Clinical Investigation Plan

for the

BIO|MASTER.Ilivia Family / Plexa

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List of principal investigators, investigation sites, and institutions

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

TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Association
AIMD	Active implantable medical device
ASADE	Anticipated serious adverse device effects
ATM	Automatic Threshold Monitoring
ATP	Antitachycardiac Pacing
BiV	Bi-Ventricular
BP	Bipolar
CA	Competent Authority
CCI	Coordinating Clinical Investigator
CCR	Center for Clinical Research; BIOTRONIK SE & CO. KG study department
CDMS	Clinical Data Management System
CE	CE mark, a stylized "CE" (Conformité Européenne) placed on products to signify conformance with European Union regulations
CIP	Clinical Investigation Plan
cm	centimeter
CRA	Clinical Research Associate
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy Defibrillator
DD	Device Deficiency
DE	ISO Country Code for Germany
DR-T	Dual chamber device with telemonitoring function
DX	**D**iagnostic e**X**tension
DXA	Dexamethasone Acetate
EC	Ethic Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FDA	US Food and Drug Administration (www.fda.gov)
FPI	First Patient In
FU	Follow-up
GCP	Good Clinical Practice
HF	Heart Failure
HF-T	Triple chamber ICD with Home Monitoring functionality (automatic remote monitoring system)
HF-T QP	Triple chamber ICD with Home Monitoring functionality and IS4 connector
HIPAA	Health Insurance Portability and Accountability Act
HM	Home Monitoring
HMSC	Home Monitoring Service Center
HRS	Heart Rhythm Society

IB	Investigator's Brochure
ICD	Implantable Cardioverter Defibrillator
ID	Identification Number
IFU	Instructions for Use
IRB	Institutional Review Board
ISO14155	International Organization for Standardization, norm no. 14155
LPI	Last Patient In
LPO	Last Patient Out
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MEC	Main Ethic Committee
MedNet	Supplier of Clinical Data Management Software (MedNet Solutions, Inc. www.mednetstudy.com)
MPP	MultiPole Pacing, Multipoint pacing
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
ms	Millisecond
NYHA	New York Heart Association
OTW	Over-the-wire
PHD	Pre-hospital Discharge
PI	Principal Investigator
PNS	Phrenic nerve stimulation
PSA	Pacing Sensing Analyzer
QP	Quadripolar
QRS	Electrical complex on an ECG related to the depolarization of the ventricles
RA	Right Atrium
RV	Right Ventricle
SaaS	Software as a Service
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SVC	Superior Vena Cava
SW	Software
TRUST	The Lumos-T Reduces Routine Office Device Follow-Up Study
USADE	Unanticipated Serious Adverse Device Effect
USB	Universal Serial Bus
VF	Ventricular Fibrillation
Vp	Ventricular Pacing Events
VR-T	Single chamber device with telemonitoring function
Vs	Ventricular Sensing Events
VT	Ventricular Tachycardia
VTA	Ventricular Tachyarrhythmia

2 SYNOPSIS

Title	BIO|MASTER.Ilivia Family / Plexa
Patient population	Patients with indication for ICD or CRT-D therapy according to standard clinical practice
Design	Multicenter, international, prospective, open, non-controlled, non-randomized
Investigational device(s)	Ilivia ICD family (**Group A**) Plexa ICD lead (**Group B**)
Objectives	To identify and evaluate residual risks associated with the use of the Ilivia ICD family and the Plexa ICD lead that are unveiled or remained even after risk analysis, risk mitigation and successful conformity assessment
Primary endpoint	**Group A:** • Ilivia family related SADE-free rate through 3 months **Group B:** • Plexa related SADE-free rate through 3 months
Secondary endpoint(s)	**Group A:** • Percentage of patients with successful fast ventricular arrhythmia conversion by ATP one-shot at 6-month follow-up **Group B:** • Rate of appropriate right ventricular sensing at 3-month follow-up • Rate of appropriate right ventricular pacing at 3-month follow-up
Inclusion criteria	• Standard indication for ICD or CRT-D therapy according to clinical practice • *De novo* implantation or upgrade/exchange (**group A** only) from existing ICD, CRT-D or pacemaker implant • Patient is able to understand the nature of the clinical investigation and provides written informed consent • Patient is able and willing to complete all routine study visits at the investigational site

	• Patient accepts Home Monitoring concept • Age ≥ 18 years
Exclusion criteria	• Contraindication to ICD or CRT-D therapy, respectively • For CRT-D patients in **group A** only: physician not willing to activate MultiPole Pacing in the patient • Cardiac surgical procedure planned within 6 months after implantation (including also interventional procedures like ablation, valve replacement etc.). Procedures to occur during or prior to implantation are not exclusionary. • Expected to receive heart transplant or ventricular assist device within 6 months • Life expectancy less than 6 months • Participation in any other interventional clinical investigation • Pregnant or breastfeeding at time of enrollment
Sample Size	up to 290 patients (**Group A**: 105 pts.; **Group B**: 185 pts.)
Investigational sites	~ 30
Study duration	~ June 2016 – Jan 2018 (~ 20 months)
Number of follow-ups per patient	5
Follow-up scheme	Enrollment – Implantation – PHD – 3 Month – 6 Month - Termination
Coordinating Clinical Investigator	Prof. Dr. Christian Sticherling
Sponsor	BIOTRONIK SE & Co.KG Woermannkehre 1 12359 Berlin, Germany

3 INTRODUCTION

Implantable cardioverter defibrillators (ICD) are a common therapy approach to improve the survival of patients at risk of sudden cardiac death[1] 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 if 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. Still, the PainFREE Rx[2] and PainFREE Rx II[3] studies have shown that in 77%[2] and 72%[3] of cases, a single attempt of ATP delivery is sufficient to stop a VTA episode detected in the VF zone (> 188 bpm), thus prevents the patient from experiencing a shock. These studies used a certain ATP form (burst with 8 pulses delivered at 88% of the VTA cycle length), which was thus shown to be highly effective to terminate fast VTA[3].

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[4].

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 patients[5], [6]. Furthermore, inappropriate shocks frequently result from supraventricular tachyarrhythmias such as sinus tachycardia, atrial fibrillation or atrial flutter[7-9], 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%; $p<0.02$)[9]. 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[10;11]. 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[12].

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[13]. CHF is a major public health issue with a current prevalence of 2-3% in the total and 10-20% in the aged population[14]. 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[15].

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 dyssynchrony (QRS width ≥120 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%)[15;16].

CRT-D devices are normally implanted with 3 leads stimulating the right atrium and the right and left ventricle. However, in a proportion of patients, for example in those with permanent AF, physicians decide to not implant the atrial lead. Gasparini et al. discuss that in patients, in whom an atrial lead was not implanted, a subsequent implantation of an atrial lead might be required, which would be an additional surgical risk [17]. However, it is also recognized that implanting all patients with permanent AF with an atrial lead may be considered as an unnecessary increase in lead burden[17].

In fact, the implantation of three leads in a CRT candidate increases the risk of complications, such as early lead dislodgement, lead infections and venous stenosis compared to implantation of only 2 leads[18-20]. Nery et al. demonstrated a "dose response effect" of the number of leads as each lead added to a system increased the risk of cardiac device infection[21]. Atrial lead dislodgement occurs in around 1% of CRT patients [18;22]. Ideally, one would like to reduce the number of leads in CRT without sacrificing atrial information, if the atrial lead is not needed for stimulation. DX leads in combination with the HF-T devices of the Ilivia ICD family enable the monitoring of the atrial activity via the right ventricular lead without the implantation of an atrial lead.

Multisite Pacing

Despite the proven benefit of cardiac resynchronization therapy in the total population with an accepted indication, some individuals in this population do not profit. The number of non-responders remains quite high[23;24]. Currently around 30 % of patients[24] do not respond to the therapy, i.e. they do not improve clinical parameters like LV remodeling or LVEF improvement. A common cause of non-responsiveness is that the left ventricle is not fully resynchronized[23].

Many approaches have been started to reduce the rate of non-responders to CRT therapy. This includes the use of quadripolar electrodes, which offer a choice of pacing vectors and thus allow optimizing the stimulation success. Based on the same technology, a further approach is to use more than one LV stimulation site parallel (multisite pacing)[24]. Studies have shown that within 12 months the rate of non-responders can be reduced by left ventricular pacing via two stimulation vectors from 43% (conventional pacing) to 24%. Furthermore the number of super-responders is increased by multisite pacing compared to the conventional biventricular pacing[25]. Also the individual benefit of patients is increased, which can be shown by a higher increase in LVEF (10.5% vs. 5.3%), in stroke volume (10.4% vs. 4.1%), in the pressure change (15.9% vs. 13.5%) and further parameters compared to conventional bipolar pacing[26-28]. A significant reduction of endsystolic volume and ejection fraction increase could be shown 12 months after implantation [25].

Aims of this study

Besides the standard ICD/CRT-D function, the medical products under investigation, the Ilivia ICD family and the Plexa right ventricular ICD lead, offer a broad spectrum of features, including the new ATP cycle length of 88%, MultiPole Pacing (MPP) (= multisite pacing) in CRT devices when connected to a quadripolar lead and atrial sensing via the right ventricular lead in ICDs and CRT-Ds. This study is designed to provide post-market data and supporting data of the new ICD family and the Plexa ICD lead for regulatory approval outside the CE region.

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 Ilivia ICD family and the Plexa ICD lead.

The ICDs/CRT-Ds of the Ilivia 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.

The Plexa ICD lead is intended for implantation in the right ventricle to deliver ATP and shock therapies during ventricular tachycardia. Furthermore the lead provides sensing and pacing in the right ventricle, and sensing in the right atrium for the Plexa ICD DX lead. The Plexa leads are available as DF4 and DF-1 variants.

In the following text, the investigational devices listed above are referred to as *Ilivia ICD family* and *Plexa ICD lead*, unless otherwise stated.

4.2 Manufacturer

The manufacturer of the Ilivia ICD family and the Plexa 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

The devices undergoing clinical investigation are the following BIOTRONIK devices:

Ilivia ICD family (**group A**):

- Ilivia 7 VR-T, VR-T DX, DR-T, HF-T QP
- Intica 7 VR-T, VR-T DX, DR-T, HF-T QP
- Inlexa 7 VR-T, VR-T DX, DR-T, HF-T QP
- Intica 5 VR-T, VR-T DX, DR-T

Plexa ICD lead (**group B**):

- Plexa S, SD
- Plexa DF-1 S, SD, S DX

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

Group A:

- Any commercially available ICD lead (Plexa ICD lead types recommended)

- For CRT-D: The Sentus OTW QP left ventricular lead
- Any commercially available bipolar atrial lead providing IS-1 connection, preferably a BIOTRONIK lead.
- BIOTRONIK accessories are recommended

Group B:

- Any commercially available BIOTRONIK ICD or CRT-D device (Ilivia ICD family recommended)
- For CRT-D: Any commercially available LV lead, preferably a BIOTRONIK lead. If a HF-T QP device is implanted, Sentus OTW QP lead is recommended
- 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).
- BIOTRONIK accessories are recommended

All groups:

- BIOTRONIK Renamic
- BIOTRONIK programmer software SW 1505.A and subsequent versions
- BIOTRONIK CardioMessenger II, II-S or successor devices
- BIOTRONIK Home Monitoring Service Center (HMSC) 3.0 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 and every Plexa ICD 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 study data base enabling to create a list with all used devices within the study.

4.5 Intended purpose of the device in the study

Ilivia ICD family (group A)

The Ilivia/Intica/Inlexa is a family of implantable cardiac defibrillators. The primary objective of the therapy is to prevent sudden cardiac death. Furthermore, the device is capable of treating bradycardia arrhythmias and to provide cardiac resynchronization therapy with multisite ventricular pacing. The implantation of the ICD is a symptomatic therapy with the following objective (intended use):

- Termination of spontaneous ventricular fibrillation (VF) through shock delivery
- Termination of spontaneous ventricular tachycardia (VT) through antitachycardiac pacing (ATP); in case of ineffective ATP or hemodynamically not tolerated VT, 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); however, the VR-T DX device and the HF-T QP devices with DX functionality are only indicated for patients not requiring atrial pacing

Plexa ICD lead (group B)

In combination with a compatible ICD, Plexa ICD leads are intended for the following (intended use and indication):

- Permanent pacing and sensing in the right ventricle
- Delivery of defibrillation/cardioversion therapies
- Permanent sensing in the right atrium (Plexa DF-1 S DX leads only)

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).

