectives are the Kaplan-Meier estimate of the SADE-free rate at 3 and 12 months after implantation, the assessment of the automatic LV VectorOpt test, as well as the assessment of the CRT AutoAdapt feature.

## 7.2 Endpoints and hypotheses

### 7.2.1 Primary endpoint and hypotheses: Cor Family-related SADE-free rate until 3-month follow-up

The safety of the Cor Family ICDs will be evaluated by asking the investigator to record any adverse event. While all adverse events have to be recorded throughout the study, only the Serious Adverse Device Effects (SADE) possibly or securely related to the Cor Family devices (SADE-$d_{Cor}$) until 3-month follow-up are counted for this primary endpoint. Purely procedure related Serious Adverse Device Effects (SADE-$p_{Cor}$) are not counted. Further definitions are given in section 18.5.1. The primary hypothesis evaluates the SADE-$d_{Cor}$ free rate ($Cor_{SADE\_free}$). It is expected, that the rate will be significantly above 90%, the corresponding hypotheses definitions are:

Null hypothesis: $H_{0\_Cor}$ : $Cor_{SADE\_free} \leq 90\%$

Alternative hypothesis: $H_{A\_Cor}$ : $Cor_{SADE\_free} > 90\%$

The parameter of interest "$Cor_{SADE\_free}$" is the rate or device-related SADE-d free patients, which will be calculated by

$Cor_{SADE\_free}$ = [1 - number of patients with one or more ICD related SADEs (SADE-$d_{Cor}$) until 3-month follow-up divided by all patients in the analysis set] * 100%.

The following patients are not included in the analysis set for this endpoint:

- Patients without endpoint but premature study termination before or exactly at 61 days after implantation (3 months defined as 92 days after implantation – 30 days would still be in accordance to the CIP) are not included in the analysis set to avoid an over-estimation of the SADE-free rate.

SADEs will be adjudicated by an internal adjudication board, whereby the seriousness and device relatedness will be re-examined. If any amply documented external physical influence (e.g. accident, sport, twiddling) or medical AE caused the SADE, it does not contribute to this endpoint. SADEs that occur later than the 3-month follow-up, and SADEs with onset date later than or exactly at 123 days after implantation (3 months defined as 92 days after implantation + 30 days would still be in accordance to the CIP) in case the 3-month follow-up was not conducted or conducted outside the specified time interval do not contribute to this endpoint.

### 7.2.2 Secondary endpoints

#### 7.2.2.1 Secondary endpoint 1: Kaplan-Meier estimate for the Cor Family related SADE-free rate

The Kaplan-Meier method will be applied to estimate the 3-month SADE-free rate at 92 days after implantation (sensitivity analysis of the primary endpoint) and the 12-month SADE-free rate at 365 days after implantation. Thereby all patients will be included in the analysis.

#### 7.2.2.2 Secondary endpoint 2: Automatic LV VectorOpt test (CRT only)

At pre-hospital discharge or at the latest at 3-month follow-up, the following endpoints related to the automatic LV VectorOpt test will be assessed:

a. time needed to perform the LV threshold measurement manually
b. time needed to perform the LV threshold measurement automatically
c. investigator appraisal (score) of RV-LV conduction time test
d. investigator appraisal (score) of intuitiveness of the threshold test
e. investigator appraisal (score) of ease to find the best LV pacing configuration
f. investigator appraisal (score) of overall handling of the Auto LV VectorOpt feature
g. investigator agreement (score) to different statements relating to programmer-based LV vector optimization

Furthermore, the choice of tested vectors, the number of performed PNS threshold measurements, the finally programmed settings and details on the use of the test page will be recorded as further data of interest (see 7.5.2).

#### 7.2.2.3 Secondary endpoint 3: CRT AutoAdapt (CRT only)

At the 3-month follow-up the CRT AutoAdapt feature will be assessed with regard to the following endpoints:

a. percentage of CRT pacing since last follow-up
b. percentage of adaptive BiV pacing since last follow-up
c. percentage of programmed BiV pacing since last follow-up
d. percentage of adaptive LV pacing since last follow-up
e. mean adapted AV delay after pace/sense
f. rate of patients in whom the programming of CRT Autoadapt is maintained beyond the 3-month follow-up
g. reasons for deactivation of CRT AutoAdapt
h. investigator appraisal (score) of programmability
i. investigator appraisal (score) of clinical acceptability
j. investigator appraisal (score) of overall assessment of the CRT AutoAdapt feature

Furthermore, information on the programming of the feature and an overall assessment at the 12-month follow-up (if applicable) contribute to the further data of interest (see 7.5.2).

## 7.3 Claims and intended performance

Evidence for the following claims (Table 4) is expected from this study according to the Promotional Claim Specification (PCS):

**Table 4: Promotional claims to be assessed within the BIO|MASTER.Cor Family study**

| Promotional Claim | Feature | Related endpoints/ data of interest |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |
| [redacted] | | [redacted] |
| [redacted] | | [redacted] |
| [redacted] | [redacted] | [redacted] |

## 7.4 Safety assessments

Risks and anticipated adverse effects as described in section 6.2 will be assessed.

## 7.5 Further data of interest

Besides endpoint-relevant data, the following further data will be collected and assessed.

### 7.5.1 General data

- Baseline characteristics and medical history
- Assessment of ICD/CRT-D design (size and shape)
- AV delay optimization feature (AV Opt)
- Lead measurements (pacing threshold(s), sensing amplitude(s), shock impedance, lead impedance(s))
- Sensing and pacing assessment
- Arrhythmias and their treatment by the ICD/CRT-D system
- Usage of QuickCheck
- Assessment of statistic for ATP optimization
- RV/LV active capture control at permanent DDI mode
- MRI examinations, if performed independently from the study
- Adverse Events (including assessment of causality – device or procedure relation)
- Device Deficiencies

### 7.5.2 CRT Devices (HF-T and HF-T QP)

- Handling assessment of Selectra catheter
- Reports about cases with better CRT response using one of the new vectors
- Usage and settings of MultiPole pacing (MPP)
- Detailed information on SADEs related to MPP
- Detailed information on SADEs related to the CRT AutoAdapt feature
- Measurement of phrenic nerve stimulation, choice of tested vectors, finally programmed settings and details on the use of the test page using LV VectorOpt
- Programming of CRT AutoAdapt and overall assessment at 12-month follow-up

### 7.5.3 Plexa ProMRI S DX

- Lead handling assessment
- Atrial sensing assessments
- Adverse events related to the Plexa S DX
- Early detection of atrial fibrillation

# 8 DESIGN OF THE CLINICAL INVESTIGATION

## 8.1 General considerations

### 8.1.1 Type of clinical investigation

The study is designed as a multicenter, international, non-randomized, open-label and prospective study.

### 8.1.2 Measures taken to minimize or avoid bias

The clinical investigation is designed and will be conducted, analyzed, and reported based on an internal Standard Operating Procedure (SOP) system to minimize and avoid any bias.

A Kaplan-Meier estimate for the SADE-free rate at 3 months was included as secondary endpoint in order to account for a potential bias that might arise if the scheduling of the 3-month follow-ups within the allowed time window (± 30 days) is unbalanced.

A maximum number of patients per investigational site is defined in order to avoid a center effect (see section 11.13).

### 8.1.3 Selection of measurements for endpoints

For the primary endpoint, the SADE-free rate will be assessed by collecting and evaluating adverse events until the 3-month follow-up. This assessment was chosen to comply with preceding studies regarding result consistence and comparability and regarding acceptance by regulatory authorities outside Europe. As one objective of secondary endpoint 1 is a sensitivity analysis for the primary endpoint, the assessment of data – collection and evaluation of adverse events within a pre-specified timeframe – must be consistent between these endpoints. Secondary endpoint 2 aims at evaluating the Automatic LV VectorOpt test feature. The measurements were selected in order to collect data to support the intended claims for this feature (see section 7.3). As the CRT AutoAdapt feature (secondary endpoint 3) will be turned on at pre-hospital discharge (if applicable), its acceptance and performance is assessable through the measurement of device parameters – such as reprogramming, percentage CRT pacing etc. – at subsequent follow-ups. The percentage of CRT pacing is a crucial parameter for the effectiveness of cardiac resynchronization therapy. Evaluation of the CRT AutoAdapt performance using CRT response parameters is not feasible due to the small sample size of this study.

For both endpoints, Auto LV VectorOpt and CRT AutoAdapt, usability, user acceptance, clinical acceptability and overall assessments by the investigator play an important role, also with respect to validation of claims. However, these characteristics are very subjective, hardly measurable through device parameters, and hence commonly assessed by questionnaires. Therefore, scores with five categories (e.g. "Very good/good/adequate/poor/very poor") were chosen to rate these properties. Comment fields will be used to justify the chosen category.

### 8.1.4 Methods

During the course of the study, all clinical procedures are performed according to clinical routine. More detailed information can be found in the technical manual and in supporting study documents. The Automatic LV VectorOpt test for LV vector selection, and the AV Opt test or CRT AutoAdapt feature for AV delay optimization have to be used mandatorily in the respective devices unless contraindicated. The corresponding time schedule is described in section 9.1. All parameters and measurements that are recorded within the study are described in this section and are documented on the corresponding electronic case report forms (eCRFs). The investigator is required to use an electronic signature to approve the content of the data reported in the eCRFs. BIOTRONIK will monitor the content of the eCRFs as described in section 10. Data will be documented at the following points in time:

- Enrollment/Baseline
- Implantation
- Pre-hospital discharge
- 3-month follow-up
- 6-month follow-up
- 12-month follow-up
- Termination

The following events can be documented at any time:

- Adverse Events
- Device Deficiencies
- Premature termination

Source data, e.g. medical records, has to be available for all data entered in the eCRFs, unless specified differently by this CIP (compare sections below). Generally, the eCRF may be accepted as source document for the assessment of design, usability, acceptance and other subjective assessments by the investigator. However, the use of a site-specific source data sheet is recommended in these cases. Electronic CRFs will be verified at monitoring visits by the sponsor's representative.

Information from electronically delivered source data (e.g. via ReportShare, exported programmer files or medical records about (S)AEs) can be used for remote source data verification when pseudonymization thereof has been verified.

Patients have to consent to the use of their medical data in the patient file by signing the informed consent form.

#### 8.1.4.1 Assessment of enrollment criteria

The inclusion and exclusion criteria (see sections 8.3.2 and 8.3.3) must be assessed before the subject is enrolled by signing the informed consent form.

#### 8.1.4.2 Patients' demographics and medical history

Demographic information including age, gender, height and weight will be collected for all subjects at Baseline. Furthermore, information about the medical condition of the patient and the indications for CRT-D therapy or ICD therapy are interrogated. Further collected information is the medical history of the patient, current cardiovascular medication, NYHA class and ECG diagnostics within 3 months prior to implantation, if routinely available.

#### 8.1.4.3 Implantation

The implantation of the Cor Family ICD as well as the implantation of the Plexa S DX lead is performed according to standard procedures as described in the technical manual of the respective device. Any lead delivery system can be used; however, BIOTRONIK accessories are recommended.

During implantation lead measurements via pacing sensing analyzer (PSA) (BIOTRONIK device recommended) and device based measurements via programmer will be conducted (see 8.1.4.15), but only the device based measurements will be documented on the respective eCRF.