4.6 Intended patient population and indications

4.6.1 Intended patient population for Ilivia ICD family (group A)

The Ilivia ICD family is 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).

Indications

Ilivia/Intica/Inlexa single-chamber and dual-chamber ICDs are indicated for patients with the following risk:

- Sudden cardiac death caused by ventricular arrhythmias

Ilivia/Intica/Inlexa 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
- Such frequent VT or VF that the therapies would cause an unacceptably rapid depletion of the device batteries

- VT with few or without 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 ICD lead (group B)

The indications and contraindications for the Plexa ICD lead are similar to those of the respective ICD. The implanting surgeon is responsible for choosing the lead type, fixation and length variants. 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.

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

Indications:

In combination with a compatible ICD, Plexa ICD leads are intended for the following (intended use and indication):

- Permanent pacing and sensing in the right ventricle
- Permanent sensing in the right atrium (Plexa DF-1 S DX leads only)
- 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).

Contraindications:

The use of Plexa SD and Plexa S is contraindicated in patients with:

- Mechanical tricuspid heart valves or severe tricuspid valve disease
- Intolerance against dexamethasone acetate

In addition the use of the Plexa DF-1 S DX lead is contraindicated in patients with:

- Sick sinus syndrome
- Unsuitable atrium anatomy (e.g. following partial resection of the atrium)

4.7 Description of the investigational device

4.7.1 Ilivia ICD family

The Ilivia/Intica/Inlexa ICD family includes the following devices:

- Ilivia 7 VR-T, VR-T DX, DR-T and HF-T QP
- Intica 7 VR-T, VR-T DX, DR-T and HF-T QP
- Intica 5 VR-T, VR-T DX, DR-T
- Inlexa 7 VR-T, VR-T DX, DR-T and HF-T QP

Further models are available but are not part of this clinical investigation.

Ilivia and Intica devices are available as ProMRI versions only. The Inlexa series is also identical to the Ilivia and Intica devices, but in contrast the Inlexa series is available as non-ProMRI labelled version 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" and triple chamber devices that support the IS4 standard for the LV lead, will have the suffix "HF-T QP" (see figure 1). Triple chamber HF-T QP devices have to be programmed accordingly if used with a DX lead. Triple chamber devices that support IS-1 standard for LV lead ("HF-T") are not used in this clinical investigation.

Fig.1: Devices of the Ilivia ICD family

The Ilivia ICD family offers devices with DF-1, DF4 and with IS-1 and IS4 connectors, and the connector is therefore compatible with the respective leads. In the Ilivia ICD family a header variant will be offered that can be connected to DF-1 shock leads and an IS4 quadripolar LV lead. This variant allows upgrades to HF-T QP devices, if the patient has already a DF-1 RV shock lead implanted. Additionally this device variant allows physicians, who prefer to use DF-1 RV shock leads, to use IS4 LV leads for their systems. Beyond the modified header, the functionality of the CRT-D system will not differ from the functionality of the currently available DF4/IS4 HF-T QP systems.

4.7.2 MultiPole Pacing

In the field of cardiac resynchronization therapy the adaption of the IS4 connector standard was the most prominent improvement within the recent past. This IS4 connector allows the usage of LV leads that offer 4 separate poles which results in an increased number of

effectively different pacing polarities. Along with the quadripolar LV leads comes the possibility of stimulating more than one left ventricular pacing site within one cardiac cycle.

MultiPole Pacing is a new feature in the HF-T QP devices of the 7-series of the Ilivia ICD family (Ilivia, Intica and Inlexa-7 HF-T QP). MultiPole Pacing enables pacing of the left ventricle in two different vectors to improve synchronization of the contraction pattern. The timing of the paces can be programmed individually with several options from no delay to 50 ms, programmable in 5 ms steps. Furthermore the pacing of the LV vectors can be programmed individually in regard to delay to the RV pace. However, both LV impulses have to be administered in a row, RV pace can either be administered prior to LV or after LV pacing occurred. Furthermore, both ventricles can be stimulated simultaneously. However, RV-LV delay and LV-LV delay can only be programmed both to 0ms if RV first is programmed.

The following vectors are available in the HF-T QP devices (Tab.1):

Tab. 1: LV pacing and sensing configuration in the HF-T QP devices

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

For the use of MultiPole Pacing (MPP) all pacing vectors shown in table 1 can be combined freely according to the requirements of the respective patient. However, as an exception, the same vector cannot be programmed twice. Table 2 shows all possible MPP combinations which can be used. Taking the possible different sequences into account 132 programming possibilities are available (see Tab.2).

Tab. 2: Possible programming combinations of MultiPole Pacing vectors

Pacing first LV vector			Pacing second LV vector	
From (-) →	**To (+)**	**#**	**From (-) →**	**To (+)**
LV1 tip →	LV2 ring	1	LV1 tip →	LV4 ring
		2	LV1 tip →	RV coil
		3	LV1 tip →	ICD
		4	LV2 ring →	LV4 ring
		5	LV2 ring →	RV coil
		6	LV3 ring →	LV2 ring
		7	LV3 ring →	LV4 ring
		8	LV3 ring →	RV coil
		9	LV4 ring →	LV2 ring
		10	LV4 ring →	RV coil
		11	LV2 ring →	LV1 tip

Pacing first LV vector			Pacing second LV vector	
From (-) →	**To (+)**	**#**	**From (-) →**	**To (+)**
LV1 tip →	LV4 ring	1	LV1 tip →	LV2 ring
		2	LV1 tip →	RV coil
		3	LV1 tip →	ICD
		4	LV2 ring →	LV1 tip
		5	LV2 ring →	LV4 ring
		6	LV2 ring →	RV coil
		7	LV3 ring →	LV2 ring
		8	LV3 ring →	LV4 ring
		9	LV3 ring →	RV coil
		10	LV4 ring →	LV2 ring
		11	LV4 ring →	RV coil

Pacing first LV vector			Pacing second LV vector	
From (-) →	**To (+)**	**#**	**From (-) →**	**To (+)**
LV1 tip →	RV coil	1	LV1 tip →	LV2 ring
		2	LV1 tip →	LV4 ring
		3	LV1 tip →	ICD
		4	LV2 ring →	LV1 tip
		5	LV2 ring →	LV4 ring
		6	LV2 ring →	RV coil
		7	LV3 ring →	LV2 ring
		8	LV3 ring →	LV4 ring
		9	LV3 ring →	RV coil
		10	LV4 ring →	LV2 ring
		11	LV4 ring →	RV coil

Pacing first LV vector			Pacing second LV vector	
From (-) →	**To (+)**	**#**	**From (-) →**	**To (+)**
LV1 tip →	ICD	1	LV1 tip →	LV2 ring
		2	LV1 tip →	LV4 ring
		3	LV1 tip →	RV coil
		4	LV2 ring →	LV1 tip
		5	LV2 ring →	LV4 ring
		6	LV2 ring →	RV coil
		7	LV3 ring →	LV2 ring
		8	LV3 ring →	LV4 ring
		9	LV3 ring →	RV coil
		10	LV4 ring →	LV2 ring
		11	LV4 ring →	RV coil

Pacing first LV vector			Pacing second LV vector	
From (-) →	**To (+)**	**#**	**From (-) →**	**To (+)**
LV2 ring →	LV1 tip	1	LV1 tip →	LV4 ring
		2	LV1 tip →	RV coil
		3	LV1 tip →	ICD
		4	LV2 ring →	LV4 ring
		5	LV2 ring →	RV coil
		6	LV3 ring →	LV2 ring
		7	LV3 ring →	LV4 ring
		8	LV3 ring →	RV coil
		9	LV4 ring →	LV2 ring
		10	LV4 ring →	RV coil
		11	LV1 tip →	LV2 ring

Pacing first LV vector			Pacing second LV vector	
From (-) →	**To (+)**	**#**	**From (-) →**	**To (+)**
LV2 ring →	LV4 ring	1	LV1 tip →	LV2 ring
		2	LV1 tip →	LV4 ring
		3	LV1 tip →	RV coil
		4	LV1 tip →	ICD
		5	LV2 ring →	LV1 tip
		6	LV2 ring →	RV coil
		7	LV3 ring →	LV2 ring
		8	LV3 ring →	LV4 ring
		9	LV3 ring →	RV coil
		10	LV4 ring →	RV coil
		11	LV4 ring →	LV2 ring

Pacing first LV vector			Pacing second LV vector	
From (-) →	**To (+)**	**#**	**From (-) →**	**To (+)**
LV2 ring →	RV coil	1	LV1 tip →	LV2 ring
		2	LV1 tip →	LV4 ring
		3	LV1 tip →	RV coil
		4	LV1 tip →	ICD
		5	LV2 ring →	LV1 tip
		6	LV2 ring →	LV4 ring
		7	LV3 ring →	LV2 ring
		8	LV3 ring →	LV4 ring
		9	LV3 ring →	RV coil
		10	LV4 ring →	LV2 ring
		11	LV4 ring →	RV coil

Pacing first LV vector			Pacing second LV vector	
From (-) →	**To (+)**	**#**	**From (-) →**	**To (+)**
LV3 ring →	LV2 ring	1	LV1 tip →	LV2 ring
		2	LV1 tip →	LV4 ring
		3	LV1 tip →	RV coil
		4	LV1 tip →	ICD
		5	LV2 ring →	LV1 tip
		6	LV2 ring →	LV4 ring
		7	LV2 ring →	RV coil
		8	LV3 ring →	LV4 ring
		9	LV3 ring →	RV coil
		10	LV4 ring →	LV2 ring
		11	LV4 ring →	RV coil

Pacing first LV vector			Pacing second LV vector	
From (-) →	**To (+)**	**#**	**From (-) →**	**To (+)**
LV3 ring →	LV4 ring	1	LV1 tip →	LV2 ring
		2	LV1 tip →	LV4 ring
		3	LV1 tip →	RV coil
		4	LV1 tip →	ICD
		5	LV2 ring →	LV1 tip
		6	LV2 ring →	LV4 ring
		7	LV2 ring →	RV coil
		8	LV3 ring →	LV2 ring
		9	LV3 ring →	RV coil
		10	LV4 ring →	LV2 ring
		11	LV4 ring →	RV coil

Pacing first LV vector			Pacing second LV vector	
From (-) →	**To (+)**	**#**	**From (-) →**	**To (+)**
LV3 ring →	RV coil	1	LV1 tip →	LV2 ring
		2	LV1 tip →	LV4 ring
		3	LV1 tip →	RV coil
		4	LV1 tip →	ICD
		5	LV2 ring →	LV1 tip
		6	LV2 ring →	LV4 ring
		7	LV2 ring →	RV coil
		8	LV3 ring →	LV2 ring
		9	LV3 ring →	LV4 ring
		10	LV4 ring →	LV2 ring
		11	LV4 ring →	RV coil

Pacing first LV vector			Pacing second LV vector	
From (-) →	**To (+)**	**#**	**From (-) →**	**To (+)**
LV4 ring →	LV2 ring	1	LV1 tip →	LV2 ring
		2	LV1 tip →	LV4 ring
		3	LV1 tip →	RV coil
		4	LV1 tip →	ICD
		5	LV2 ring →	LV1 tip
		6	LV2 ring →	RV coil
		7	LV3 ring →	LV2 ring
		8	LV3 ring →	LV4 ring
		9	LV3 ring →	RV coil
		10	LV4 ring →	RV coil
		11	LV2 ring →	LV4 ring

Pacing first LV vector			Pacing second LV vector	
From (-) →	**To (+)**	**#**	**From (-) →**	**To (+)**
LV4 ring →	RV coil	1	LV1 tip →	LV2 ring
		2	LV1 tip →	LV4 ring
		3	LV1 tip →	RV coil
		4	LV1 tip →	ICD
		5	LV2 ring →	LV1 tip
		6	LV2 ring →	LV4 ring
		7	LV2 ring →	RV coil
		8	LV3 ring →	LV2 ring
		9	LV3 ring →	LV4 ring
		10	LV3 ring →	RV coil
		11	LV4 ring →	LV2 ring

The configuration for the second stimulus has no influence on the sensing. The left ventricular sensing will be done via an independent sensing configuration with different vector choice

available (Tab.1). Please note: LV sensing is not used for tachycardia diagnosis. For Tachycardia diagnosis only RV sensing is applicable.

4.7.3 DX functionality of HF-T models

BIOTRONIK introduced single chamber ICDs with atrial sensing via an atrial dipole several years ago. Connected to the appropriate DX ICD lead the VR-T DX ICD can gain atrial signals without the need of an atrial lead. In the Ilivia ICD family, the possibility to use atrial signals from the floating atrial dipole will also be offered in HF-T QP devices of the 5 and 7 series devices. The atrial input stage can be adjusted to the settings from the VR-T DX systems in the atrial sensing details and with this activation any stimulation via the atrial channel will be disabled. This way a triple chamber device with only two leads can be realized.

4.7.4 88% R-S1 interval for ATPs

In former BIOTRONIK devices the available options for the R-S1 interval for ATP used to be 70 to 95% in 5% steps. Based on customer feedback, according to the results of the PainFREE trial[2;3] and in accordance to the programmable values in the competitors' devices, Ilivia/Intica/Inlexa will additionally offer the R-S1 setting of 88% for all ventricular ATP approaches.

4.7.5 Early ATP one-shot

The new function Early ATP one-shot enables a delivery of ATP prior to fulfilment of the programmed detection counter in the VF zone if a stability criterion is fulfilled and if a VF detection counter of at least 16 of 20 is programmed. If the early delivery of ATP one shot is activated, it uses a separate counter (12 out of 16). If this separate counter is fulfilled and if the stability is given, the early ATP one shot is delivered. For the time of ATP delivery, the VF counter is frozen and it continues to count after the ATP delivery for the initial detection. If the early delivery of ATP one shot is successful, the VF counter will not be fulfilled and no shock therapy will be delivered.

With the help of this feature the potential drawback of the prolonged VF detection counter shall be mitigated that initially stable fast VTs might deteriorate into irregular VF that cannot be treated successfully with ATP.

With the help of this feature, the activation rate and success rate of the ATP one shot feature is expected to be improved resulting in a potential decrease of shock therapy especially in devices with very long VF counters. In patients whose devices are programmed with VF counters lower than 16 out of 20, early ATP one-shot cannot be programmed.

4.7.6 Automatic detection of MR environment (MRI AutoDetect)

Following initial activation within 14 days prior to the planned MRI scan, the MRI AutoDetect feature allows the implant to determine the presence of an MRI scanner and automatically switch the patient therapy into the MRI mode when a strong magnetic field is detected. The MRI AutoDetect system uses Giant Magneto Resistance (GMR) sensor as the MRI sensor.

The GMR detects the MRI static magnetic field to determine, if the implant is in or near an MR scanner. When the patient gets close enough to an MR scanner, the implant detects the MRI static magnetic field and switches from the permanent program to the stored MRI program. When the patient exits the MR scanner, the implant detects the "drop" in the MRI static

magnetic field and switches from the MRI program to the permanent program after a "hysteresis time" of one minute. The intent of the "hysteresis time" is to eliminate frequent switching of the patient therapy, as the patient may move in and out of the MRI scanner. The MRI AutoDetect feature minimizes the time spent in the MRI program, as the implant is in the MRI program only for the duration the patient is in the MR scanner. This offers the benefit of improved patient safety and comfort. Since the implant automatically switches back to the permanent program after the patient exits the MR scan, a post-MR follow-up to reprogram the implant is no longer necessary.

4.7.7 Plexa ICD lead

In this study, patients participating in **group B** or both groups, **A** and **B,** are implanted with the new 8F Plexa ICD lead. The Plexa ICD lead family presents a further development of the well-proven CE-marked Linox^{Smart} and Protego ICD leads. Due to the continued trend towards active fixation ICD leads, Plexa ICD leads will only be made available as active fixation leads with a DF4 or DF-1 lead connector design (for a complete listing of the different lead models, please refer to table 3). DX lead variants are only available with DF-1 connector design. While their basic structure and functionality is identical to that of the Linox^{Smart} and Protego ICD leads, Plexa differs from these leads in having a slightly modified design of the fixation mechanism for an improved retention force of the screw, and a twisted conductor design between the proximal end of the distal shock coil and the distal end of the proximal shock coil that helps minimizing the mechanical stress acting on the cables and the lead body. The modification of the screw mechanism includes a slightly modified cut of the screw and a modified contact spring inside the housing of the screw.

Like their predecessors, Plexa ICD leads have a SilGlide surface treatment to enhance the gliding properties of the lead body and are offered in three different lengths of 61, 65 and 75cm (Plexa DF-1 S DX: only 65 cm).

Located at the distal end, the Plexa ICD leads have one tip electrode and one ring electrode for bipolar sensing and stimulation. 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 detection and pacing pole. The modified lead tip of Plexa is intended to provide a better retention force of the fixated lead.

Plexa SD leads have two shock coils for defibrillation, which, after placement of the lead, are positioned in the right ventricle and in the area of the superior vena cava (SVC), respectively. Plexa SD leads are available with 16 cm or 18 cm distance between the proximal shock coil and the lead tip to ensure optimal positioning of the proximal shock coil in the transition area between the right atrium and the superior vena cava for different anatomical conditions. Plexa S and Plexa DF-1 S DX leads are equipped with just one ventricular shock coil (Fig.2).

For identification of the lead when connecting to the ICD during implantation, all IS-1/DF-1 and DF4 connectors are marked, respectively.

The active surface of the leads shows a fractal iridium coating. The steroid collar is made of silicone and 0.93mg dexamethasone acetate (DXA).

Tab. 3: Available lead variants of the Plexa ICD lead indicating length of the lead, distance between SVC shock coil and tip and connector type.

Item	Length	Connector	SVC coil/tip distance
Plexa S 60	61 cm	DF4	-
Plexa (ProMRI) S 65	65 cm		-
Plexa (ProMRI) S 75	75 cm		-
Plexa SD 60/16	61 cm		16 cm
Plexa (ProMRI) SD 65/16	65 cm		16 cm
Plexa (ProMRI) SD 65/18	65 cm		18 cm
Plexa (ProMRI) SD 75/18	75 cm		18 cm
Plexa (ProMRI) DF-1 S 65	65 cm	DF-1	-
Plexa (ProMRI) DF-1 S 75	75 cm		-
Plexa (ProMRI) DF-1 SD 65/16	65 cm		16 cm
Plexa (ProMRI) DF-1 SD 65/18	65 cm		18 cm
Plexa (ProMRI) DF-1 SD 75/18	75 cm		18 cm
Plexa (ProMRI) DF-1 S DX 65/15	65 cm		-
Plexa (ProMRI) DF-1 S DX 65/17	65 cm		-

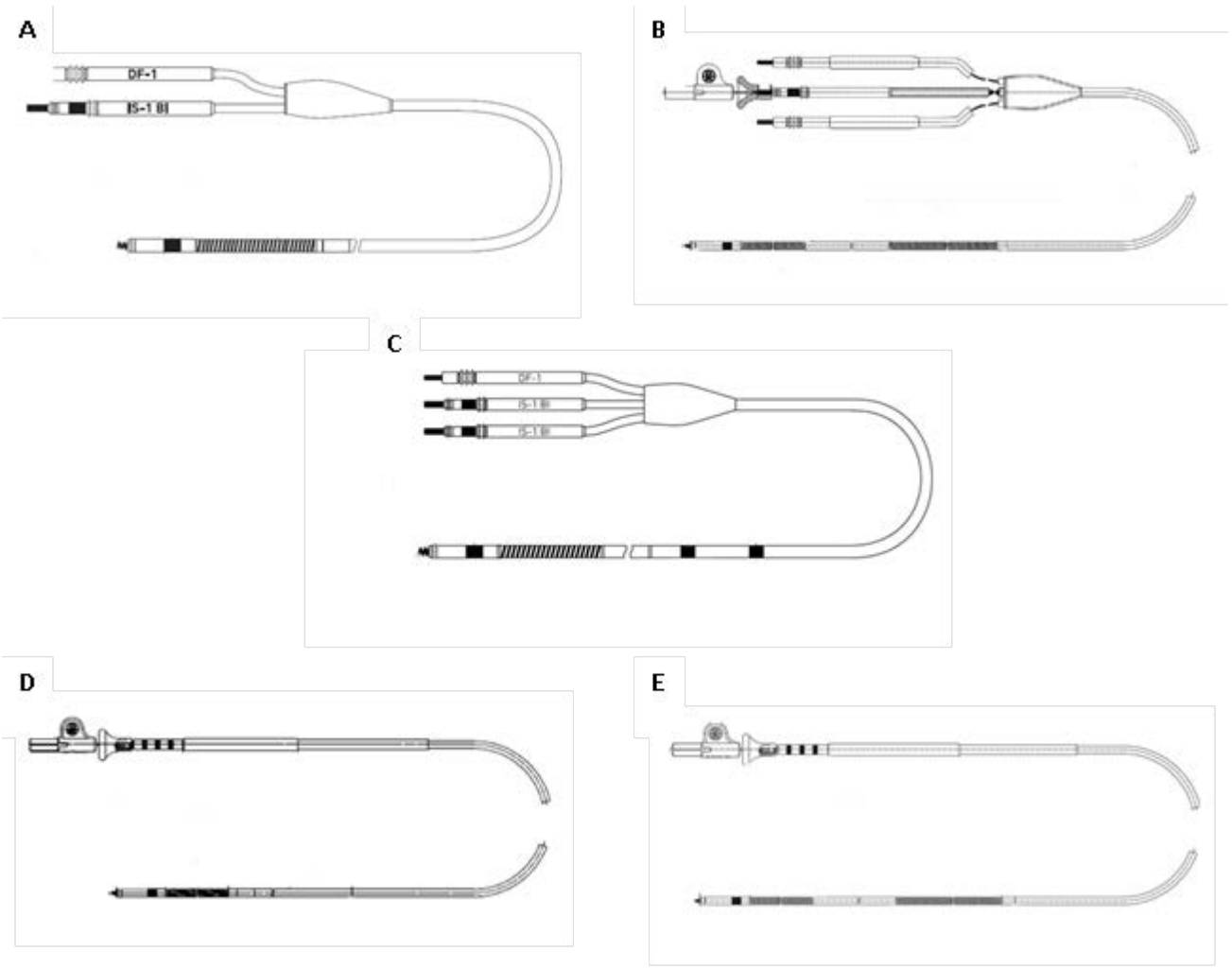

Fig. 2 A-E: Lead variants of the Plexa right ventricular lead. Leads are available with DF-1 connector as single (A) (DF-1 S leads) or dual (B) (DF-1 SD leads) shock coil. Furthermore the DX lead is available with DF-1 connector and 2 IS-1 connectors with 1 shock coil (C). Leads with DF4 connector are available as single (D) (S leads) or dual (E) (SD leads) shock coil variants.

4.7.8 DX functionality

The DX functionality in ICDs and CRT-Ds can be used for patients, in who atrial pacing is not required but information on the atrial rhythm should be available, to be used for example on timing algorithms or tachycardia discrimination. The DX functionality can be used by combining the Plexa DX right ventricular lead with floating atrial dipole with either a VR-T DX device or a HF-T / HF-T QP device with DX functionality available. By using this combination it is possible to obtain atrial sensing without the need to implant a separate atrial lead. The DX functionality uses a modification of the atrial input stage to ensure proper atrial sensing in order to support all atrial based features and functionalities except for atrial pacing.

The device allows monitoring and diagnostic of the atrial chamber, including IEGM recording, with a single right ventricular lead. An implantation of an atrial lead is not required.