#### 8.1.4.4 Device Log

All elements of the implanted system that were part of an implantation process shall be entered into the device log. Therefore, also information on unsuccessful implantations of investigational medical devices shall be entered into the log. In case a new device or a new lead is added or exchanged, the new information on the device system shall be added to

device log and an AE eCRF shall be filled out by the study team. The implantation or exchange of devices follows the clinical routine procedures.

The following information shall be recorded in the device log:

- Information on the used medical devices (ICD/CRT-D, RA-, RV-, LV-lead, catheter)
- Serial number(s) of the device(s)
- Lead position
- Type of venous access for the leads
- Implantation site for the device

#### 8.1.4.5 Assessment of ICD/CRT-D design (size and shape)

The implanting investigator will be asked to assess the new design of the Cor Family devices with regard to the following aspects in the categories "Very good/good/adequate/poor/very poor":

- Required length of incision
- Assessment of lead connection
- Assessment of lead body leading out of the header

Furthermore, the investigator will be asked to compare the following properties with predecessor and competitor devices (to be specified) in the categories "Much more convenient/more convenient/similar/worse/much worse" and to justify his choice:

- Ease/time needed for making the pocket
- Assessment of size and shape for the patient's comfort
- Ease of device insertion, securing in pocket, and placement of leads
- Cosmetic outcome (categories "Much better/better/similar/worse/much worse")
- Interference with normal functions and mechanisms working in the human body ("physiological" shape) (categories "Much less/less/similar/more/much more")

In case of device exchanges, the patient will be asked about their wearing comfort compared to their previous device at the 3-month follow-up.

The eCRF may be accepted as source document for the assessment of design. However, the use of a site-specific source data sheet is recommended.

#### 8.1.4.6 Assessment of Plexa S DX lead handling (if applicable)

During implantation, the handling of the Plexa S DX lead will be assessed by the implanting physician. The following characteristics have to be assessed:

- How do you rate the flexibility of the Plexa ProMRI S DX ?
- How do you rate the push-ability of the Plexa ProMRI S DX?
- How do you rate the positioning behavior of the Plexa ProMRI S DX in the RV?
- How do you rate the extension/retraction behavior of the Plexa ProMRI S DX screw?
- How do you rate the X-ray visibility of the extended screw of the Plexa ProMRI S DX?
- How do you rate the fixation behavior of the Plexa ProMRI S DX?
- How do you rate the X-ray visibility of the Plexa ProMRI S DX in its final position?
- How do you rate the stylet handling in regard to the Plexa ProMRI S DX?

Ratings will be scored in the categories "Very good/good/adequate/poor/very poor".

The eCRF may be accepted as source document for the Plexa handling assessment. However, the use of a site-specific source data sheet is recommended.

#### 8.1.4.7 Assessment of Selectra catheter handling (if applicable)

If a Selectra catheter (outer or outer and inner) is used to position the left ventricular lead, the implanting investigator will be asked to assess its features with regard to the following characteristics:

- Torqueability
- Flexibility (distal end)
- Gliding properties
- Lead delivery
- Slitability (i.e. the ease of slitting of the Selectra catheter)
- x-ray visibility
- Overall handling

Furthermore the investigator will be asked to assess the features of the Selectra Slitter Tool:

- Lead fixation mechanism
- Handling and design
- Slitting performance
- Overall handling

These ratings will be scored in the categories "Very good/good/adequate/poor/very poor". In addition, information about the use of further accessories will be collected.

The eCRF may be accepted as source document for the Selectra handling assessment. However, the use of a site-specific source data sheet is recommended.

#### 8.1.4.8 Automatic LV VectorOpt test

The Automatic LV VectorOpt test has to be mandatorily performed in CRT-D patients. It is recommended to perform the test at pre-hospital discharge, but testing at implantation or at 3-month follow-up (if not done before) is also acceptable.

It is recommended to perform the measurement of RV/LV conduction times at the beginning of the test to facilitate the selection of vectors that are to be measured. In order to allow for a comparison of manual and automatic testing, the investigator is asked to perform the manual LV VectorOpt test first, the choice of at least 3 vectors being at the investigator's discretion. After that the automatic LV VectorOpt test shall be performed for the same subset of vectors. Finally, the automatic LV VectorOpt test will be performed for all 20 available vectors. Alternatively, a different subset of vectors at the investigator's discretion may be chosen for the automatic LV VectorOpt test.

Finally, the PNS thresholds shall be measured manually for a selection of vectors at the investigator's discretion.

The documentation in the eCRF will comprise of the following items:

- Did you perform the RV-LV conduction time test (RVp-LVs, RVs-LVs or both)? [Yes/No]
- Time needed to run the LV threshold measurement manually (and indication of the number of vectors tested)
- Time needed to run the Auto LV threshold measurement of the same subset of vectors (that were selected for the manual test)
- Time needed to run Auto LV threshold measurement (using all 20 vectors or for the selected vectors)
- Listing of pacing vectors that were tested during the automatic and/or manual procedure [Multiple choice]
- Number of vectors for which the PNS threshold was measured

- Values for sensing amplitude, pacing impedance, pacing threshold and PNS threshold of the finally programmed pacing vector
- Assessment of the Auto LV VectorOpt test by the investigator:
  - Do you consider the RV-LV conduction time test helpful? [Yes/No/Not done]
  - How did you preselect the pacing vectors that were measured automatically?
  - Intuitiveness of the threshold test (Score: "Very intuitive/intuitive/adequate/poor/very poor")
  - Ease to find the best LV pacing configuration (Score: "Very easy/easy/adequate/ difficult/very difficult")
  - Did you program the permanent pacing vector directly from the result table of the Auto LVVO? [Yes/No]
  - Overall handling assessment of Auto LV VectorOpt feature (Score: "Very good/good/ adequate/poor/very poor")
  - To what extent do you agree to the following statement relating to programmer-based LV vector optimization ("Strongly agree/Somewhat agree/Neither agree nor disagree/Somewhat disagree/Strongly disagree"):
    - "The parameters RV-LV conduction time, PNS threshold and impact on device longevity (pacing threshold) provide a good decision basis and are sufficient for a clinically acceptable LV vector optimization."
    - "Auto LV VectorOpt is an ergonomic tool for informed decision making and recommending which vector to select."
    - "The automatic measurement process simplifies the process of finding a suitable LV pacing vector for CRT."

The eCRF may be accepted as source document for the LV VectorOpt test assessment. However, the use of a site-specific source data sheet is recommended.

#### 8.1.4.9 CRT AutoAdapt (only Acticor 7 and Rivacor 7 CRT-Ds)

At implantation and/or pre-hospital discharge CRT AutoAdapt shall mandatorily be programmed 'ON' in all CRT-D patients that are implanted with Acticor 7 or Rivacor 7, with the exception of patients with AV block, for whom this feature is contraindicated. (Note: CRT AutoAdapt is not available in Rivacor 5.) The feature may be programmed 'OFF' in exceptional cases without causing a deviation from this clinical investigator plan, provided that the investigator gives a sound reasoning for his decision, e.g. special medical condition of the patient.

At 3-month follow-up the following data will be recorded:

- Was the feature programmed 'ON'?
- If "no", why not?
- Programmed setting for ventricular pacing and programmed AV delays
- Mean percentage of CRT pacing since last follow-up
- Mean percentages of adaptive BiV pacing, programmed BiV pacing and adaptive LV pacing, respectively, since last follow-up
- Mean adapted AV delay after pace/sense
- Assessment of the feature by the investigator:
  - Programmability (Score: "Very easy/easy/adequate/difficult/very difficult")
  - Clinical acceptability of the algorithm's decisions (Score: "Very good/good/ adequate/poor/very poor")
  - Overall assessment of the CRT AutoAdapt feature (Score: "Very good/good/ adequate/poor/very poor")

The eCRF may be accepted as source document for the assessment of the CRT AutoAdapt feature. However, the use of a site-specific source data sheet is recommended.

- Is the programming of CRT AutoAdapt maintained at the end of the follow-up? If "no", why not?

At 3-month and subsequent follow-ups it is the investigator's decision to leave the feature activated or to deactivate it.

If the feature remained active until the 12-month follow-up, the investigator will again be asked for an overall assessment of CRT AutoAdapt.

In addition to the data collected during follow-up visits, Home Monitoring data may be analysed with regard to the behaviour of the algorithm, e.g. mean percentage of adaptive BiV pacing, programmed BiV pacing and adaptive LV pacing, respectively.

#### 8.1.4.10 AV delay optimization (for VR-T DX, DR-T, and Rivacor 5 HF-T and HF-T QP devices)

For all patients with VR-T DX or DR-T devices (only if clinically indicated), and for patients with Rivacor 5 triple-chamber devices (as Rivacor 5 is not equipped with CRT AutoAdapt) with sinus rhythm of sufficient intrinsic rate, the AV Opt test has to be performed during the PHD follow-up[3]. Performance of the test during the 3-month follow-up is acceptable if it was not done at PHD.

It is the decision of the investigator whether to perform additional AV delay optimization procedures, e.g. Echo, or not.

The eCRF will comprise questions about measured data as well as the assessment of the test procedure(s):

- Did you run the AV Opt test? [yes/no]
    - If not, why?: [Multiple choice - Select all that apply]
        - General lack of trust in automated test routines
        - Personal or institutional preference for use of alternative methods
        - Patient conditions prescribe AV delay settings without need for additional diagnostic aids
        - Atrial fibrillation
        - No sufficient intrinsic rate
        - Other [please describe]
    - If yes: Did the test suggest sensed and paced AV delay values? [yes/no]
- Please give the values for the final, programmed AV delay settings (after pace):
    - AV delay @ 60 bpm: [value]
    - AV delay @ 80 bpm: [value]
    - AV delay @ 100 bpm: [value]
    - AV delay @ 120 bpm: [value]
    - AV delay @ 140 bpm: [value]
- Please provide the clinical basis for the final, programmed AV delay settings [yes/no; Select all that apply]
    - Based upon the AV Opt test output
    - Based upon the use of a personal/institutional preference
    - Based upon data from other follow-up affiliated diagnostics
    - Adoption of values from the device's standard program

[3] If the implantation and PHD are not on one or two consecutive days, the measurements can be done between implantation and patient discharge.

- Retention of AV delay settings from interrogated program
- Long AV delay to avoid ventricular pacing
- Other reason [please describe]

- If programmed setting is *not* based on AV Opt test output, or if a long AV delay was programmed to avoid ventricular pacing: Do you consider the suggested AV delay clinically acceptable? [yes/no; Reason]
- Overall assessment of the AV Opt tool (Score: "Very good/good/adequate/poor/very poor")

The eCRF may be accepted as source document for the assessment of the AV Opt feature. However, the use of a site-specific source data sheet is recommended.

#### 8.1.4.11 QuickCheck

The use of QuickCheck is optional during the study. However, if QuickCheck was used, the following data should be recorded:

- Reason for activation of QuickCheck – select from the following:
    - Routine check (instead of or in addition to scheduled HM follow-ups)
    - Observation in Home Monitoring Data
    - Home Monitoring Alert
    - Patient demand (reassurance)
    - Patient demand (symptoms)
    - Other (please describe)
- QuickCheck was triggered – select from the following:
    - while patient was on the phone
    - after the patient has contacted the site
    - after the site has contacted the patient
    - without patient contact
- QuickCheck was triggered by - select from the following:
    - nurse
    - physician
    - cardiac technician
    - other (please describe)
- Was the QuickCheck transmission fast enough? [yes/no/no opinion]
- Please estimate: How often will you use QuickCheck for this patient over the course of the next year? (not at all/once/bi-annually/quarterly/monthly/more than monthly/no opinion)
- To what extent do you agree to the following statement (Score: "Strongly agree/Somewhat agree/Neither agree nor disagree/Somewhat disagree/Strongly disagree"):
    - QuickCheck is a useful tool for remote patient management.
    - QuickCheck allows informed therapy decisions.
    - I perceive QuickCheck as a reassuring feature of the ICD therapy.
    - My patient perceives QuickCheck as a reassuring feature of the ICD therapy.
- Overall assessment of the QuickCheck feature (Score: "Very good/good/adequate/poor/very poor")

The eCRF may be accepted as source document for assessment of QuickCheck. However, the use of a site-specific source data sheet is recommended.

In addition, the time needed for data transmission (from triggering to availability in HMSC) will be retrieved from the HMSC.

#### 8.1.4.12 Usage and settings of MultiPole pacing (MPP)

The use of MultiPole Pacing (MPP) is optional within the study. However, if MPP was used in HF-T QP patients, the following data should be recorded:

Programmed vectors, pacing thresholds, programmed pacing amplitudes, LV sensing polarity, sensing amplitude, LV-LV delay and LV-RV delay.

#### 8.1.4.13 Improved CRT response after change of LV pacing vector

At the 6- and 12-month follow-up the investigator is asked to evaluate if a previous change of the LV pacing vector improved CRT response. The formerly used and the new vectors have to be documented.

#### 8.1.4.14 MRI examinations

If an MRI examination was performed during the course of the study (independently from the study), the following data will be recorded:

Use of MRI AutoDetect, Use of MRI Test Mode, Adverse Events/Device Deficiencies related to the MRI procedure or activation of MRI AutoDetect.

#### 8.1.4.15 Lead measurements with Renamic programmer at implantation and each follow-up

The system performance, i.e. appropriate sensing and pacing is evaluated at the end of the implantation procedure and **at the end** of each follow-up by either manually or automatically triggered lead measurements. For this purpose the investigator performs the threshold tests, determines pacing impedance and painless shock impedance and performs P/R-wave amplitude measurements in all available channels (in DX leads also sensing measurements in the atrial channel). In the RA and RV the pulse width must be 0.4 ms, in the LV any pulse width can be chosen. For CRT-D patients measurement of LV pacing vectors with the Automatic LV VectorOpt feature is **mandatory**, either at Pre-hospital discharge or at time of the 3-month follow-up. Pacing polarities of the LV channel must be documented. The type of programmer is also documented.

If no manual measurements were performed during the on-site follow-up, the values which were automatically measured by the device the previous day are acceptable.

The investigator is asked to assess the sensing and pacing performance at the end of each follow-up (including storing of an IEGM snapshot): The sensing of the lead will be assessed as "adequate" (= the device sensed the current rhythm correctly) or "inadequate". In the ventricles the additional option "no intrinsic rhythm" (= patient is fully paced) is available to describe if an evaluation of sensing is not possible. In case the sensing is considered inadequate, the reason "oversensing", "undersensing", "not measurable" (= quality/content of IEGM does not allow any discrimination if senses are correct (e.g. lead dislodgement)) or "other" will be determined. The pacing of the lead will be assessed as "adequate" (=successful stimulation) or "inadequate". In case the pacing is considered inadequate, the reason for the evaluation is required. Possible options are "non-capture" (= no evidence of depolarization after pacing), "no output" (= failure to pace: impulses are generated by the device but is not transferred to the myocardium), "not measurable" (= quality/content of IEGM does not allow any discrimination if stimulation is successful) or "other".

At the end of the on-site follow-up procedure the full follow-up data set shall be provided to the sponsor and will be used for source data verification '(see section 8.1.4.19).

#### 8.1.4.16 Tachyarrhythmia episodes

During the course of the study the following tachyarrhythmia episodes have to be recorded, analyzed and evaluated on the tachyarrhythmia episode form:

- All episodes detected in the VT-1, VT-2 or VF-zone
- All episodes with attempted and/or delivered therapies (ATP and/or shock)
- The first new and last two AF and/or SVT episodes between two follow-ups.

The appropriateness of the episode detection and the success of the delivered ATPs and/or shocks to terminate the episode will be evaluated. The corresponding IEGM should be stored by opening it manually and provided to the sponsor (see section 8.1.4.19). In case of new onset of AF, the investigator will be asked if the episode was detected by Home Monitoring prior to the follow-up.

#### 8.1.4.17 Assessment of statistic for ATP optimization

If ATP optimization was programmed 'ON' (optional), the investigator will be asked to assess the statistics for ATP optimization at the 12-month follow-up for patients that experienced tachyarrhythmia episodes treated with ATP in the course of the study.

The investigator will be asked to assess the comprehensibility and the usefulness in the categories "Very good/good/adequate/poor/very poor".

The eCRF may be accepted as source document for the assessment ATP statistics.

#### 8.1.4.18 RV/LV Capture Control at permanent DDI mode

Home Monitoring data will be analyzed to identify any patients in permanent DDI mode in whom capture control is activated in at least one of the ventricular channels (RV, LV and/or LV2). The AE database will be searched for Adverse Device Effects related to loss of capture that occurred in these patients.

#### 8.1.4.19 Provision of programmer data and IEGMs

During the study, programmer data containing all measurements have to be provided to the sponsor for implantation and each follow-up. To ensure that all threshold measurements are available in the programmer data, it has to be ensured that for each measured vector the pacing threshold value is actually chosen and stored. IEGMs, e.g. of tachyarrhythmia episodes, have to be actively opened once to ensure storage and export.

The programmer data and IEGMs shall be provided to the sponsor as follows:

- Delivery via ReportShare function to the Home Monitoring Service Center

  **Automatic export**

  Pre-setting of Renamic Programmer: open the 'Options' dialog in the Data Manager.

  Activate the automatic upload by enabling the 'Automatic export' (3) checkbox (see Figure 10)

  After implantation or FU was performed: click 'end' to close the application.

  The upload will start automatically.

  **Or Manual export**

  Pre-setting of Renamic Programmer: open the 'Options' dialog in the Data Manager.

  Activate the manual upload by enabling the 'HMSC export' (2) checkbox (see Figure 10)

  Select one follow-up from Data Manager

  Click on 'Preview' and select all checkboxes

  Click on 'Export'

**Figure 10: Onterface for the export of programmer data to HMSC via ReportShare**

In the exceptional case that ReportShare is not available, e.g. for organizational or technical reasons, the following alternatives may be used for delivery of programmer data and IEGMs:

- Upload to the EDC system
- Delivery via email to
- Delivery via USB stick

For every export it has to be ensured that data are pseudonymized.

#### 8.1.4.20 BIOTRONIK Home Monitoring® Data

The sponsor will collect the patient data obtained by telemetry over the period of study participation. This will include P- and R-wave sensing, pacing impedance, painless shock impedance and thresholds, periodic IEGMs and recording episodes IEGMs and further data. The observation of Home Monitoring data by the sponsor cannot be used as an emergency system. The investigator is responsible to follow-up the patients via Home Monitoring and during in-office follow-ups.

#### 8.1.4.21 Medication Log

The medication shall be documented in the medication log. Changes or additions during study participation shall be entered in this log as well. The following data shall be entered in the log:

- Name of the medication
- Date of start and stop of application, if applicable

#### 8.1.4.22 Adverse Events

During the course of the study, all adverse events will be reported to the sponsor and to local Ethics Committees, if required by local regulations (see also section 18.9). All adverse events will be classified according to their seriousness, the relation to the investigational devices and to the procedure. Furthermore, relation to MPP and CRT AutoAdapt, respectively, will be documented. Reporting of adverse events is required starting from the time of signature on the patient informed consent until study termination. In case serious adverse device effects (SADE) are not solved at study termination, those shall be followed up for a maximum of 4 weeks after study termination of the patient.

The definition of event classification is described in section 18.1.

#### 8.1.4.23 Device Deficiencies

In case of a Device Deficiency (DD) the type and serial number of the affected device, a description of the deficiency and an assessment whether the deficiency could have led to a medical occurrence and/or a serious adverse device effect will be documented.

### 8.1.5 Equipment to be used for the assessment of variables

The following equipment is used for the assessment of the above described variables:

| | |
|---|---|
| Device: | BIOTRONIK Acticor/Rivacor 7 series or Rivacor 5 series: VR-T, VR-T DX, DR-T, HF-T, HF-T QP |
| RA-lead: | Freely selectable |
| RV-lead: | For VR-T DX system: Plexa ProMRI S DX lead |
| For all other systems: | Freely selectable |
| LV-lead: | For HF-T system (with IS-1 connector): Freely selectable |
| | For HF-T QP system (with IS-4 connector): BIOTRONIK Sentus OTW QP lead is recommended |
| External programming device: | BIOTRONIK Renamic (or successors) (with UMTS-Module and software version 1801.A/4 or higher) |
| Programmer software: | BIOTRONIK PSW 1801.A/4 and subsequent versions |
| Remote monitoring tools: | BIOTRONIK CardioMessenger Smart (or successors) |
| Remote monitoring software: | BIOTRONIK Home Monitoring Service Center (HMSC) 3 and subsequent versions |
| Accessories: | |
| | BIOTRONIK Selectra LV delivery system (recommended) |
| | BIOTRONIK accessories kit (recommended) |

Note: even though the choice of leads is left to the investigator, it is recommended to use the specific BIOTRONIK lead combinations that would allow the whole system (ICD + leads) to be MR conditional. Please refer to the specifications in the IFUs.

### 8.1.6 Replacement of subjects

During the course of the study, patients that drop out prior to any implantation attempt can be replaced as long as enrollment in the study is still ongoing. Patients who are not implanted with an investigational device and who did not come in contact with any investigational device during implantation attempt can also be replaced.

Due to replacements, the total number of enrolled patients might exceed the planned sample size.

Patients that will be lost to follow-up or prematurely terminate the study for any reason after a successful implantation will not be replaced.

## 8.2 Used devices and comparators

### 8.2.1 Description of exposure to the investigational device and/or comparator

The investigational devices used in this study are Active Implantable Medical Devices (AIMD). According to the nature of implantable devices, the devices will be implanted into the patient's body and will typically remain there for the lifetime of the device, also beyond the duration of the study.

### 8.2.2 Justification of the choice of comparators

No comparator is used in this study.

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

See section 8.1.5 for all medical devices to be used during this investigation. The medication is at the investigator's discretion according to the medical condition of the patient.

### 8.2.4 Number of investigational devices to be used and a justification

According to the sample size calculation for the primary endpoint, 127 patients (including dropouts) will be enrolled in this study. Each patient will be implanted with one ICD or CRT-D of the Cor Family. All patients that are implanted with a VR-T DX device will additionally receive a Plexa S DX lead.

The distribution of the different types of devices is planned as follows:

- 15 VR-T
- 30 VR-T DX, combined with 30 Plexa S DX leads
- 15 DR-T
- 15 HF-T
- 52 HF-T QP

This distribution was chosen in order to provide data for all device types of the Cor Family ICDs, while focusing on two groups: 30 VR-T DX devices are planned so that a dataset for the assessment of the Plexa S DX lead is obtained, comparable to the dataset for Plexa ProMRI S DX DF-1 leads that was collected within the BIO|MASTER. Ilivia Family/Plexa study. The second focus lies on HF-T QP devices: two of the secondary endpoints relate to features that are only available in CRT-Ds. At the same time, triple-chamber devices provide all features/properties that are also included in single- and dual-chamber devices, and thus contribute to overall results for the Cor Family ICDs. Within the triple-chamber devices more HF-T QP than HF-T devices are planned, reflecting the current state-of-the-art and market demand that favours devices with IS4 connection for quadripolar leads.