4.7.9 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. 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 3).

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

Fig. 3: 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.

During the course of the study the sponsor will have access to patient data transmitted via Home Monitoring and/or Report Share function in a pseudomized form. Using Report Share the investigator triggers the submission of onsite collected measurement data to the BIOTRONIK Home Monitoring Service Center after each study procedure. The transmitted data will be used for evaluation and publication of the BIO|MASTER.Ilivia Family / Plexa 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.

4.8 Summary of training and experience needs

The devices of the Ilivia ICD family and the Plexa ICD lead are medical implants intended for physicians who are familiar with the implantation of a 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. No additional training or experience is necessary.

4.8.1 Description of medical and surgical procedures

The devices of the Ilivia ICD family and the Plexa ICD 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

will be continuously observed via Home Monitoring by the investigator. For CRT-D patients of **group A** the MultiPole Pacing feature will be activated after implantation.

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 Ilivia ICD family four clinical studies contribute to the evaluation of clinical data:

- the Lumax 740 Master Study (NCT01454050),
- the DF4 Master Study (first use of the DF4 connector with the Ilesto/Iforia ICD family, predecessors to Ilivia family) (NCT01790841),
- the Iperia Family / Sentus QP Master Study (predecessor of the Ilivia family in combination with BIOTRONIK´s first IS4 left ventricular lead, which is used for LV MultiPole Pacing in the current study) (NCT02181686), and
- the Pre-CRAFT study (first data on the DX functionality in CRT-D devices) (NCT01930695).

For the Plexa ICD leads the following studies are taken into consideration:

- the Linox SD/TD Master Study (not registered)
- the DF4 Master Study (including BIOTRONIK´s first DF4 lead "Protego") (NCT01790841).

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

5.2.1 Lumax 740 Master Study[a]

This clinical study was designed to confirm the safety and efficacy of the Lumax 740 ICD family in particular with a focus on the implemented Capture Control feature in the right and left ventricle. 183 patients from 17 clinical sites from Denmark, Germany, Israel, Slovakia, and United Kingdom were observed during 6 months. The period of investigation was between November 2011 and October 2012. The efficacy of the Capture Control algorithm was assessed on the basis of the difference between the measured results of the triggered automatic threshold test and the manual threshold test which were determined at each follow-up. Assessment of the safety of the Lumax 740 ICD was accomplished by collection of data concerning all adverse events possibly or securely related to the ICD that occurred up to the 6-month follow-up.

Results

- 183 Lumax 740 ICDs have been implanted successfully: 42 VR-T, 23 VR-T DX, 61 DR-T, 57 HF-T
- The triggered automatic and manual pacing threshold in the right ventricle can be regarded as equivalent within the specified range. The p-value is below 0.001. Thus, efficacy of RV Capture Control is confirmed.

[a] Final Report of the Lumax 740 Master study, October, 09 2013

- The difference between the triggered automatic and manual pacing threshold in the left ventricle can be regarded as equivalent within the specified range. The p-value is below 0.001. Thus, efficacy of LV Capture Control is confirmed.
- The ventricular tachyarrhythmia conversion rate was found to be 98.9%, CI [96.0%-99.9%]
- In total 130 adverse events (105 serious, 25 non-serious) were reported, whereof 5 events were possibly or securely related to the ICD.
- Two of 183 patients had an adverse event classified as device related SADE. Therefore the SADE-d free-rate is 98.9%, CI [96.1%-99.9%] at 6 months follow-up.
- 3 patient deaths have been reported, 2 were cardiac in nature. None were related to the ICD therapy.

Conclusion

The results demonstrate that the Lumax 740 ICDs are safe and effective. The RV and LV Capture Control feature can accurately measure thresholds and adjust the pacing output.

5.2.2 DF4 Master Study (Ilesto and Iforia)[b]

The objective of this study was to demonstrate the safety and efficacy of the new BIOTRONIK Ilesto/Iforia ICD system which is also available with DF4 connection.

231 patients from 20 clinical sites from Germany, Singapore, Austria, Denmark, Italy, France and Hong Kong were observed for 24 months. The period of investigation was between February 2013 and February 2014. The efficacy of the Protego lead family (the new DF4 lead) was assessed on the basis of the difference between the measured results of the triggered automatic threshold test between DF-1 and DF4 systems. Safety primary endpoints were the painless shock impedance shift between 3 and 6 months as well as SADE rates.

Results

- 231 Ilesto/Iforia ICDs have been implanted successfully: 64 DF-1 systems and 167 DF4 systems with Protego leads
- In total 238 adverse events (156 serious, 82 non-serious) were reported.
- 8 of the 167 patients with Protego leads had adverse events classified as lead related SADE. Therefore, the SADE-d Protego rate is 4.8%, 95% CI [2.1%, 9.2%]
- No adverse event was classified as SADE related to the ICD with DF4 connection. Therefore, the SADE-d DF4-ICD rate is 0.0%, 95% CI [0.0%, 2.2%].
- There was no significant difference in painless shock impedance measured between DF-1 and DF4 systems.
- There was no significant difference in RV pacing threshold measured between DF-1 and DF4 systems.

Conclusion

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

[b] Interim Report for the DF4 Masterstudy, April, 08 2015

5.2.3 Iperia Family / Sentus QP Master Study

The clinical study was designed to confirm the safety and efficacy of the new BIOTRONIK Sentus OTW QP left ventricular lead and the new Inventra/Iperia/Itrevia ICD family.

The study was conducted as a prospective multicenter international clinical trial. 152 patients were enrolled in 22 clinical sites worldwide. All participating patients obtained an ICD or CRT-D device of the Iperia product family. A subgroup of 89 patients with CRT indication received the Sentus QP LV lead. Study participation for each patient started prior to the implantation. Implantation, pre-hospital discharge and a 3-month follow-up were part of the study procedure.

Safety was assessed by evaluating device related serious adverse device effects of the used investigational devices. The performance of the new quadripolar LV lead was evaluated by the LV pacing threshold during the 3-month follow-up.

Enrollment started on July 14, 2014 and follow-up period was completed on June 25, 2015. A total of 152 patients were enrolled. All patients gave their written informed consent.

Results:

- 143 Iperia ICDs/CRT-Ds were implanted successfully: 27 VR-T, 27 DR-T and 89 HF-T QP.
- 89 Sentus OTW QP LV leads were implanted successfully.
- In total 98 adverse events (55 serious, 43 non-serious) were reported,
- One of 89 patient with a Sentus QP lead had an adverse event that was related to the lead. Hence, the SADE free-rate related to the Sentus QP lead was 98.9%, 97.5% CI [93.04% – 99%].
- One of 143 patients with Iperia devices had an adverse event that was possibly related to the Iperia ICD. Hence, the SADE free-rate related to the Iperia ICD family is 99.3%, 97.5% CI [95.6% - 99.9%].
- All 89 CRT-D patients had an acceptable LV pacing threshold of ≤ 3.5V measured in the final pacing configuration at the 3-month follow-up.
- The study met all primary and secondary endpoints.

Conclusion:

The results confirm the safety and efficacy of the new Iperia ICD family and the Sentus QP left ventricular lead

5.2.4 Pre-CRAFT[c]

This study was designed to evaluate the performance and safety of DX functionality in a CRT-D based on the quality of IEGM recordings and the Adverse Device Effects occurring during the study course. 18 patients have been enrolled from 3 clinical sites in Germany and Switzerland, one patient withdrew consent to participation, thus 17 patients were included in the analysis. The period of investigation was from August 2013 to October 2014.

The performance of the CRT-DX system was assessed by judging whether atrial intracardiac electrogram (IEGM) recordings allowed to adequately classify the atrial rhythm.

[c] Clinical Investigation Report for the Post MaRkEt Clinical Follow-up of CRT-DX Therapy with LumAx 640/740 HF-T study, April, 08 2015

The safety of the CRT-DX system was assessed by an analysis of adverse events related to the DX functionality.

Results:

- In all patients at least 1 IEGM was classified "suitable for atrial diagnosis" (primary endpoint)
- 99% of episodes were classified suited for atrial diagnosis
- The study has found sinus rhythm at any time after implantation in 29 % of the patients. In no patient, new sinus rhythm was found in the remote monitoring IEGM later than the first IEGM transmission at three days after discharge.
- One serious adverse event related to the DX system was reported. However, this kind of adverse event is observed with all ICD systems. Hence, the study did not identify any safety relevant issues of the DX system.

Conclusion

No specific risks were identified with the investigated DX-system. It allows the classification of the atrial rhythm by remote monitoring without the implantation of an atrial lead.

5.2.5 Linox SD/TD Master Study[d]

The study was designed to evaluate VT/VF conversion efficacy, pacing and sensing effectiveness at 3 months and the complication rate at 3-month follow-up. 159 patients were enrolled in 25 clinical sites, therof 75 patients with a Linox SD lead and 84 patients with a Linox TD lead. The period of investigation was from February 2006 to April 2007.

Results:

- The tachyarrhythmia conversion rate was found to be 99.8% [95% CI 98.1 – 99.9].
- Pacing at three-month follow-up was found to be appropriate in 98.4% (95% CI 91.5 – 99.7%) for Linox SD, and 100% (95% CI 95.1 - 100%) for Linox TD.
- Sensing at three-month follow-up was found to be appropriate in 98.4% (95% CI 91.4 – 99.7%) for Linox SD, and 98.6% (95% CI 92.7 – 99.8%) for Linox TD.
- In total 43 anticipated adverse events have been reported. 4 of these were complications possibly related to the Linox lead: 3 for Linox SD, and 1 for Linox TD. Hence ventricular lead related complication rates are 0.040 complications per patient [4.0%, 95% CI 1.4 - 11.1%] for Linox SD, and 0.012 complications per patient [1.2%, 95% CI 0.2 – 6.4%] for Linox TD. All complications were lead dislodgements within 3 months after implantation.

Conclusion

In conclusion, the Linox ICD leads have been shown to be safe and effective and have demonstrated appropriate function.

5.2.6 Relevant clinical data of competitor devices

Since the availability of multisite pacing CRT-D systems in 2010 as a research feature and 2013 as an approved and available feature, multisite pacing has been tested in a series of

[d] Final Report for the Master Study of the Linox SD and Linox TD Dual-coil ICD Leads, August 10, 2007

clinical trials. In several trials beneficial effect of multisite pacing over conventional CRT pacing could be shown with the help of different surrogate parameters, i.e. LVEF [25;26], LVESV [25;26], LV dP/dt [28] and speckle tracking [29]. Most of the trials measured acute effects only, i.e. through different measurements during the implantation or acute measurements during the follow-up. Some trials, however, followed the patients for a longer period of time (3-12 months) and reported long-term improvements, i.e. in LVESV or NYHA. Pappone could show a significant improvement in LVESV at 3- and 12-months follow-up as well as a significant NYHA improvement at 3-months follow-up – however, statistical significance was not given at 12-months follow-up anymore [25;26].

The PainFREE Rx and PainFREE Rx II Trials evaluated the effectiveness of antitachycardia pacing (ATP) for the conversion of fast ventricular tachycardias [2;3]. It could be shown that ATP (programmed at 8 pulses with 88% of cycle length) was highly effective, was equally safe compared to shock therapy and improved quality of life.

5.3 Justification

The above mentioned studies indicate the safety and efficacy of the predecessor devices of the Ilivia ICD family and the Plexa ICD lead. The new feature, the DX functionality of the CRT-D device may have a potential benefit in heart failure patients as the number of implanted leads can be reduced without loss of atrial information in patients without the need for atrial pacing (see section 6). The MultiPole Pacing feature in CRT-D devices provides more options to the physician to reach a higher amount of synchronization of the left ventricle due to different pacing options.

However, the Notified Body in charge requests 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 are unveiled or remained 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[e]. This includes the application of new technology in medical devices.

The evaluation of the Ilivia Family and the Plexa ICD lead in one study allows for enrolling a patient in both groups A and B which means that a patient can contribute to evaluating two devices without increased risk or effort for the patient and without creating bias. This is not only efficient from an ethical point of view as it reduces the overall number of patients required for the chosen endpoints, but also from the investigators' and sponsor's perspective.