However, this planned distribution of devices should not prolong the enrollment period in case that one or two of the device sub-groups are not completed within the planned enrollment period. Therefore, VR-T and DR-T devices may be mutually substituted, and HF-T devices may be substituted with HF-T QP devices if the respective subgroup is not completed within a certain timeframe defined by the sponsor. The sponsor will issue the respective information about closure and/or re-opening of subgroups.

## 8.3 Subjects

### 8.3.1 Description of patient population

Only patients with respective ICD or CRT-D indication requiring ICD or CRT-D implantation according to current clinical practice, and who are planned to be implanted with an ICD/CRT-D of the Cor Family according to the investigators' decision may be enrolled into the BIO|MASTER.Cor Family study. Decision for implantation of the respective BIOTRONIK devices should be based on medical decisions alone and should not be influenced by the enrollment to this clinical trial.

As the further in- and exclusion criteria do not confine the patient population to specific requirements, it is expected that the investigation population is representative for the target population.

### 8.3.2 Inclusion criteria

- Standard indication for ICD or CRT-D therapy according to clinical practice.
- Planned for de novo implantation of an ICD/CRT-D, or upgrade/exchange from existing ICD/CRT-D or pacemaker implant
- Patient is able to understand the nature of study and to provide written informed consent.
- Patient is willing and able to perform all follow-up visits at the study site.
- Patient is willing and able to use the CardioMessenger and accepts the BIOTRONIK Home Monitoring® concept.

### 8.3.3 Exclusion criteria

- Contraindication to ICD and CRT-D therapy.
- Planned for implantation of a CRT-DX system.
- For VR-T DX devices: permanent atrial tachyarrhythmia.
- For VR-T DX devices: patients requiring atrial pacing.
- Patient is less than 18 years old.
- Patient is pregnant or breast feeding. (A pregnancy test may be required according to local/national regulations.)
- Patient is participating in another interventional clinical investigation according to the definition given below.[2]
- Patient's life-expectancy is less than 12 months.
- Cardiac surgical procedure planned within 12 months after implantation (including also interventional procedures like ablation, valve replacement, heart transplant etc.). Procedures to occur during or prior to implantation are not exclusionary.

Inclusion as well as exclusion criteria apply at enrollment.

[2]Patients shall not be enrolled in two interventional clinical investigations at the same time. Enrollment of patients who are already enrolled into an interventional clinical investigation is prohibited by an exclusion criterion. If the patient wants to consent for another study, and the investigator knows this beforehand, the investigator shall ask for an agreement from the sponsor, and if not granted, shall ask the patient not to participate in the second study. If the investigator finds out that the patient has been enrolled into another study, the investigator shall inform the sponsor (see section 9.10.2 "Responsibilities of the investigators"). The sponsor may decide to exclude the patient from the study only if further CIP required procedures offer a risk of a reciprocal effect with the treatment of the other study. Decisions and deviations have to be discussed upfront (if applicable, during the advisory stakeholder meeting) and documented respectively (e.g. via Note to File and reported as CIP deviation or supporting document "Internal Steering Committee").

### 8.3.4 Screening failure

No screening procedure is planned for this study.

### 8.3.5 Drop-out criteria

#### 8.3.5.1 Mandatory drop-out according to protocol

The investigator shall exclude a patient due to the following reasons (defined as drop-out according to protocol):

- Patient is not implanted with a product of the Cor Family of ICDs/CRT-Ds for any reason, e.g. unsuccessful implantation attempt (see also section 8.1.6).
- An explantation or replacement of the Cor Family ICD/CRT-D was performed.

Note: A patient shall not be excluded from study participation if he refuses the further use of Home Monitoring (after initially consenting to it).

#### 8.3.5.2 Drop-out according to physicians' discretion

The investigator may exclude a patient due to the following reasons:

- Missing acceptance/compliance of the patient to follow the instructions of the dedicated study team.
- Significant worsening of general or pre-existing condition of the patient making further participation of the patient impossible.

#### 8.3.5.3 Withdrawal of patient consent

Patients may withdraw their consent for study participation at any time without stating the reason and without any unfavorable consequences. All data which are collected until the date of withdrawal will be used in pseudonymized form as long as their further processing or retention is necessary, e.g. to fulfil a legal obligation. This also applies if the patient has requested data erasure. Depending on the patient's will the collected data will be anonymized then. A withdrawal sheet and a study termination CRF have to be filled in by the investigator.

### 8.3.6 Point of enrollment and study termination

The point of enrollment is defined as the time of signature of the informed consent form by the patient. Study related procedures, documentation and collection/following of adverse events will start from this time on.

The point of study termination is defined as date of 12-month follow-up for patients with regular study termination.

The point of non-regular study termination can be the following:

- Date of the last unsuccessful implantation attempt
- Date of withdrawal of consent
- Date of patient death
- If patient is lost to follow-up, the date of last contact of the site study team (e.g. investigator or study nurse) with the patient
- If patient is a drop-out for any other reason, the date of latest medical information of the patient (e.g. follow-up, IEGM)

Study related procedures and data collection must end at the day of study termination. However, Serious Adverse Device Effects which are not resolved at date of study termination will be followed for up to 4 weeks after study termination of the respective patient.

### 8.3.7 Timelines

| | |
|---|---|
| First Patient In (FPI)*: | ~ March 2019 |
| Last Patient In (LPI)*: | ~ December 2019 |
| Enrollment period: | ~ 9 months |
| Individual study participation: | ~ 12 months |
| Last Patient Out (LPO)*: | ~ December 2020 |
| Total study duration: | ~ 21 months |

The end of the clinical trial is defined as the date of termination of the last enrolled patient (Last Patient Out).

*Timelines subject to change without requiring protocol amendments.

# 9 **STUDY** procedures

## 9.1 Overview

**Table 5 : Overview of study procedures. The exact reference time for the 3-, 6- and 12-month follow-up is defined as 92 days, 183 days and 365 days after implantation, respectively. The applicable time window is ± 30 days around this reference time.**

| Investigations | Enroll-ment | Implan-tation | PHD | 3-Month FU | 6-Month FU | 12-Month FU |
|---|---|---|---|---|---|---|
| Verification of in- and exclusion criteria | x | | | | | |
| Patient informed consent | x | | | | | |
| Documentation of demographic and health status data | x | | | | | |
| Documentation of cardiovascular medication | x | x | x | x | x | x |
| Documentation of indication for ICD/CRT-D therapy (incl. available diagnostics) | x | | | | | |
| ICD/CRT-D implantation | | x | | | | |
| Assessment of ICD/CRT-D shape | | x | | | | |
| Assessment of Plexa S DX Lead handling | | x | | | | |
| Assessment of Selectra catheter handling | | x | | | | |
| Record device based sensing, pacing threshold and impedance values | | x | x | x | x | x |
| Evaluation of system performance | | x | x | x | x | x |
| Evaluation of tachyarrythmia episodes | | x | x | x | x | x |
| Registration at HM Service Center, hand out CardioMessenger | | (x) | x | | | |
| Home Monitoring 'ON' | | x | x | x | x | (x) |
| Recording Episode IEGMs (event triggered): 'ON' | | x | x | x | x | (x) |
| Automatic LV VectorOpt test | | (x) | x | (x) | | |
| CRT AutoAdapt 'ON' (Acticor/Rivacor 7 CRT-D) | | (x) | x | (x) | (x) | (x) |

| Investigations | Enroll-ment | Implan-tation | PHD | 3-Month FU | 6-Month FU | 12-Month FU |
|---|---|---|---|---|---|---|
| Evaluation of CRT Auto Adapt Feature (Acticor/ Rivacor 7 CRT-D) | | | | x | | (x)[4] |
| AV Opt Test (VR-T DX/ DR-T/Rivacor 5 CRT-D) | | | x | (x) | | |
| Documentation of Quick Check | | | | x | x | x |
| Documentation of MPP settings (for HF-T QP) | | x | x | x | x | x |
| Documentation of MRI examination | | | x | x | x | x |
| Assessment of patient´s wearing comfort (in case of exchange) | | | | x | | |
| Evaluation of ATP statistics page | | | | | | x |
| eCRF completion | x | x | x | x | x | x |
| Provision of programmer data via ReportShare | | x | x | x | x | x |
| Adverse event and device deficiency reporting | x | x | x | x | x | x |
| Regular study termination | | | | | | x |

x=if applicable, (x)=optional

## 9.2 Enrollment

Prior to enrollment into the clinical investigation, the investigator has to check whether all inclusion criteria are met and the absence of all exclusion criteria is confirmed. For the enrollment to be valid, the informed consent form has to be signed and dated both by the patient and the investigator. The exact time of informed consent should also be noted to document that informed consent has been obtained prior to any study-specific procedure in case date of consent is identical with date of implantation.

The informed consent process has to be documented in the patient record.

The signed informed consent will be verified by a sponsor-appointed person ("Monitor").

On the Enrollment eCRF the following data have to be recorded:

- Information on informed consent process
- Check of inclusion and exclusion criteria

On the Baseline eCRF the following data have to be recorded:

- Patient demographics
- Indication for ICD or CRT-D therapy

[4] If CRT AutoAdapt feature remained 'ON' troughout the study.

- Information on cardiovascular diseases
- Comorbidities
- Current cardiovascular medication
- ECG diagnostics (if available within 3 months prior to implantation)
- For CRT-D patients: LVEF and NYHA class evaluated within 3 months prior to implantation (if available)

## 9.3 Implantation

The implantation can only be performed after enrollment of the patient. The implantation procedure will follow the clinical routine, and the instructions for use for the investigational product have to be adhered to. Please refer to section 8.1.4.3 for further details.

All patients will be implanted with one of the Acticor 7 or Rivacor 7/5 devices and patients with VR-T DX devices will additionally be implanted with a Plexa S DX with DF4 connector (65/15, 65/17).

Patients with planned upgrade from pacemaker or ICD to ICD or CRT-D or device exchange may also be included in the study.

1. Perform lead measurements via pacing sensing analyzer (any analyzer can be used but BIOTRONIK device recommended; no documentation in eCRF required)
2. Perform device-based measurements of pacing thresholds and sensing amplitudes, pacing impedances and shock impedances via Renamic programmer (see 8.1.4.15)
3. Evaluate system performance (sensing and pacing)
4. Document and evaluate tachyarrythmia episodes, if applicable (e.g. if defibrillation threshold test was performed) (see 8.1.4.16)
5. Optional at implantation: Perform Automatic LV VectorOpt Test (see 8.1.4.8)
6. Program the following mandatory device settings:
   - Home Monitoring ‘ON’
   - For CRT-D patients implanted with Acticor 7 or Rivacor 7 devices (with exception of patients with chronic complete AV block), optional at implantation: CRT AutoAdapt ‘ON’
   - Recording episode IEGMs (event-triggered) ‘ON’
7. Document current medication on the medication log (see 8.1.4.21)
8. For HF-T QP patients: Document MPP settings, if applicable (see 8.1.4.12)
9. Assess the ICD/CRT-D design (see 8.1.4.5)
10. Assess the of Plexa S DX lead handling, if applicable (see 8.1.4.6)
11. Assess the Selectra catheter handling, if applicable (see 8.1.4.7)
12. Register to Home Monitoring Service Center (optional at implantation)
13. Complete the electronic Case Report Form (eCRF) in a timely manner
14. Provide programmer data (see 8.1.4.19)
15. Report all adverse events. In case of a serious adverse event, or adverse device effect (ADE), please provide the information immediately to BIOTRONIK, and inform the ethical committee, if required. Report adverse events within the indicated timelines (see section 18.9).