Therefore the BIO|MASTER.Ilivia Family / Plexa trial is designed to identify and evaluate residual risks associated with the use of the Ilivia ICD family and the Plexa ICD lead that are unveiled or remained even after risk analysis, risk mitigation and successful conformity assessment in a study patient population.

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

6 RISKS AND BENEFITS OF THE DEVICE AND CLINICAL INVESTIGATION

6.1 Anticipated clinical benefits

The BIO|MASTER.Ilivia Family / Plexa study is designed to identify and evaluate residual risks associated with the use of the Ilivia ICD family and the Plexa ICD lead that are unveiled or remained even after risk analysis, risk mitigation and successful conformity assessment. Furthermore, the study aims at providing additional data, as required by regulatory authorities outside the CE-region.

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

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 new Plexa ICD lead provides DF-1 and DF4 connector variants with single and dual shock coils and DX variants. Due to the new design of screw and gliding capability of the inner lumen of the lead, an increase of handling comfort of the lead is expected. The twisted cable design is expected to increase durability of the lead.

The new Ilivia family provides new features like MultiPole Pacing (MPP) and DX functionality in CRT-D devices.

MPP enables pacing in two different vectors within the left ventricle if the device is used in combination with a quadripolar left ventricular lead. Studies have shown that pacing via different vectors is beneficial to optimize synchronization of the left ventricle and thus results in an improvement of different parameters of heart failure like ejection fraction, stroke volume, endsystolic volume, and others[25-28]. Furthermore the rate of non-responders to CRT-D therapy is decreased[25]. Ginks at al. have postulated that patients with myocardial scar or absence of a functional block do benefit from multisite pacing to achieve CRT response [30]. The optimal site of acute hemodynamic response to CRT varies between patients and thus might require individualization[24]. Severe scar seems to increase the benefit of multisite pacing compared to conventional biventricular pacing[31].

The DX functionality, available in all CRT-D devices of the 5 and 7 series Ilivia family, allows right atrial sensing via an atrial bipole on the right ventricular lead if the device is combined with a DX 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[18-22].

In addition to MPP and DX functionality, an additional cycle length for ATP therapy was added to the device programming according to the result of the painFREE trial, which showed that an ATP R-S1 coupling interval of 88% of the cycle length of a fast ventricular tachycardia administered in 8-pulse burst is highly effective to terminate the tachycardia and thus reduces shock administration[2;3].

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[32].

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 MultiPole Pacing.

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

Implantation of the Ilivia ICD family and the Plexa ICD 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.

6.2.3 Risk associated with participation in the study

Patients included in the BIO|MASTER.Ilivia Family / Plexa study have an indication for ICD or CRT-D therapy and will be implanted with an implantable cardiac rhythm management device independently from the study. As implantation of the investigational devices used in this study does not differ from standard operation procedure, no study specific risks are associated with the implantation procedure.

Risks associated with MultiPole Pacing

The use of MultiPole Pacing in CRT-D patients requires the implantation of a quadripolar lead (BIOTRONIK Sentus OTW QP). In some cases this lead might not be suitable for implantation due to the individual anatomy of the coronary venous system. The physician will determine if the lead is appropriate for a specific patient during the implantation procedure. In most cases the decision can be made during visualization of the coronary veins, thus the Sentus QP lead will only be implanted in those patients most likely eligible for this LV lead. However, in single cases unsuccessful positioning of a left ventricular lead might occur, requiring lead exchange during implantation. Unsuccessful positioning of a left ventricular lead and exchange of the lead during implantation is common in about 7% to 19% of patients during CRT implantation[33] and can therefore not be accounted for as additional risk of the use of the MultiPole Pacing option. It has even been shown that the use of multipole electrodes increases the implantation success of left ventricular leads since potential problems like phrenic nerve stimulation or high pacing thresholds can be overcome by choosing from the many available pacing vectors.

For the study it is mandatory to measure all available 12 pacing vectors of the LV lead prior to programming of MPP. This measurement will prolong the pre-hospital discharge follow-up of the patient by about 10 minutes.

In about 40% of cases phrenic nerve stimulation occurs in one or more vectors of quadripolar leads, potentially resulting in temporary hiccups or muscle contractions[34;35], which disappear

as soon as the threshold is switched off. However, due to the high number of available vector options for MultiPole Pacing, it should be possible to avoid occurrence of phrenic nerve stimulation in the final programmed vectors in nearly all cases.

In total, the use of a second left ventricular pacing stimulus results in a calculated longevity reduction of the CRT-D battery of approximately 10% (6.9 years vs. 6.2 years; assumption: 60ppm, 100% pacing with 2.5V @ 0.4ms in all chambers). For the mandatory activation of the MPP feature during the 6 months duration of the study, this results in a reduction of longevity of about 2.4 weeks, which is clinically not significant and considered acceptable.

The use of the MPP functionality shows no additional risks compared to any standard use of quadripolar left ventricular leads. The expected battery reduction is limited due to the short duration of the study.

Risks associated with DX functionality in CRT-D devices

The use of DX functionality 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.

In AF patients, the risk of symptomatic bradycardia may be increased after conversion to sinus rhythm due to CRT therapy[36] and stimulation of the atrium may be required in case of slow, insufficient sinus rhythm after conversion. However, often it is standard clinical practice that no atrial lead is implanted in patients with permanent atrial fibrillation[37;38]. Therefore the risk for additional atrial lead implantation would be equal in patients implanted with a DX system and in patients not planned to be implanted with an atrial lead. In hospitals with a standard implantation of the atrial lead in AF patients, the implantation risk will be increased by the use of CRT-DX due to a potential later implantation of an atrial lead. However, the standard implantation of an atrial lead in patients who will not experience conversion to sinus rhythm due to CRT therapy is an unnecessary increase in lead burden[17].

Furthermore, the atrial sensing of the CRT-D device connected to a DX lead might be inferior to a standard atrial lead, despite mostly positive clinical experiences[39-41]. However this is predominantly a factor for patients in sinus rhythm. In patients with AF the atrial sensing is only diagnostic and not used for the timing of ventricular pacing and not needed for discrimination of different supraventricular tachycardias.

As the use of the DX functionality is not predefined by the BIO|MASTER.Ilivia Family / Plexa study but only based on a physicians` decision in regard to the respective patient, this cannot be counted as a general risk of the study participation.

Further Risks

In the course of the study, event-triggered IEGMs will be transmitted via Home Monitoring®. The transfer of these data will result in a reduction of battery lifetime. However, the transmission of event-triggered IEGMs provides 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[6;32;42] 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.

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

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 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 ICD lead is the successor of the well-proven Linox^{smart} / Protego DF-1 (DX) and DF4 leads. The Ilivia/Intica/Inlexa ICDs are based technically and functionally on the CE-approved Inventra/Iperia/Itrevia family. Furthermore most of the new features are based on already market approved and proved BIOTRONIK pacemaker and ICDs.

The devices combine the classical benefit of ICD therapy with bradycardia and CRT therapy. All functional extensions of the ICD family are functions that have proven to be beneficial in clinical usage and their therapeutic benefit has been demonstrated.

The use of MPP in CRT-D patients carries the same risks as the use of any quadripolar lead. Furthermore the battery depletion of the feature with 2.4 weeks reduction of longevity for the duration of the study is negligible. However, multisite pacing has been shown already beneficial to increase the responder rate to CRT-D therapy. Possible occurrence of phrenic nerve stimulation can easily be avoided due to the high number of available vector combinations.

The use of DX functionality in CRT-D patients 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. As the use of DX functionality is not mandatory in the present study, the decision to use the DX functionality is based on the physicians` discretion and thus cannot be accounted for as additional risk of the study.

The mandatory use of Home Monitoring and transmission of IEGMs decreases battery lifetime. However, the transmission of recording episodes IEGMs provides 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 even if not participating in the study.

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 justifiable.

7 OBJECTIVES

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 Ilivia ICD family and the Plexa ICD lead that are unveiled or remained even after risk analysis, risk mitigation and successful conformity assessment. Furthermore, the study aims at providing additional data, as required by regulatory authorities outside the CE-region. The results will be used for updating the clinical evaluation.

7.1.1 Primary Objectives

7.1.1.1 **Group A**: Ilivia family related safety through 3 months

This objective of the clinical investigation is to confirm the clinical safety of the Ilivia ICD family by the analysis of the Ilivia related SADEs within 3 months after implantation.

7.1.1.2 **Group B**: Plexa related safety through 3 months

This objective of the clinical investigation is to confirm the clinical safety of the Plexa ICD lead by the analysis of the Plexa related SADEs within 3 months after implantation.

The safety objectives for both groups are defined for a 3-month follow-up period, as the majority of, for example, lead complications is found within this early postoperative phase [43;44].

7.1.2 Secondary Objectives

7.1.2.1 Secondary objectives **Group A**: Ilivia family

7.1.2.1.1 Conversion of fast ventricular arrhythmia (detection in VF zone) by ATP one shot through 6 months

This efficacy objective is to confirm the effectiveness of ATP one-shot at the newly recommended programming (8 pulses with 88% R-S1) in the Ilivia ICD family within 6 months after implantation. This objective will be assessed through 6 months after implant to increase the chance of appropriate ICD therapy experienced by patients, as the number to be expected is relatively low. Moss et al. reported an incidence of about 10% within 6 months after implantation [45].

7.1.2.2 Secondary objectives **Group B**: Plexa

7.1.2.2.1 Right ventricular sensing at 3-month follow-up

This efficacy objective of the clinical investigation is to confirm the appropriate sensing in the Plexa ICD lead within 3 months after implantation. This objective will be assessed at the 3-month follow-up, as lead ingrowth is expected to be completed until that time and thus measured values display the normal function in the patient. The purpose of the secondary endpoint is to evaluate the ability of the Plexa ICD lead to appropriately sense the intrinsic cardiac signal.

7.1.2.2.2 Right ventricular pacing at 3-month follow-up

This efficacy objective of the clinical investigation is to confirm the appropriate pacing in the Plexa ICD lead within 3 months after implantation. This objective will be assessed at the 3-month follow-up, as lead ingrowth is expected to be completed until that time and thus

measured values display the normal function in the patient. The purpose of this secondary endpoint is to evaluate the ability of the Plexa ICD lead to appropriately stimulate the cardiac tissue.

7.1.3 Further efficacy objectives

The further objectives are to describe the performance and efficacy of the new available features in the Ilivia ICD family and the Plexa ICD lead.

7.2 Safety assessments

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

8 DESIGN OF THE CLINICAL INVESTIGATION

8.1 General considerations

The study is designed as a multicenter, international, non-randomized, open-label and prospective study including two subgroups: **group A** with the Ilivia ICD family and **group B** with the Plexa right ventricular ICD lead.

Patients can be enrolled into both groups, if they receive both study devices, see below for details.

Group A

Ilivia ICD family

Enrollment:

In group A, a total of 105 patients will be enrolled. With an expected drop-out rate of 10% a minimum number of 94 patients will be included in the analysis set. In total, 26 patients should receive a single chamber ICD, 26 patients a dual chamber ICD and 53 patients a triple chamber ICD (CRT-D).

Group B

Plexa ICD lead

Enrollment:

In group B, a total number of 185 patients will be enrolled. With an expected drop-out rate of 10% a mimimum number of 166 patients will be included in the analysis set.

Tab. 4: Required visit windows (1 month is defined as 30 days)

	Window	Days post-implant
Pre-hospital discharge or wound check	+ 10 days	0 to 10
3 months post-implant	± 30 days	61 to 121
6 months post-implant	± 30 days	151 to 211

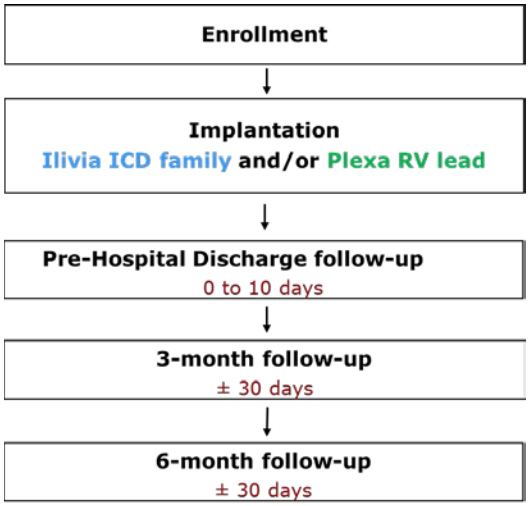

Fig. 4: Follow-up scheme of group A (Ilivia ICD family) and group B (Plexa ICD lead)

Patients in group A and/or group B will be followed for duration of 6 months in the BIO|MASTER.Ilivia Family / Plexa study. During this time 5 visits are planned per patient: Enrollment, Implantation, Pre-hospital discharge, 3-month follow-up and 6-month follow-up (Fig. 4). The implantation shall be performed within 30 days after enrollment of the patient. The other windows associated with each visit are provided above in Table 4. This schedule should be followed as closely as possible. If circumstances prevent the presence of the patient at the follow-up visit, the reason for the missed follow-up has to be indicated on the eCRF. In addition, interim evaluations for device related revisions will be performed.

Patients in both groups A and B: It is recommended that patients are implanted with both investigational devices, the Ilivia ICD family **and** Plexa ICD lead, Figure 5. Such patients can belong to both study groups and should then complete all follow-ups as required by both groups. The participation in both groups instead of only in group A or in group B can be freely chosen by the investigator based on his/her medical opinion. However, the investigation should be compliant with the study protocol for group A, group B or both, respectively.

The enrollment of patients in both study groups will be stopped independently. The project management of the BIO|MASTER.Ilivia Family / Plexa study will inform all investigators in advance in written form about the stop of enrollment of patients to both groups A and B.

After 105 patients have been enrolled into group A, or 185 into group B, further patients can receive both Ilivia and Plexa implants, but can only be enrolled into the group which is still open for enrollment. These patients are not subject to CIP required procedures related to endpoints of the group into which they have not been enrolled, and if endpoints are recorded by oversight of the investigator, they will be excluded from the analysis.

Furthermore, in case a patient enrolled in both groups, is exited from one of the groups, only data for the still active group will be provided and used for analysis from that point in time on.

Fig. 5: Overlap of both study groups. Patients implanted with an ICD device of the Ilivia family and a Plexa ICD lead can belong to both groups A and B

A study duration of about 14 months enrollment plus 6 months FU = 20 months is expected in total. First Patient In (FPI) is expected for beginning of June 2016. Last Patient In can be expected for end of July 2017 (LPI), which means that the last patient will leave the study end of January 2018 (LPO, Last Patient Out).

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

8.3 Endpoints and hypotheses

8.3.1 Primary endpoints and hypotheses

The global primary hypothesis consists of two primary hypotheses related to the SADE-free rate in group A and SADE-free rate related in group B, respectively. The global primary alternative hypothesis is accepted when the primary alternative hypothesis for group A or the primary alternative hypothesis related to group B, or both can be accepted.

8.3.1.1 **Group A**: Ilivia family related SADE-free rate through 3 months

The safety of the Ilivia ICD family 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 Ilivia ICD family devices (SADE-d_{Ilivia}) until 3-month follow-up are counted for this primary endpoint. Securely procedure related Serious Adverse Device Effects (SADE-p_{Ilivia}) are not counted. Further definitions are given in section 18.11. The primary hypothesis evaluates the SADE-d_{Ilivia} free rate ($Ilivia_{SADE\_free}$). It is expected, that the rate will be significantly above 90%, the corresponding hypotheses definitions are:

Null hypothesis: H_{0_Ilivia} : $Ilivia_{SADE\_free} \leq 90\%$

Alternative hypothesis: H_{A_Ilivia} : $Ilivia_{SADE\_free} > 90\%$

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

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

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-months follow-up do not contribute to this endpoint.

8.3.1.2 **Group B**: Plexa related SADE-free rate through 3 months

The safety of the Plexa right ventricular lead 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 Plexa ICD lead (SADE-d_{Plexa}) until 3-month follow-up and meeting predefined criteria (see 18.11) are counted for this primary endpoint. Securely procedure related Serious Adverse Device Effects (SADE-p_{Plexa}) are not counted. The primary hypothesis evaluates the SADE-d_{Plexa} free rate ($Plexa_{SADE\_free}$). It is expected, that the rate will be significantly above 90%, the corresponding hypotheses definitions are:

Null hypothesis: H_{0_Plexa} : $Plexa_{SADE\_free} \leq 90\%$

Alternative hypothesis: H_{A_Plexa} : $Plexa_{SADE\_free} > 90\%$

The parameter of interest "$Plexa_{SADE\_free}$" is the SADE-free rate per patient, which will be calculated by

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

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-months follow-up do not contribute to this endpoint.

8.3.2 Secondary endpoints and hypotheses

The following secondary endpoints have been defined for the two groups:

8.3.2.1 Secondary endpoints **Group A**: Ilivia family

8.3.2.1.1 Percentage of patients with successful fast ventricular arrhythmia conversion by ATP one-shot at 6-month follow-up

This endpoint examines the percentage of patients with successful conversion of ventricular arrhythmia detected in the VF zone by ATP one-shot of all patients with such episodes.

Events will only be included in the analysis of this endpoint if

1) the arrhythmia was detected in the VF detection zone, and
2) if it was classified as true ventricular tachyarrhythmia by the investigator, and
3) if ATP one-shot was delivered with the recommended programming (8 pulses with 88% R-S1).

The period under observation starts with the implantation and lasts until the 6-month follow-up. The parameter of interest $Conversion_{R\text{-}S1\_88\%}$ is defined as following:

$Conversion_{R\text{-}S1\_88\%}$ = (Number of patients with at least one successful conversion / Number of patients with events as defined here) * 100%.

Thereby, a patient is considered to have experienced successful conversion if at least one episode detected in the VF zone in that patient was converted by ATP one-shot therapies at the recommended programming, i.e ATP one-shot was beneficial and shock delivery could be avoided.

No hypotheses are pre-specified for this endpoint due to the low expected number of episodes.

8.3.2.2 Secondary endpoints and hypotheses **Group B**: Plexa

8.3.2.2.1 Rate of appropriate right ventricular sensing at 3-month follow-up

This secondary hypothesis evaluates the rate of appropriate right ventricular sensing ($Plexa_{Sensing}$) of all patients in which sensing measurement was performed. It is expected, that the rate will be significantly above 93%, the corresponding hypotheses definitions are:

Null hypothesis: $H_{0\_Sensing}$: $Plexa_{Sensing} \leq 93\%$

Alternative hypothesis: $H_{A\_Sensing}$: $Plexa_{Sensing} > 93\%$

The investigator is asked to determine if the lead system is appropriately sensing the intrinsic ventricular signals at the end of each scheduled follow-up. The evaluation of ventricular sensing is based on the assessment of 10 consecutive intrinsic signals documented with markers on an IEGM (see 8.5.11). Only the evaluation of the 3-month follow-up is taken into account towards data analysis of this endpoint. Only patients with measurements performed at the 3-month follow-up will be included in this analysis set. Specifically, the percentage of patients with an appropriate RV sensing at the 3-month follow-up will be determined.

The parameter of interest $Plexa_{Sensing}$ is the rate of patients with appropriate sensing which will be calculated by

$Plexa_{Sensing}$ = (Number of patients with appropriate sensing ($Sensing_{app}$) divided by number of patients with sensing measurements performed) * 100%.

Patients, in whom the sensing performance cannot be evaluated or has not been evaluated, will not contribute to the analysis set ("no intrinsic rhythm" and "not done").

8.3.2.2.2 Rate of appropriate right ventricular pacing at 3-month follow-up

This secondary hypothesis evaluates the rate of appropriate right ventricular pacing ($Plexa_{Pacing}$) of all patients in which pacing measurement was performed. It is expected, that the rate will be significantly above 93%, the corresponding hypotheses definitions are:

Null hypothesis: H_{0_Pacing} : $Plexa_{Pacing} \leq 93\%$

Alternative hypothesis: H_{A_Pacing} : $Plexa_{Pacing} > 93\%$

The investigator is asked to determine if the pacing system is appropriately pacing the ventricle at the end of each scheduled follow-up. The evaluation of ventricular pacing is based on the assessment of 10 consecutive beats documented with markers on an IEGM (see 8.5.11). Only the evaluation of the 3-month follow-up is taken into account towards data analysis of this endpoint. Only patients with measurements performed at the 3-month follow-up will be included in the endpoint.

Specifically, the percentage of patients with an appropriate RV pacing at the 3-month visit will be determined.

The parameter of interest $Plexa_{Pacing}$ is the rate of patients with appropriate pacing which will be calculated by

$Plexa_{Pacing}$ = (Number of patients with appropriate pacing ($Pacing_{app}$) divided by number of patients with pacing measurements performed) * 100%.

According to the definitions provided in section 8.5.11, the pacing performance can be "adequate" or "inadequate". If reason for inadequate performance is "No capture", the evaluation will not be considered an endpoint-related event in case the underlying reason is a medical event (e.g. hyperkalaemia, myocardial infarction or drug therapy). Patients, in whom the pacing performance has not been evaluated, will not contribute to the analysis set ("not done").

8.4 Further data of interest

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

8.4.1 Further data of interest in group A (Ilivia ICD family)

- MPP settings

  The MPP settings used by the physicians will be collected for all CRT-D patients programmed to MPP "on". This includes the programmed vectors, the pacing threshold, the programmed pacing amplitudes, the LV sensing polarity, the sensing amplitude, the LV-LV and RV-LV delay as well as any change of setting during the course of the study.

- Handling of MPP programming (interface programmer)

  The physician is asked to evaluate the handling of the MPP programming in an eCRF "MPP handling".

- SADE related to MPP during 6 months

SADEs which are possibly or securely related to MPP will be listed in a descriptive manner.

- Rate of responders/ non-responders to CRT therapy

  These data will be collected from all patients implanted with a CRT-D device of the Ilivia family. The physician should evaluate at the 6-month follow-up if the respective patient is a responder or a non-responder to CRT-D therapy. Patients who did not tolerate MPP and had to be reprogrammed to MPP "off" during the course of the study contribute to the MPP "off" group.

- NYHA class, change of NYHA class in CRT-Ds

  The NYHA class will be collected at baseline from all patients and at 6-month follow-up for CRT-D patients only. The mean change of NYHA class in CRT-D patients between enrollment and 6-month follow-up will be evaluated.

- Percentage of DX devices among devices, DX in CRT, atrial sensing amplitude in DX devices

  Data of DX devices will be collected, including the percentage of used DX devices in ICD and CRT-D therapy. Furthermore the atrial sensing amplitude of DX devices as well as CRT statistics will be collected and the mean values evaluated at 3- and 6-month follow-up.

- Ventricular therapy episodes

  Ventricular therapy and therapy attempt episodes will be collected and documented in a tachyarrhythmia episode eCRF, IEGMs of the episodes will be collected.

- Programming of Early ATP one-shot

  The number of programming of Early ATP one-shot will be documented for all patients with programming of ATP one-shot in the VF zone. Number of occurred Early ATP one-shot will be collected based on the documented ventricular tachycardia IEGM episodes.

- Lead measurements (sensing amplitude, pacing threshold, pacing impedance, shock impedance) via pacing sensing analyzer (PSA) during implantation

  Lead measurements via PSA will be performed prior to connection of the leads to the ICD device. Mean values from all patients will be calculated for each type of lead for each type of measurement.

- Lead measurements (sensing amplitude, pacing threshold, pacing impedance, shock impedance)

  Lead measurements will be performed during each follow-up for all available leads. Mean values from all patients will be calculated for each type of lead and for each type of measurement.

- Evaluation of sensing and pacing performance

  The sensing and pacing performance of the device will be evaluated by the physician in all available channels. Mean values will be determined for each type of lead.