## 9.4 Pre-hospital discharge

Prior to discharge from the hospital (at least 4 hours after the implantation procedure but not later than 10 days afterwards) the implanted system has to be checked again. All data obtained during the pre-hospital discharge follow-up visit (PHD) have to be recorded on the respective eCRF.

The following procedures are required.

1. Reprogram ICD settings as applicable to optimize ICD/CRT-D function
2. Perform device-based measurements of pacing thresholds and sensing amplitudes, pacing impedances and shock impedances via Renamic programmer (see 8.1.4.15)
3. Evaluate system performance (sensing and pacing)
4. Document and evaluate tachyarrythmia episodes, if applicable (see 8.1.4.16)
5. Perform Automatic LV VectorOpt Test (if not yet done at implantation) for all CRT-D patients (mandatory, see 8.1.4.8)
6. Perform AV Opt Test for all patients with VR-T DX or DR-T devices and for patients with Rivacor 5 triple-chamber devices (see 8.1.4.10)
7. Program the following mandatory device settings:
   - Home Monitoring: 'ON'
   - For CRT-D patients implanted with Acticor 7 or Rivacor 7 devices (with exception of patients with chronic complete AV block): CRT AutoAdapt 'ON'
   - Recording episode IEGMs (event-triggered): 'ON'
8. Program the following recommended device settings:
   - For patients implanted with Acticor 7 or Rivacor 7 devices: QuickCheck 'ON'
   - For patients implanted with VR-T DX devices: activate alert for 'detection of atrial monitoring episode' in HMSC
9. Document current medication on the medication log (see 8.1.4.21)
10. For HF-T QP patients: Document MPP settings, if applicable (see 8.1.4.12)
11. Document MRI examinations since implantation, if applicable (see 8.1.4.14)
12. Register to Home Monitoring Service Center and hand over the CardioMessenger, if not yet done

    The patient should be familiar with the transmission function and right placing of the CardioMessenger and has to be trained accordingly before leaving the hospital.

    In the time between the follow-up visits it is recommended to check the Home Monitoring transmission on a regular basis. If data transmission is missing, the investigator or study nurse has to contact the patient to clarify the reason for non-transmission.
13. Complete the electronic Case Report Form (eCRF) in a timely manner
14. Provide programmer data (see 8.1.4.19)
15. Report all adverse events. In case of a serious adverse event, or adverse device effect (ADE), please provide the information immediately to BIOTRONIK, and inform the

ethical committee, if required. Report adverse events within the indicated timelines (see section 18.9).

## 9.5 3-month follow-up

Three months (92 ± 30 days) after the implant procedure, the patient has to return to the hospital for assessment of the implanted system. The investigator reviews the system performance and adjusts the programmed parameters as necessary to optimize the ICD/CRT functions. The requirements of this procedure are listed below:

1. Reprogram ICD settings as applicable to optimize ICD/CRT-D function
2. Perform device-based measurements of pacing thresholds and sensing amplitudes, pacing impedances and shock impedances via Renamic programmer (see 8.1.4.15)
3. Evaluate system performance (sensing and pacing)
4. Document and evaluate tachyarrythmia episodes, if applicable (see 8.1.4.16)
5. Perform Automatic LV VectorOpt Test (if not yet done at implantation or PHD) for all CRT-D patients (mandatory, see 8.1.4.8)
6. Perform AV Opt Test (if not yet done at PHD) for all patients with VR-T DX or DR-T devices and for patients with Rivacor 5 triple-chamber devices (see 8.1.4.10)
7. Evaluate CRT AutoAdapt feature for CRT-D patients implanted with Acticor 7 or Rivacor 7 devices (see 8.1.4.9)
8. Program the following mandatory device settings:
   - Home Monitoring: 'ON'
   - Recording episode IEGMs (event-triggered): 'ON'
9. Program the following recommended device settings:
   - For patients implanted with Acticor 7 or Rivacor 7 devices: QuickCheck 'ON'
   - For patients implanted with VR-T DX devices: activate alert for 'detection of atrial monitoring episode' in HMSC
10. Document current medication on the medication log (see 8.1.4.21)
11. Document use of QuickCheck, if applicable (see 8.1.4.11)
12. For HF-T QP patients: Document MPP settings, if applicable (see 8.1.4.12)
13. Document MRI examinations since implantation, if applicable (see 8.1.4.14)
14. If the initial study implantation was a device exchange: ask the patient about their wearing comfort compared to the previous device
15. Complete the electronic Case Report Form (eCRF) in a timely manner
16. Provide programmer data (see 8.1.4.19)
17. Report all adverse events. In case of a serious adverse event, or adverse device effect (ADE), please provide the information immediately to BIOTRONIK, and inform the ethical committee, if required. Report adverse events within the indicated timelines (see section 18.9).

## 9.6 6-month follow-up and 12-month FU

Patients have to return for two more follow-up visits, six months (183 ±30 days) and twelve months (365 ±30 days) after the implantation procedure. The study procedures performed at these visits are identical with the procedures for the 3-month follow-up except for the AV delay optimization and the automatic LV VectorOpt test that don't need to be documented again. The evaluation of CRT AutoAdapt is not required at the 6-month follow-up, but should be performed at 12-month follow-up if the feature remained active throughout the study. Only at the 12-month follow-up the investigator is asked to evaluate the ATP Statistics page.

1. Reprogram ICD settings as applicable to optimize ICD/CRT-D function
2. Perform device-based measurements of pacing thresholds and sensing amplitudes, pacing impedances and shock impedances via Renamic programmer (see 8.1.4.15)
3. Evaluate system performance (sensing and pacing)
4. Document and evaluate tachyarrythmia episodes, if applicable (see 8.1.4.16)
5. Only at 12-month follow-up: Assess the ATP Statistics page, if applicable (see 8.1.4.17)
6. Only at 12-month follow-up, if feature remained 'ON' throughout the study: Evaluate CRT AutoAdapt feature for CRT-D patients implanted with Acticor 7 or Rivacor 7 devices (see 8.1.4.9)
7. Program the following mandatory device settings (only at 6-month follow-up):
   - Home Monitoring: 'ON'
   - Recording episode IEGMs (event-triggered): 'ON'

   At 12-month follow-up (study termination) the programming is at the discretion of the investigator.
8. Program the following recommended device settings:
   - For patients implanted with Acticor 7 or Rivacor 7 devices: QuickCheck 'ON'
   - For patients implanted with VR-T DX devices: activate alert for 'detection of atrial monitoring episode' in HMSC
9. Document current medication on the medication log (see 8.1.4.21)
10. Document use of QuickCheck, if applicable (see 8.1.4.11)
11. For HF-T QP patients: Document MPP settings, if applicable (see 8.1.4.12)
12. Document MRI examinations since last follow-up, if applicable (see 8.1.4.14)
13. Complete the electronic Case Report Form (eCRF) in a timely manner
14. Provide programmer data (see 8.1.4.19)
15. Report all adverse events. In case of a serious adverse event, or adverse device effect (ADE), please provide the information immediately to BIOTRONIK, and inform the ethical committee, if required. Report adverse events within the indicated timelines (see section 18.9).

## 9.7 Termination and post treatment

The patients terminate the study regularly after the completion of the 12-month follow-up. An eCRF "Study Termination" has to be filled in.

In case of any premature study termination, the eCRF "Study Termination" has to be completed with the reason for study termination. If the implantation of the investigational

devices could not be completed successfully, the reason must be provided. If the patient is lost to follow-up, the attempts to get in contact with the patient or his/her relatives have to be documented in the patient file. The process of consent withdrawal is described in section 8.3.5.3.

After study termination the patients are treated according to standard routine care. The device programming is at the investigator's discretion. No special arrangements are necessary due to the previous study participation.

## 9.8 Description of those activities performed by sponsor representative

Although sponsor representatives are not planned to take over specific study activities for the onsite patient care, they might support the investigator during the implantation or follow-up procedures as well as with the device programming, if it is part of the clinical routine. Nevertheless, it is the responsibility of the investigator and the trained study team to adhere to the study protocol. Qualified sponsor representatives from BIOTRONIK may support the investigator and study nurse in uploading or sending programmer data to BIOTRONIK as part of their general technical assistance service.

Monitoring will be performed by a sponsor representative according to the monitoring plan. The following sections will describe the responsibilities of the relevant sponsor representatives.

## 9.9 Responsibilities

### 9.9.1 Responsibilities of the sponsor

The sponsor of the BIO|MASTER.Cor Family Study is:

BIOTRONIK SE & Co. KG

Woermannkehre 1

12359 Berlin

Germany

The sponsor ensures that all documents, information and necessary human resources are made available for initiation, conduct and termination of the study.

In addition, the sponsor is obliged to fulfill the following tasks (selection of items):

- Maintaining insurance cover or indemnification of subjects in case of injury in accordance with applicable laws.
- Contracting of investigational sites and investigators, specifically determining the agreement between sponsor and the research site with respect to but not limited to the following: conducting the contract research, obligations of the sponsor / the investigational site / the investigator, fee payments of the sponsor, intellectual property and publication of research results, confidentiality, insurance coverage and compliance with applicable laws / regulations and ethical standards.
- Selection of suitable investigational sites, investigators and clinical monitors.
- Obtaining of a favorable ethics vote(s) for conduct of the clinical study.
- Obtaining approval of the involved competent authorities (if applicable).
- Responsibility for all payments and financial coverage of the study.
- Supervision of study conduct according to the legal regulatory requirements and the requirements of the CIP.
- Fulfill reporting duties of the sponsor to the ethic committees and regulatory authorities.
- Data analysis and data management.
- Performance of on-site audits as planned routine audits, on demand in case of detected non-compliances, or as preparation for an announced inspection by a Competent Authority.

- Provision of the final clinical investigation report (CIR) in accordance with applicable legal requirements and ethical principles.

#### 9.9.1.1 Project management

The clinical project manager is responsible for the following (selection of items):

- Development of the clinical investigation plan and possible amendments.
- Coordination of all study-related activities dedicated to the sponsor.
- Support of investigational sites during the study (obtaining ethic committee votes, etc.).
- Continuous information of investigational sites and clinical monitors on study progress.
- The clinical project manager is supported by other staff members of the sponsor (e.g. in-house clinical project associates, data assistants, data managers).

#### 9.9.1.2 Data Management

The data manager is responsible for the following items (selection of items):

- Development and maintenance of the clinical data management system (CDMS; iMedNet of the company MedNet Solutions Inc, Minnetonka, MN 55305 USA).
- Development of the data management plan.
- Development of the eCRF user guide.
- Data management.

#### 9.9.1.3 Biostatistician

The statistician is responsible for the following items (selection of items):

- All statistical aspects within the clinical investigation plan.
- Statistical analysis for clinical investigation report.

The statistician will be supported by other staff members of the sponsor.

#### 9.9.1.4 Monitor

The sponsor names clinical monitors for each participating investigational site prior to initiation of the respective site. Names and contact data will be provided to the investigational sites in due time. In case of changes, the investigational site will be informed by the sponsor. An adequate monitoring will be ensured by the sponsor. Monitoring will be conducted according to the SOPs of the sponsor. Responsibilities of the clinical monitors are described in section 10 of this document.