- IEGMs of non-sustained VTs, fast intervals and atrial episodes

All IEGMs of non-sustained VTs, fast intervals and atrial episodes will be collected for possible further evaluation. In addition the last 3 occurred episodes prior to the respective follow-up will be evaluated and entered in the tachyarrhythmia episode form

- Home Monitoring data

  Pseudonymized Home Monitoring data will be collected throughout study duration for potential further evaluations of continuously available device data.

- Adverse Events / Device Deficiencies

  All AEs and DDs will be collected during the course of the study in a descriptive manner.

- MRI AutoDetect functionality

  Information on MRI AutoDetect functionality will be collected for patients undergoing MRI during the course of the study. This includes available Home Monitoring Data and further information provided by the cardiologist (if available).

8.4.2 Further data of interest in group B (Plexa)

- Handling of the lead

  The physician will evaluate the handling of the lead during the implantation procedure and document the results in a Plexa handling eCRF

- Lead measurements (RV pacing threshold, sensing amplitude, shock impedance, lead impedance)

  Lead measurements of the RV lead will be performed during each follow-up. Mean values will be calculated from all patients for each type of measurement.

- RV Lead measurements at implantation with PSA

  Measurements of the RV lead will be done during implantation with an pacing sensing analyzer (PSA). Data will be documented and mean values from all patients will be calculated for each type of measurement.

- Evaluation of sensing performance in the atrial channel

  The sensing performance of Plexa DX leads will be evaluated by the physician for the atrial channel. Mean value will be determined.

- Percentage of DX leads among leads, atrial sensing amplitude in DX leads

  Data of DX leads will be collected, including the percentage of used DX leads in ICD and CRT-D therapy. Furthermore the atrial sensing amplitude of DX leads will be collected and the mean values evaluated at 3- and 6-month follow-up.

- IEGMs of all episodes

  All IEGMs of all medical episodes (excluding episodes based on technical triggers) will be collected for possible further evaluation.

- Home Monitoring data

  Pseudonymized Home Monitoring data will be collected throughout study duration for potential further evaluations of continuously available device data.

- Adverse Events / Device Deficiencies

All AEs and DDs will be collected during the course of the study in a descriptive manner.

8.5 Methods

8.5.1 General

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

- Enrollment Form
- Baseline Form
- Implantation Form
- Pre-Hospital Discharge Form
- MultiPole Pacing form (**group A** only)
- Plexa Lead Handling (**group B** only)
- 3-month follow-up form
- 6-month follow-up form
- Interim Intervention form
- Tachyarrhythmia episode form
- MRI AutoDetect form (**group A** only)
- Study termination Form
- Adverse Event Form
- Device Deficiency Form

For patients who are in both **groups A and B** all group-specific eCRFs need to be filled in.

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

8.5.2 Patients' demographics and medical history

Demographic information including age, gender, height and weight will be collected for all subjects on the Baseline eCRF. 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.

8.5.3 Implantation

The implantation of the Ilivia/Intica/Inlexa VR-T, VR-T DX, DR-T and HF-T QP as well as the implantation of the Plexa ICD 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) will be conducted (see 8.5.10).

8.5.4 Mandatory programming

Before the patient is discharged from hospital the investigator has to activate the Home Monitoring function. Furthermore capture control should be "ON" or "ATM" in all available channels (**group A**) or the RV channel only (**group B**). For both groups recording of IEGMs of episodes should be programmed to "ON".

For patients of **group A** ATP one-shot has to be programmed in the VF detection zone (see 8.5.5).

For CRT-D patients of **group A**, MPP has to be activated prior to discharge (see 8.5.6).

8.5.5 ATP one-shot programming

Prior to discharge ATP one-shot has to be programmed for patients participating in **group A** of the study. ATP one-shot has to be programmed with 8 pulses and a cycle length of 88% of the ventricular tachyarrhythmia cycle length for all patients eligible for the programming. If patients are programmed to other parameters a reason for deviation from the programming has to be provided. Furthermore, programming of Early ATP one-shot is recommended and will be documented.

8.5.6 MPP programming and measurements

In patients implanted with an HF-T QP device of the Ilivia ICD family (**group A**, CRT-D), activation of MultiPole Pacing at implantation or pre-hospital discharge is mandatory.

According to Pappone et al. 2014, in 71% of patients the highest effect of MPP is found with maximal anatomical spacing between the two stimulation vectors. Furthermore, in 57% of cases the minimum LV-LV delay was better than the longest LV-LV delay[26].

Thus, for programming of the feature it is recommended to choose the two vectors with maximal anatomical distance with a pacing threshold of less than 2.5 V and without phrenic nerve stimulation. For maximal anatomical distance it is recommended that pacing pulse 1 originates from LV1 ring and pacing pulse 2 originates from LV4 ring. For the LV-LV delay a programming of 0 ms is recommended. However, the programming should be adapted to the individual anatomical condition of the patient as appropriate.

During implantation, it is recommended to measure at least the pacing threshold of the recommended vectors via pacing sensing analyzer to ensure that lead placement offers adequate vector availability.

Furthermore, prior to programming, it is **mandatory** to measure all **12** available pacing vectors to determine pacing thresholds and threshold of phrenic nerve stimulation to ensure that adequate vectors are chosen. Programming has to be completed latest at pre-hospital discharge.

Figure 6 and Table 5 show the possible recommended vector combinations in regard to the anatomical distance.

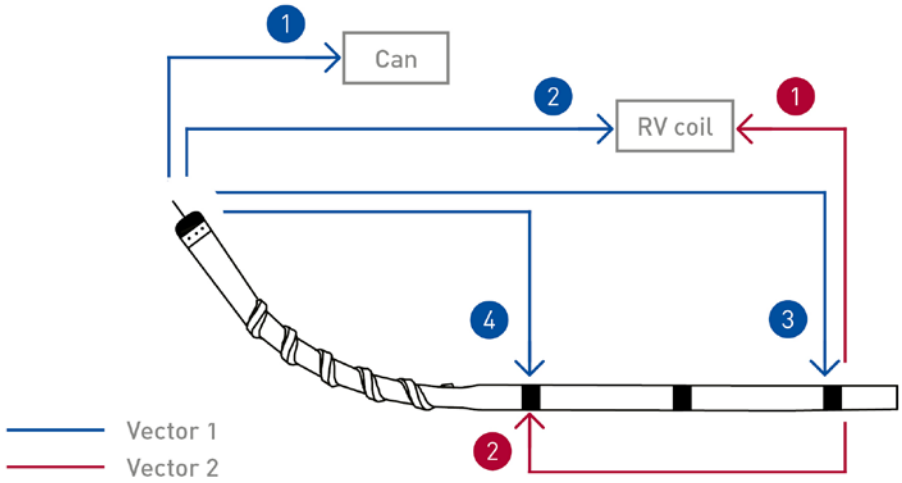

Fig. 6: Recommended pacing vectors of the left ventricular lead to be used for MPP pacing

Tab. 5: Recommended vectors to be used in multipole pacing

Pacing first LV vector

#	From (-) →	To (+)
1	LV1 tip →	ICD
2	LV1 tip →	RV coil
3	LV1 tip →	LV4 ring
4	LV1 tip →	LV2 ring

Pacing second LV vector

#	From (-) →	To (+)
1	LV4 ring →	RV coil
2	LV4 ring →	LV2 ring

Programming of the vectors can be freely chosen. However, if programming deviates from the recommended programming a reason for the deviation has to be documented.

For MultiPole Pacing the following information has to be documented after programming: Programmed vectors, pacing thresholds, programmed pacing amplitudes, LV sensing polarity, sensing amplitude, LV-LV delay and LV-RV delay. The physician will be asked to evaluate the usability of the MPP programming interface on the programmer.

Furthermore at each follow up, changes of the MPP programming during the course of the study have to be documented.

To determine the responsiveness of CRT-D patients to MultiPole Pacing, physicians are asked to document if a respective patient is a responder or a non-responder to CRT-D therapy at the 6-month follow-up based on his/her expert assessment of the patient status.

Furthermore, the NYHA class will be assessed and documented at implantation (values within 3 months prior to implant are acceptable) and at 6-month follow-up.

8.5.7 ICD therapy episodes and Recording episodes (event-triggered episodes)

During the course of the study IEGMs of all spontaneous occuring event-triggered medical episodes detected in both groups should be stored and forwarded to the sponsor. This includes IEGMs of non-sustained VTs, atrial episodes as well as ventricular episodes with or without ICD therapy. IEGMs based on a technical trigger do not need to be provided.

For all ICD therapy episodes and ICD therapy attempt episodes in **group A** it is mandatory to provide an IEGM and evaluate the episode in the tachyarrhythmia episode form. The investigator should evaluate the appropriateness of the episode and the success of the delivered ATPs and/or shocks to terminate the episode. Furthermore physician is asked to evaluate the last 3 episodes with fast ventricular rhythm (SVT, nsVT) prior to the follow-up (if available) and enter the evaluation in the tachyarrhythmia episode form. Evaluation of atrial tachyarrhythmias is not required. However, IEGMs of all available episodes should be provided independet of the type of episode.

The Recording episodes IEGM is activated by default and has to remain activated during the course of this clinical investigation[f] in both study groups (**A** and **B**). It is possible to check the activation on the Renamic programmer, by selecting the following tabs, see Figure 7:

Parameters → Diagnostics → Recording episodes → AT/AF, SVT and nsVT ON

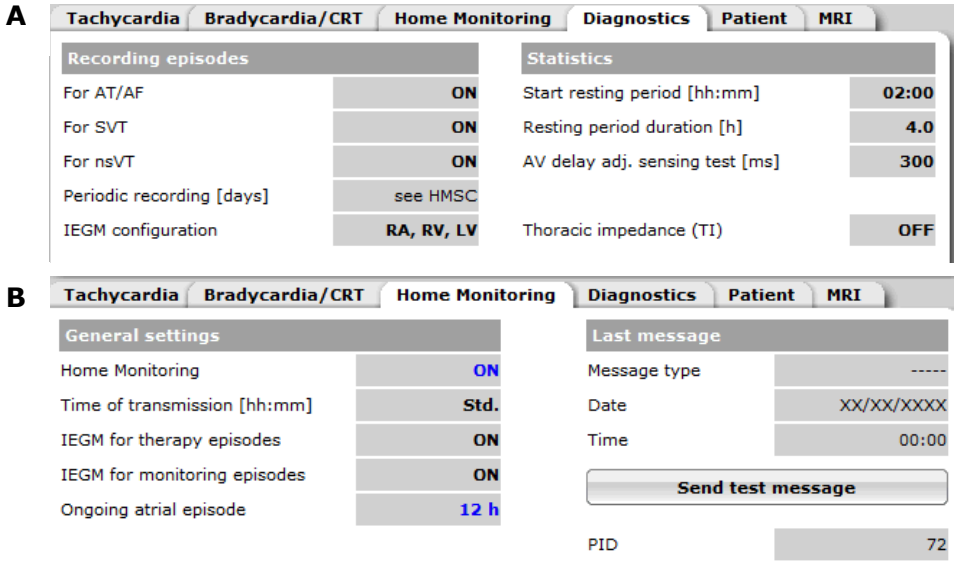

Fig. 7: Check of activation of event triggered IEGM transmission on the programmer. A: Check of activation of all recording types; B: Check of activation of IEGM transmission via Home Monitoring

To store the IEGMs, each event has to be opened manually:

The event-triggered IEGM (Figure 8) can be displayed by selecting the button [Recordings] in the menu bar on the right.

[f] Longevity of the device battery according to the Manual is calculated with recording episodes permanently set. However, it is in the investigators` decision to deactivate the function after study termination of the patient to save battery.