### 9.9.2 Responsibilities of the investigators

#### 9.9.2.1 Coordinating Investigator (CI)

The clinical study BIO|MASTER.Cor Family is coordinated by:

[redacted]

The responsibilities of the CI are listed in the following:

- Development and review of the clinical investigation plan.
- Procurement of the central vote of an ethics committee.
- 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 Coordinating Investigator is supported by the clinical Project Manager and other members of the sponsor.

In addition, the CI has the same rights and duties as other principal investigators.

#### 9.9.2.2 Investigator

The study shall be conducted by qualified investigators.

Rights and duties of the investigators are specified in the clinical investigation plan and are further regulated in the contract for study conduct. The principal investigator named in the study contract may share the rights and duties with investigators and other staff at the investigational sites. Nevertheless, the principal investigator retains the main responsibility for proper study conduct with respect to the following duties:

- Registration of the study to the bodies responsible for the investigational site (e.g. hospital administrative department).
- Notification to competent authority (if applicable) responsible for the investigational site.
- If required, obtaining of a positive vote of the ethics committee responsible for the investigational site.
- Adverse Event reporting according to the clinical investigation plan.
- Recruitment of suitable patients in an adequate time frame.
- Patient information and obtaining of written informed consent of the patient according to the requirements of the CIP.
- Safe and efficient use of devices.
- Inform the sponsor about new study team members before authorizing them for study related activities.
- Provide the sponsor with required documentation for assessing the qualification of study team members.
- Authorize co-investigators only after documented adequate study specific training.
- Discourage patients to consent for other interventional clinical investigations, in case the investigator is aware of such intentions beforehand. Inform the sponsor and follow the sponsor’s guidance, in case a patient has already been enrolled into another interventional clinical investigation. Obtain the sponsors permission before enrolling the patient into another interventional clinical investigation.
- Conduct of the study according to the CIP.
- Data collection and data entry in accordance with the requirements of the CIP.
- Providing supporting material, if necessary.
- Submission of safety reports and protocol deviations to ethics committee and competent authorities (if applicable).
- Support of monitoring and auditing activities.
- Confidential treatment of all study-related documents and information.

In case the principal investigator (or authorized staff) does not fulfill the requirements defined, the sponsor is entitled to exclude the respective investigational site or principal investigator from further study participation.

## 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 this time.

# 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 devices under investigation are 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 trial agreement, the clinical investigation plan, applicable laws and/or local regulations and any conditions of approval imposed by the reviewing 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 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 actively enrolling sites will have at least an initiation visit, one early monitoring visit after the first patients have been enrolled in order to detect and prevent systematic errors in study conduct or documentation, and a close-out visit. Additional monitoring visits will be conducted based on risk related criteria such as e.g. recruitment rate and documentation quality. Details on criteria for initiating monitoring visits as well as strategy and extent of source data verification are subject to a detailed monitoring plan developed by BIOTRONIK as an internal document.

Monitoring visits will assure, amongst others, that the facilities are still acceptable, that the CIP is being followed, that the EC/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.

Assessments of the study site will include but will not be limited to the following:

1. Completion and submission of the required electronic case report forms (eCRFs) and other applicable study documentation
2. Continued acceptability of the facilities
3. Adherence to the clinical investigation plan
4. Adherence to current version of ISO 14155 and applicable 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 investigational site (see section 14 and 20).

# 11 STATISTICAL CONSIDERATIONS

## 11.1 Statistical design, method and analytical procedures

To test the primary hypothesis an exact binomial tests is carried out. Additionally, an exact 2-sided 95% confidence interval will be generated.

For continuous variables descriptive statistics (mean, standard deviation, median, minimum, maximum and quartiles) will be calculated. For nominal variables absolute and relative frequencies will be calculated based on non-missing data. Ordinal variables are described similarly as continuous data (minimum, 1. quartile, median, 3. quartile, and maximum) or by absolute and relative frequencies based on non-missing data of each category.

All calculations will be carried out using validated software, e.g. SAS 9.4 © or upgrade.

Further details will be provided in the separate Statistical Analysis Plan (SAP).

## 11.2 Sample size

The sample size for the primary hypothesis is based on an exact test for binomial proportions. Thereby a SADE-free rate in the population of 98% was assumed, which yields together with the null proportion from the primary hypothesis to a sample size N=114.

Considering potential non-replaceable drop-outs after implantation, $N_{incl\ do}$ = 127 patients have to be enrolled.

## 11.3 Level of significance and the power of the study

Because of the importance of accepting a true primary alternative hypothesis in this clinical investigation of a new device family that will serve as a basis for future developments, a minimum statistical power of 95% was used for sample size calculation based on the primary hypothesis. Thereby the power saw-tooth function for binomial endpoints is always above this limit for the given or any higher sample size.

For the statistical test of the two-sided primary hypothesis, a two-sided p value less than 5% will be considered statistically significant.

## 11.4 Expected drop-out rate

It is expected that approximately 10% of the enrolled patients cannot be included in the analysis set for the primary hypothesis, e.g. due to lost-to follow-up or withdrawal of patient consent of patients without primary endpoint before the pre-specified time window, respectively. This was already considered in the sample size calculation.

## 11.5 Pass/fail criteria

The clinical investigation is deemed to be passed, if the primary Alternative Hypothesis can be accepted based on the given level of significance.

## 11.6 Provision for an interim analysis

An interim analysis is planned after the completion of the 3-month follow-ups of all enrolled patients without prior study termination and final documentation of all prior primary endpoints. After this point in time, the data for testing the primary hypothesis will not be changed until the final analysis, and thus no multiplicity adjustment is required. Analysis of all other data and endpoints is explorative, therefore no multiplicity adjustment is required, either.

On request specific data might be provided to the competent authorities. Such kind of preliminary analysis would not bias the further data because no investigator except the Coordinating Investigator will be informed about the results. Except for safety reasons, no

instruction for the further conductance of the clinical investigations will be made based on such preliminary analysis.

### 11.7 Termination criteria

As this study is part of the overall post-market clinical follow-up plan, no termination criteria are pre-defined for the study based on statistical considerations.

Criteria and procedures for suspension or premature study termination are defined in section 20.1.

### 11.8 Procedures for reporting of deviations to the statistical plan

A separate Statistical Analysis Plan will be finalized at least 3-months after CDMS-go-live and can be updated before CDMS-freeze or closure. Any deviation from the valid version of the Statistical Analysis Plan will be indicated in the Statistical Analysis Report and Clinical Investigation Report.

### 11.9 Specification of subgroups

For this clinical investigation there is no specification of subgroups in the sense that analyses will be repeated for subsets of the pre-specified analysis set. However, there are different analysis sets defined for the primary and secondary endpoints.

### 11.10 Procedure for accounting of all data for analysis

All data are entered in a CDMS by the investigators via an electronic data capture system (iMedNet, MedNet Solutions). The Home Monitoring data are stored in the BIOTRONIK Home Monitoring Service Center (HMSC). For the analysis of such data, exports from the Clinical Data Warehouse will be used, a validated pseudonymized mirror of the HMSC. Exports from these databases will be analyzed with common validated statistical software packages (e.g. SAS 9.4 or updates, SAS Institute GmbH).

### 11.11 Handling of missing, unused and spurious data

Missing or spurious data will not be imputed.

### 11.12 Exclusion of data from confirmatory data analysis

In the following cases, data are to be excluded from analysis or prevented from inclusion into analysis:

- Exclusion of patients from the analysis set of the primary hypothesis:
  - No data is allowed to be collected and included in the absence of a documented informed consent
  - Patients that are erroneously enrolled despite violation of inclusion or exclusion criteria at the time of enrollment
  - Patients without primary endpoint but premature study termination as defined for the primary endpoint are not included in the analysis set to avoid an over-estimation of the SADE-free rate.
- Exclusion of data from patients included in the analysis set of the primary hypothesis:
  - Any event occurred later than the pre-specified time window after implantation as defined for the primary endpoint.
  - SADEs will be adjudicated by an internal adjudication board, whereby the seriousness and device relatedness will be re-examined. If any amply documented external physical influence (e.g. accident, sport, twiddling) or other causative AE led to the SADE, the SADE does not contribute to the endpoint.

Details are provided in the Statistical Analysis Plan.

### 11.13 Minimum and maximum number of patients per site

To minimize site-specific bias, the maximum number of patients per investigational site will be n=24. Each investigational site is expected to implant at least 6 patients (including drop-outs).

# 12 DATA MANAGEMENT

## 12.1 Data protection

According to corresponding national laws the patient (or his or her legal representative) must declare in the Informed Consent Form (ICF) that he or she agrees to the recording of his or her medical data and their pseudonymized transfer to the sponsor, and, if necessary, to responsible Ethic Committee (EC) and Competent Authority (CA). The patient agrees that authorized personnel or designees of the sponsor and the involved EC or CA (if applicable) may gain insight in the patient file to ensure that the patient was adequately informed about the clinical investigation and that the clinical investigation plan was followed properly.

All patient-related data and information received from the clinical study will be handled confidentially. The collected data will be transmitted to the sponsor for electronic data processing, safety reporting and analysis in compliance with the data protection law. The data will be pseudonymized at the sites before transmission, without using patient initials, to ensure traceability of data, but preventing unauthorized identification of individual patients. All clinical data will be stored in a validated system environment with adequate protection against unauthorized access. Insight will be given to responsible EC and CA upon request.

All involved parties, including subcontractors, are bound to data privacy according to the applicable data protection law. All patients will be informed on all relevant regulations concerning data secrecy and data protection which are applicable for the BIO|MASTER.Cor Family study in the patient informed consent form. Specifically, all patients will be educated about their rights concerning data access, data correction, and data deletion according to applicable legislation.

The patient identification log sheet, in which the patient ID code, name, date of birth and date of informed consent is entered, will remain at the investigational sites. No copies of the patient identification log sheet will be provided for the sponsor. The patients will be informed on the fact that exact identification of the patient is only possible for the investigator.

## 12.2 Data collection

All study-relevant patient data will be documented pseudonymously in electronic case report forms (eCRF). 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 current internet browsers, there is no specific local software to support (cloud based "Software as a Service" SaaS). iMedNet supports industry standards (FDA 21 CFR Part 11 and HIPAA) and fulfills the requirements of the European GDPR.

Use of the clinical data management system (CDMS) will allow 24 hours 7 days a week access to the module. The PI as well as those co-investigators to whom the PI delegates data entry and authorization of eCRFs need to be trained on iMedNet. After appropriate documentation of the training, user access is granted. Site staff with user access will be directed to a page where they will enter their assigned user ID and password in order to access the system. Once these have been validated, there will be options for entering a new patient or new patient data into the system.

For the majority of the eCRF entries source data needs to be maintained at the site and will be collected in adequate files (e.g. patient files). The data have to be stored and shall be made available upon request in order to allow source data verification. Exceptions for which the eCRF entry can be regarded as source data are indicated in in the Monitoring Plan or at the respective section of the CIP.

## 12.3 Procedures used for data review, CDMS cleaning, and issuing and resolving data queries

After data entry into the Clinical Data Management System (CDMS), the clinical data is automatically checked with programmed quality checks. Additionally, the eCRF will be checked

against source data by clinical monitors during periodic monitoring visits as described in the Monitoring Plan. Errors, discrepancies, missing data, and entries out of range are resolved by automatically (CDMS) and manually (clinical monitor, clinical data manager) generated data queries and deviation forms.

The investigational site is obliged to answer all incoming data queries and deviation forms in due time to clarify the open issues. Corrections to the eCRF can only be done by the designated site personnel and have to be signed by an authorized investigator approving thereby the completeness and correctness of the data. The CDMS supports detailed tracking of the query process since all changes are automatically recorded in the system's audit-trail.

Clarification of all open queries is a precondition for site closure in case of premature or regular study termination.

Prior to the final data analysis, all endpoint relevant data are checked for consistency and plausibility by the biostatistician ("Blind Review").

## 12.4 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 Data Management System (CDMS). 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 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.

## 12.5 Data retention and archiving

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 CDMS closure, all eCRF data and the audit trail and other relevant CDMS content are exported and stored electronically for at least 15 years on the archive server.

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.

All relevant study related documents have to be stored in the Investigator Site File. Documents containing patient's data, raw data and other study related documents have to be archived in the investigational site. In case of electronic source data (e.g. electronic patient files) adequate actions have to be taken to ensure data availability during the whole archiving period.

# 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 Investigator. All principal investigators have to acknowledge the receipt of an amendment by either signing the CIP acknowledgement page which is part of the CIP, or by signing the amendment agreement form if no new CIP version was created.

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.

# 14 DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

## 14.1 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 and applicable laws, 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.

**No waivers** from the CIP are allowed.

## 14.2 Recording, reporting and analyzing deviations

All deviations are recorded and reported electronically in the CDMS system iMedNet. If the eCRF logic has detected a CIP deviation based on the data entry, deviation forms are triggered automatically by iMedNet. Additionally, deviation forms can be created manually via iMedNet by the site or by the sponsor personnel.

### 14.2.1 Site specific deviations

Investigational sites are obliged to record any deviation immediately 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 assessed for the need of corrective or preventive actions.

### 14.2.2 Other deviations

Deviations by sponsor personnel or third parties shall be reported immediately to the sponsor by anyone who becomes aware of it. They are recorded in the deviation log BIOTRONIK personnel/Third parties, 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.

## 14.4 Actions

Actions are taken in order to repair or to avoid any negative consequences caused by a deviation. Furthermore, 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 report 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 in iMedNet or in the corresponding deviation log BIOTRONIK personnel/Third parties, and later 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.

# 15 DEVICE ACCOUNTABILITY

All devices used in this clinical study carry a CE mark and will be used within their intended use. Therefore special device accountability procedures are not applicable. However, the implanted Cor Family ICDs and Plexa S DX leads are identifiable by a unique serial number. This number will be recorded on the respective eCRF at implantation or in case of device/lead exchanges in the course of the study**.** By need or at least at the end of the study, a list with all used devices will be created.

# 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). Each step in the clinical investigation, from the initial consideration of the need and justification for the study to the publication of the results, if any, will be carried out in accordance with recognized ethical principles.

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* "Clinical investigation of devices for human subjects – Good clinical practice".

In deviation to ISO 14155:2011, no dedicated Investigator's Brochure is provided, because the investigational device will only be implanted after CE approval, and therefore the Instructions for Use (IFU) are considered as sufficient.

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

## 16.3 Ethics committee and competent authority

The study will not begin at an investigational 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.

# 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. Special attention has to be paid to the individual information needs of the patient, and the appropriate methods used for the interview. The investigator has to verify that the patient has understood all information. The patient is given adequate time to consider his or her decision to participate in the clinical investigation.

When the patient agrees in the study participation, the patient personally writes the date and time and signs on the informed consent form. Afterwards, the investigator who performed the informed consent discussion writes the date and signs on the informed consent form. Both parties should sign on the same day. By signing the informed consent form, the patient is included in the study. Pre-screening of the patient chart in respect to the inclusion and exclusion criteria is not a study specific procedure.

Date and time of the informed consent discussion as well as date of patient's signature of the informed consent form should be documented in patient's medical record. A copy of the signed and dated written informed consent form is provided to the patient. Both signatures need to be obtained before any study related procedure. 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.

If the patient is unable to write, consent may be given and recorded through appropriate alternative means in the presence of at least one impartial witness, who then signs and dates the informed consent form.

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.

Each informed consent form contains the emergency contact details for the respective principal investigator.

# 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 eCRF pages provided within the clinical data management system (CDMS) iMedNet. 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 device. This includes:

- Events related to the investigational 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 devices.

*see ISO 14155 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 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 ISO 14155 3.1

### 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 AE 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 device or procedures and the sponsor will review the investigators categorization:

***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 where 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 be 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 adverse events related to the investigational device and those related to the device procedures (any procedure specific to the investigational device). Procedure related events refers to the procedure related to the application of the investigational 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.

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.

## 18.3 Definition of device deficiency

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

*see ISO 14155 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
- 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 ISO 14155 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.

18.4.1 Patient death

If the death of a patient emerges during the study this SAE might be subject to special reporting requirements in some countries. Therefore as much information as possible should be provided to enable BIOTRONIK to explain the circumstances leading to the death. At least a pseudonymized copy of the death records, an autopsy report (if performed) and a doctor's letter detailing the medical history and the circumstances of the death should be sent to BIOTRONIK promptly.

On the AE-CRF, the following information should be provided, if available:

- Cause of death
- Date and time of death
- Place death occurred
- Device status at the time of death
- Statement whether the event was device or study procedure related

In addition to the adverse event eCRF a study termination form has to be completed.

Whenever possible, devices that are explanted must be returned to BIOTRONIK SE & Co. KG for analysis.

## 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 ISO 14155 3.36

18.5.1 Definition of endpoint-related SADEs

The SADE-free rate calculated for the primary endpoint will be based on the total number of subjects with at least one SADE related to a Cor Family ICD until 3-month follow-up. SADEs that occur later than the 3-month follow-up, and SADEs with onset date later than or exactly at 123 days after implantation in case the 3-month follow-up was not conducted or conducted outside the specified time interval do not contribute to this endpoint.

However, SADEs until the 12-month follow-up will contribute to secondary endpoint 1.

Endpoint-related SADEs are complications, which are device-related adverse events that are corrected using invasive measures or require invasive measures to correct or which result in the loss of significant device function. Device-related adverse events, which are corrected by non-invasive measures (e.g. reprogramming) are considered observations and will not contribute to the primary endpoints.

Only SADEs directly related to the device (SADE-d) will be included in the endpoint. SADEs which are securely related to the implantation procedure (SADE-p) (e.g. pocket infection, etc.) will not be considered for the primary endpoint. Inappropriate ICD therapies which are not related to a device defect (e.g. if the device function is according to device specification) will also not be considered for primary endpoint analysis. Furthermore 'Twiddler's' syndrome will not be considered for the endpoint analysis. If any amply documented external physical influence (e.g. accident, sport, twiddling) or medical AE caused the SADE, it does not contribute to this endpoint.

All serious adverse device effects that meet these primary endpoint criteria (confirmed by an internal endpoint committee) for the Cor Family ICDs will be included in the primary endpoint event analysis. Adverse events with a device relation of "not related" will not contribute to or be included in the evaluation of the primary safety endpoint.

## 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 ISO 14155 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

The following AEs may possibly occur as medical complications of an ICD or CRT system implantation. The most common AEs related to the ICD and CRT therapy are listed in Table 6 as sorted by their incidence rates. For all references used for this chapter, refer to the list at the end of this section.

**Table 6: Anticipated AEs based on literature research sorted by incidence rate**

| Frequency | Event Type | Reference ID |
|---|---|---|
| **Very frequent**<br>>1 out of 10 patients | Extracardiac stimulation (due to LV lead or unspecified lead) | 21, 22, 23, 24, 25, 27, 29, 30, 32, 37, 39, 42, 43, 49, 60, 63, 73, 74, 75, 93 |
| | Contrast nephropathy/transient creatinine increase | 39, 40 |
| **Frequent**<br>1 to 10 patients out of 100 | Lead dislodgement (overall, lead not specified) | 1, 2, 12, 14, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 33, 36, 37, 38, 39, 42, 43, 45, 46, 48, 51, 53, 57, 60, 61, 63, 65, 77, 83, 87 |
| | Lead dislodgement (RA-lead) | 23, 24, 26, 37, 39, 45, 46, 60, 73, 75, 76 |
| | Lead dislodgement (RV-lead) | 1, 2, 7, 12, 14, 26, 37, 39, 45, 46, 53, 60, 73, 75, 76 |
| | Lead dislodgement (LV-lead) | 21, 23, 24, 27, 28, 37, 39, 42, 43, 45, 53, 60, 63, 73, 74, 93 |
| | Elevated/High pacing threshold (LV) | 21, 60, 73, 74, 75 |
| | Lead malfunction (unspecified) | 6, 9, 14, 45 |
| | Loss of capture (RA) | 54 |
| | Loss of capture (RV) | 7, 12, 54, 60, 75 |
| | Loss of capture (LV) | 32, 54, 73, 74, 75 |
| | Implant failed (LV-lead) | 42, 63, 73 |
| | Inappropriate ICD therapy/shock | 26, 31, 34, 35, 58, 60, 73 |
| | Dissection/perforation (venous, coronary sinus) | 21, 28, 29, 30, 36, 41, 49, 52, 53, 57, 65, 73, 75, 93 |
| | Pain (pocket/wound) | 51, 60, 73, 75, 76 |

| Frequency | Event Type | Reference ID |
|---|---|---|
| | Hematoma (pocket) | 15, 22, 24, 26, 28, 29, 31, 36, 37, 39, 44, 46, 47, 49, 50, 51, 52, 53, 55, 57, 59, 60, 61, 65, 73, 75, 76, 77, 83, 87, 88, 93 |
| | Infection (wound/device) | 12, 14, 22, 23, 24, 25, 26, 31, 46, 49, 57, 60, 61, 77, 78, 93 |
| | Pneumothorax | 1, 15, 22, 24, 25, 28, 36, 37, 39, 42, 46, 47, 49, 50, 51, 53, 56, 59, 60, 61, 65, 73, 75, 77, 79, 81, 86, 87, 90, 93 |
| | Pericardial effusion | 17, 30, 31, 49, 60 |
| | Bleeding/Hemorrage (peri-/post-op) | 25, 60, 73, 79, 86 |
| | Endocarditis | 18, 22, 25, 61, 78, 82 |
| | Pericarditis | 17, 32, 61, 89 |
| | Thrombosis (implant/procedure related) | 23, 61, 73, 76 |
| **Occasionally**<br>1 to 10 patients out of 1.000 | Elevated/High pacing threshold (RA) | 60, 73, 75, 76 |
| | Elevated/High pacing threshold (RV) | 60, 73, 75 |
| | Shock impedance out of spec. | 7, 12 |
| | Sensing issue (undersensing, loss of sensing) | 5, 7, 12, 32, 76 |
| | Sensing issue (oversensing) | 7, 9, 22, 32 |
| | Lead fracture | 3, 6, 7, 9, 29, 42, 60 |
| | Lead insulation defect | 7, 9, 60 |
| | Lead connection failure | 37, 50, 51, 73 |
| | Pulse generator failure | 61, 75, 76 |
| | Perforation (cardiac/myocardial) | 1, 5, 7, 15, 21, 25, 30, 31, 37, 45, 50, 51, 65, 73, 74, 75, 76, 77, 81, 83, 86, 93 |
| | Tamponade (cardiac, pericardial) | 17, 26, 29, 37, 39, 44, 47, 52, 57, 59, 65, 77 |
| | Pulmonary edema | 24, 41, 49 |
| | Pulmonary embolism (device/implant related) | 28, 61, 75, 76, 90, 92 |
| | Erosion, extrusion (device, lead) | 12, 25, 37, 42, 61, 75, 76 |
| | Device migration | 24, 42, 60, 75 |
| | DFT unsuccessful/failure to convert (procedure related) | 39, 60 |
| | Cardiac arrest or VT/VF (procedure related) | 52, 65, 77 |
| | Drug reaction/allergic reaction (procedure related) | 15, 65, 73, 77 |

| Frequency | Event Type | Reference ID |
|---|---|---|
| | Twiddler's syndrome | 73, 75, 76 |
| **Rare**<br>1 to 10 patients out of 10.000 | Device failure to detect arrhythmia (VT/VF) | 12 |
| | Embolus (peripheral) | 1, 15, 65, 77 |
| | Hemothorax | 1, 15, 24, 25, 30, 65, 77, 87 |
| | Myocardial infarction (procedure related) | 15, 65, 77 |
| | Ischemic attack or stroke (transient, procedure related) | 15, 65, 77, 83 |
| | Phlebitis (deep or superficial) | 65, 77 |
| | Mortality (procedure related) | 14, 50, 59 |
| **Very rare**<br><1 patient out of 10.000 | Arteriovenous fistula | 65, 77 |
| | Cardiac valve injury | 15, 19, 65 |
| **Not known**<br>Frequency not assessable on the basis of the available data | Misplacement of lead | 11 |
| | Injury due to implantation accessories | 67, 68 |
| | Perforation (arterial) | 29, 52 |
| | Premature battery depletion | 31 |
| | Wound healing impaired | 25, 76 |
| | Surgery discontinued for hemodynamic reasons | 14 |
| | High x-ray load due to extended fluoroscopy times | 69 |
| | Pleural effusion | 22 |
| | Pneumopericardium | 72 |
| | Pneumonia (peri-implant) | 24 |
| | Respiratory arrest/distress (procedure related) | 52, 73 |
| | Peripheral nerve damage/injury | 15, 65, 77 |
| | Implant issue (venous access problem) | 46 |
| | Subclavian vein occlusion | 70 |
| | Coronary sinus occlusion | 71 |
| | Obstruction of V. cava superior | 13 |
| | Regurgitation, tricuspid valve (implant related) | 10, 61 |
| | Arrhythmia (device/implant related) | 38, 73 |
| | Conduction block (procedure related) | 39, 65 |

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## 18.8 Reporting responsibilities

18.8.1 Reporting responsibilities of the investigator to sponsor

The investigator shall document all events on the respective eCRF pages provided within the CDMS. The indicated timelines for reporting of initial cases and possible update reports shall be strictly followed (see 18.9).

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

For device deficiencies of the investigational device, a DD-eCRF 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 prematurely or until the event has been resolved, whatever comes first. Ongoing SADEs related to the investigational device will be followed for a maximum time period of either 4 weeks after pre-mature or regular study termination of the individual patient. This also applies to Adverse Events involving the explantation or replacement of an investigational device, heart transplantation or implanation of a ventricular assist device. This follow-up period is reduced if 'Last Patient Out' is announced in the study. All follow-ups on open adverse events will stop at this point in time at the latest.

Multiple events may occur simultaneously in one subject. For each medically independent event 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 this might be subject to special reporting requirements in some countries. Therefore as much information as possible should be provided to enable BIOTRONIK to explain the circumstances leading to the death. At least a pseudonymized copy of the death records and an autopsy report (if performed) should be sent to BIOTRONIK promptly. 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

According to national and international regulations some of the involved competent authorities (CAs) and ethics committees define specific safety reporting requirements. Investigators have to ensure, that they fulfil these local reporting obligations given by their competent authorities and ECs, in case they are more restrictive than the general requirements stated in the section reporting timelines below.

18.8.3 Reporting responsibilities of the sponsor

BIOTRONIK SE & Co. KG will report all serious Adverse Events (SAEs)/Serious Adverse Device Effects (SADE) and all Device Deficiencies with an 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 an 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

The reporting timelines for the investigator are displayed in Table 7.

**Table 7: Reporting timelines**

| Event | Report to | Timeline |
|---|---|---|
| Adverse Event (AE)/ Adverse Device Effect (ADE) | CCR BIOTRONIK SE & Co. KG: Documentation in the AE CRF | Preferably within 14 days |
| 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 |
| Device Deficiencies | CCR BIOTRONIK SE & Co. KG: Documentation in the DD-CRF | Preferably within 14 days |
| Device Deficiency with SADE potential | CCR BIOTRONIK SE & Co. KG: Documentation in DD-CRF | Within 24 hours |

The obligation to assess and report SA(D)Es and Serious Device Deficiencies to the sponsor without unjustified delay is an important part of the Principal Investigator's responsibilities as defined by ISO 14155:2011. This obligation is not restricted to scheduled patient follow-ups according to the CIP, but it is a continuous responsibility for the duration of the study, making sure that any unexpected risks originating from the study procedures or the investigational product are identified as soon as possible and patients are adequately protected. The Principal Investigator is responsible to set up appropriate workflows at his/her site, making sure that:

- the site study team is continuously informed on any relevant interactions or interventions concerning study patients at the site, regardless if members of the study team are directly involved or not;
- if the site is part of a larger organizational structure - e.g. a multi-faculty-hospital - a notification system is in place, making sure that other departments/clinics are aware of the patient's study participation and that relevant events, such as hospitalizations, are notified to the site study team without delay;
- if information on relevant events from external sources reaches the site (e.g. medical reports from other facilities), these are made available to the study team without delay.

Please note that in this context the site is defined as the organizational unit (e.g. a hospital or a department/clinic within a multi-faculty-hospital), which serves as BIOTRONIK's contract partner for the study. Information that is part of the medical records hosted by the site is considered as known to the study team and subject to reporting.

## 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: [redacted].

# 19 VULNERABLE POPULATION

There are no health needs or clinical priorities for vulnerable populations which would justify the participation of these populations. Only legally competent patients shall be enrolled in this clinical investigation. Patients aged less than 18 years, pregnant or breast-feeding women and patients which are not able to understand the nature of the clinical investigation are excluded (see 8.3.2 and 8.3.3). Therefore no provisions for vulnerable patients have to be arranged.

# 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
- On behalf of the 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 arms, 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.
- In case that the number of drop-outs is lower than expected, enrollment can be stopped earlier as soon as 114 patients are included in the analysis set of the primary endpoint. Patients are included in the analysis set if they completed at least 61 days after implantation in the study or if they experienced a primary endpoint before that date.
- Insufficient enrollment rates so that proper completion of the study cannot be expected anymore.
- Results from other clinical investigation 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 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 EC and all enrolled patients of this decision.

If the 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.

## 20.2 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 EC decision, additional requirements from the EC with respect to follow-up and data collection may apply.

If an (S)A(D)E is ongoing at time of the last study related visit or study termination, whatever comes first, the outcome of the event has to be updated to 'Ongoing at study termination'. Ongoing SADEs related to the investigational device will be followed for a maximum time period of either 4 weeks after pre-mature 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. This follow-up period is reduced if 'Last Patient Out' is announced in the study. All follow-ups on open adverse events will stop at this point in time at the latest. Patients have to be informed on this procedure in written form in the patient informed consent form.

# 21 PUBLICATION POLICY

## 21.1 Decision for publication

The study will be registered in a publicly accessible database (e.g. clinicaltrials.gov).

All furthers decisions on publications will be made by the Publication Team, consisting of the Coordinating Investigator and member(s) of BIOTRONIK. In accordance with the good publication practice guidelines, it is generally planned to publish the study results also in case of negative findings. It is currently planned to submit at least an abstract to a congress OR a manuscript within 6 months after finalization of the clinical investigational report.

In case of realizing publications, the rights in regard to publication of the main results of the study, i.e. regarding the primary and secondary endpoints, belong to the Coordinating Investigator. The manuscripts and abstracts will be reviewed and approved by the Coordinating Investigator, all authors and BIOTRONIK.

## 21.2 Authorship guidelines

### 21.2.1 Purpose and validity

Purpose of this authorship guideline is to settle criteria which of the contributors to a publication should be identified as authors. It is valid for all contributors to a publication, including investigators, sponsor employees, and individuals contracted by the sponsor. All authors of a publication must fulfil authorship criteria listed below.

If the authorship criteria of the journal or the congress differ from these guidelines, the requirements of the journal or congress are to be respected.

### 21.2.2 Authorship criteria

Following the International Committee of Medical Journal Editors (ICMJE), authorship credit should be based on all of the following conditions:

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data,
2. drafting the article or revising it critically for important intellectual content, and
3. final approval of the version to be published.

The Publication Team will assure a fair assessment of the contribution of all potential authors. Especially, the Publication Team will weigh the contribution to the study data, the membership on committees or boards, and the contribution to the publication idea and content of all potential authors.

For acquisition of data, the following scoring system is valid:

- 1/2 point for each enrolled patients, plus
- 1 additional point for each patient, who is included in the data set for the analysis of the primary endpoint, plus
- 1 additional point for each patient with a complete and fully compliant data set until regular study termination according to the clinical investigational plan

### 21.2.3 Authors' tasks and responsibilities

This will include but may not necessarily be limited to the following:

First author:

- Guarantor for the integrity of the study and its publication
- Lead for writing and managing the publication
- Submit the publication to allocated reviewers (co-authors, BIOTRONIK etc.) according to the publication plan
- Preparation and submission of the publication according to timelines, defined in the publication plan
- Adaptation of the manuscript, based on Journal reviewer feedback
- Disclose potential conflicts of interest

Co-authors:

- Assist the first author in planning and writing the publication, if needed
- Review of the publication and give feedback within the determined time window
- Agree on the order in which they appear in the publication
- Agree on any changes in authorship
- Disclose potential conflicts of interest

#### 21.2.4 Authorship of primary and ancillary publications

First authorship of the primary publication will be offered to the Coordinating Investigator. Investigators with the highest score will be considered for remaining positions.

The authorship of ancillary publications will be based on contribution to conception and design of the publication, analysis and interpretation of data, the score, and authorship on previous publications.

#### 21.2.5 Timelines and compliance

The publication plan gives a detailed overview of timelines for preparation and submission of publications. If the first author will not provide a manuscript within appropriate time after a reminder, a co-author may be invited to become first author.

The Publication Team will ensure that authorship guidelines are met and authorship is attributed appropriately. The Publication Team will also track timeline adherence.

#### 21.2.6 Reimbursement

No honoraria will be paid for authorship of publications.

### 21.3 Contributorship and acknowledgement

Individuals, including BIOTRONIK employees, who have substantially contributed to a study, but who do not meet the authorship criteria, should be listed in the acknowledgement section. Any support provided by a professional medical writer must also be disclosed in the acknowledgement section.

### 21.4 Ancillary publications

Ancillary publications are publications in addition to the primary publication. All study stakeholders (e.g. participating investigators, BIOTRONIK employees) may submit publication ideas through the Coordinating Investigator.

The Publication Team must approve ancillary requests and will need to ensure, that these publications do not present conflicts with other previously submitted requests. Requests for ancillary publications will be evaluated for scientific validity and the ability of BIOTRONIK to

provide resources. All manuscripts and abstracts will be reviewed and approved by the Coordinating Investigator, all authors and BIOTRONIK.

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