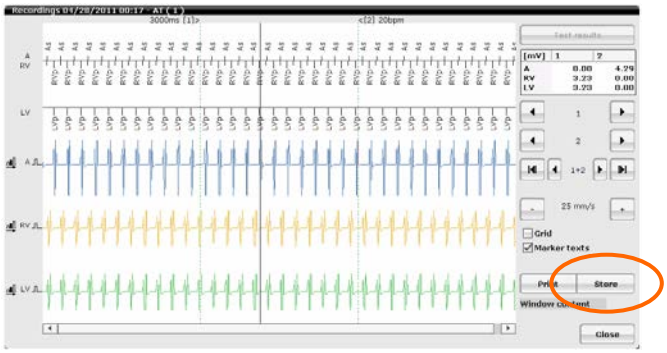

Fig. 8: Example of event-triggered IEGM as displayed on the programmer

8.5.8 MRI AutoDetect functionality

In case a patient of **group A** is planned to undergo an MRI scan, information on the MRI AutoDetect functionality will be collected if function is used. The physician should document the use of the test mode and further information. Furthermore a copy of all available doctors` letters or additional written information should be forwarded to the sponsor. Home Monitoring data will be used to collect further information on the MRI process in regard to the device behavior.

8.5.9 DX programming and measurements

Information on the use of the DX functionality will be collected. The atrial sensing amplitude should be measured either manually or automatically at each follow-up for **group A**. Furthermore for CRT-D devices of **group A** further CRT statistics and information on atrial burden according to device statistics will be documented.

8.5.10 Lead measurements with pacing sensing analyser (PSA)

During implantation the physician is asked to measure sensing amplitudes, pacing impedance and pacing thresholds via PSA in all available channels for patients in **group A**. For patients in **group B** only measurements of the right ventricular lead are required. For the measurement of pacing threshold a pulse width of 0.4ms is mandatory in the RV and RA channels. Furthermore shock impedance should be measured and documented, if routinely available, in both groups, **A** and **B**.

For patients in **group A** receiving a CRT-D device, measurement of different pacing vectors is highly recommended in the LV lead to determine if adequate vectors are available for programming of MPP later on (see also section 8.5 “MPP programming and Measurements”).

8.5.11 Lead measurements at each follow-up

The system performance and right ventricular lead performance is evaluated at the end of the implantation procedure and **at the end** of each follow-up for both groups **A** and **B** 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 the RA and RV the pulse width must be 0.4 ms, in the LV any pulse width can be chosen. For patients in **group A** measurement of all LV pacing vectors is **mandatory** prior to programming of the MPP feature, either after implantation or at time of Pre-hospital discharge. Pacing polarities of the LV

channel must be documented. For patients of **group B**, only measurement of the right channel is required (in DX leads also sensing measurements in the atrial channel).

In group A and B the appropriate sensing and pacing should be evaluated at the 3-month follow-up. In **group A** evaluation should be done in all available channel. In **group B** only the RV channel has to be assessed, for DX leads additionally also the atrial sensing. For the evaluation it is necessary to record 10 consecutive intrinsic beats and 10 consecutive pulses with markers on the IEGM, respectively. The "freeze" button needs to be pressed to store the IEGM electronically. 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".

All measurements and tests have to be stored and provided to the sponsor.

8.5.12 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. Furthermore programmer data should be provided also for interim visits of the patient at the study site. 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 (see Fig 8). IEGMs have to be actively opened once to ensure storage and export.IEGMs used during follow-up to assess pacing and sensing performance of the Plexa ICD lead (group B) have to be frozen and stored to ensure availability in the programmer export.

The programmer data and IEGMs can be provided to the sponsor by the following options:

- Upload to the EDC system
- Delivery via email to Ilivia-family-Plexa@biotronik.com
- Delivery via USB stick
- Delivery via Report Share function to the Home Monitoring Service Center (if available)

For every export it has to be ensured that data are pseudonymized. Furthermore the xml file as well as a PDF should be provided to the sponsor.

8.5.13 Plexa ICD lead handling

In **group B**, during implantation, the handling of the Plexa ICD lead will be assessed by the implanting physician. All data will be collected on the specific eCRF "Plexa lead handling".

The physician should rate the performance as "excellent", "good", "average", "fair" or "poor". The following characteristics have to be assessed:

- Tracking from deployment to target area
- Flexibility
- Pushability
- Ability to position the lead in the RV
- Ability to extend/extract the lead
- Ability to visualize the extended screw (if routinely available)
- Ability to fixate the lead tip
- Radiopacity in final position (if routinely available)

Furthermore the number of turns needed to extend the screw should be documented.

8.5.14 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.

8.5.15 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 9.10.2). All adverse events will be evaluated in their relation to the investigational devices. 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.

8.6 Replacement of subjects

During the course of the study, patients that drop out prior to any implantation attempt do not count to the total enrollment number and 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.

8.7 Used devices

8.7.1 Description of exposure to the investigational device

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.

8.7.2 List of any other medical device to be used during the investigation

Group A: The following medical devices will be used for group A (Ilivia ICD family):

Device:	BIOTRONIK Ilivia/Initica/Inlexa 7 series VR-T, VR-T DX, DR-T, HF-T QP; Intica 5 series VR-T, VR-T DX, DR-T
RA-leads:	Free of choice, if applicable
RV-leads:	Free of choice, BIOTRONIK Plexa ICD lead recommended
LV-leads:	BIOTRONIK Sentus OTW QP lead, if applicable
External programming device:	Renamic only
Programmer software:	PSW1505.A (or successors) including software for Ilivia ICD family
Remote monitoring tools:	BIOTRONIK CardioMessenger® II or II-S or Smart 3G (or successors)
Remote monitoring software:	Home Monitoring Service Center (HMSC) III (or successors)

Group B: The following medical devices will be used for group B (Plexa ICD lead):

Device:	any BIOTRONIK single, dual or triple chamber ICD; BIOTRONIK Ilivia ICD family is recommended
RA-leads:	Free of choice, if applicable
RV-leads:	BIOTRONIK Plexa ICD lead
LV-leads:	Free of choice, if applicable
External programming device:	Renamic only
Programmer software:	PSW1505.A (or successors)
Remote monitoring tools:	BIOTRONIK CardioMessenger® II or II-S or Smart 3G (or successors)
Remote monitoring software:	Home Monitoring Service Center (HMSC) III (or successors)

Group A and B: The following medical devices will be used for patients enrolled in group A and B:

Device:	BIOTRONIK Ilivia/Initica/Inlexa 7 series VR-T, VR-T DX, DR-T, HF-T QP; Intica 5 series VR-T, VR-T DX, DR-T
RA-leads:	Free of choice, if applicable
RV-leads:	BIOTRONIK Plexa ICD lead
LV-leads:	BIOTRONIK Sentus OTW QP, if applicable
External programming device:	Renamic only
Programmer software:	PSW1505.A (or successors)
Remote monitoring tools:	BIOTRONIK CardioMessenger® II or II-S or Smart 3G (or successors)
Remote monitoring software:	Home Monitoring Service Center (HMSC) III (or successors)

All medical devices are used within their intended use after CE approval or respective (study) approval by regulatory institutions in countries located outside of the CE area

8.7.3 Device settings

The mandatory device settings are summarized in the following Table 6. In general, the device programming should be medically reasonable. The following settings are **mandatory** for participation in this clinical investigation:

Tab. 6: Mandatory device programming

Parameter	Device setting
Home Monitoring	On
Capture control in all channels (**group A**) or RV channel (**group B**)	On or ATM
Recording episodes IEGM	On* (default setting)
	Programmer setting
Group A:	
MultiPole Pacing (CRT-D only)[g]	On*
ATP one shot	On*

* as described in section 8.5

8.7.4 Number of investigational devices to be used and a justification

In the BIO|MASTER.Ilivia Family / Plexa study 105 ICDs of the Ilivia family and 185 Plexa ICD leads are required to be used, which equals one Ilivia ICD device and/or one Plexa device per patient. For justification of sample size please refer to section 11.2. However, additional investigational devices may be used due to ICD device exchange during the study.

8.8 Subjects

8.8.1 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 a ICD of the Ilivia family and/or the Plexa ICD lead according to the investigators' decision may be enrolled into the BIO|MASTER.Ilivia Family / Plexa 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.

[g] Continuation or deactivation of the MPP feature after study termination is in the discretion of the treating physician. For battery use please refer to the manual of the Ilivia ICD family.

Group A:

Collective:	Patients with an indication for ICD therapy or cardiac resynchronization therapy with defibrillator (CRT-D) according to the current clinical practice.
Total number of patients:	105, thereof • 26 with indication for single chamber ICD (VR-T or VR-T DX device) • 26 with indication for dual chamber ICD (DR-T device) • 53 with indication for triple chamber (CRT) defibrillator (HF-T QP device)

Group B:

Collective:	Patients with an indication for ICD therapy or cardiac resynchronization therapy with defibrillator (CRT-D) according to the current clinical practice.
Total number of patients	185

8.8.2 Inclusion criteria

All of the following inclusion criteria have to be fulfilled for enrollment of the patient to the clinical trial:

1. Standard indication for ICD or CRT-D therapy according to clinical practice
2. *De novo* implantation or upgrade/exchange[h] (**group A** only) from existing ICD/CRT-D[i] or pacemaker implant
3. Patient is able to understand the nature of the clinical investigation and provides written informed consent
4. Patient is able and willing to complete all routine study visits at the investigational site
5. Patient accepts Home Monitoring concept
6. Age ≥ 18 years

8.8.3 Exclusion criteria

The following exclusion criteria shall **not** be fulfilled for enrollment of the patient:

1. Contraindication to ICD or CRT-D therapy, respectively
2. For CRT-D patients in **group A** only: physician not willing to activate MultiPole Pacing in the patient

[h] Upgrade or exchange is not available for patients in group B due to possible interference between the previous implanted RV lead and the new implanted Plexa ICD lead (e.g. potential Adverse Events in which relation cannot be distinguished between both leads)

[i] Exchange of CRT-D device is only possible in group A, if patient is either already implanted with BIOTRONIK Sentus OTW QP lead or replacement of the LV lead is planned.

3. Cardiac surgical procedure planned within 6 months after implantation (including also interventional procedures like ablation, valve replacement etc.). Procedures to occur during or prior to implantation are not exclusionary.
4. Expected to receive heart transplant or ventricular assist device within 6 months
5. Life expectancy less than 6 months
6. Participation in any other interventional clinical investigation[j]
7. Pregnant or breast feeding at time of enrollment

8.8.4 Drop-out criteria

8.8.4.1 Mandatory drop-out according to protocol

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

- **Group A:** Patient is not implanted with a member of the Ilivia ICD family for any reason
- **Group A:** Patient in whom explantation or replacement of the Ilivia ICD is performed
- **Group B:** Patient in whom implantation of Plexa ICD lead was planned but not performed
- **Group B:** Patient in whom explantation, replacement or repositioning of the Plexa ICD lead is performed
- Patient undergoes heart transplantation or receives ventricular assist device during the course of the study.

If a patient participates in both groups, drop-out in one group does not result in drop-out of the other group, thus the patient can continue participation in the other study group.

8.8.4.2 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 which render a further participation of the patient impossible.

8.8.4.3 Withdrawal of patient consent

Patients may withdraw their consent for study participation at any time without stating the reason and without any unfavourable consequences. All data which are collected until the date

[j] Based on the European clinical trial directive 2001/20/EC, we consider a clinical investigation as non-interventional, if the products under investigation are prescribed in the usual manner in accordance with the terms of the marketing authorization, the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice, the prescription of the product under investigation is clearly separated from the decision to include the patient in the study, no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data. Otherwise the study is considered as interventional.

of withdrawal will be used in pseudonymized form. However, patients can request anonymization of the data at the study site. A study termination sheet has to be filled in by the investigator.

8.8.5 Point of enrollment and study termination

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

The point of study termination is defined as date of 6-month follow-up for patients with regular study termination.

For a non-regular study termination, the following rules apply:

- If none of the investigational devices could successfully be implanted, date of study termination should be the date of the last unsuccessful implantation attempt.
- In case of replacement or repositioning of the Plexa ICD lead in patients of **Group B** date of study termination should be date of revision.
- In case of withdrawal of a patient's consent, date of study termination should be the date of withdrawal of consent.
- In case of patient death, the date of study termination should be the date of the patient's death.
- If patient is lost to follow-up, date of termination should be the date of last contact of the physician to the patient.
- If patient is defined as drop-out patient for any other reason, date of study termination should be the date of latest medical information of the patient (e.g. follow-up, IEGM).

Study related procedures and documentation should 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.

8.8.6 Timelines

First Patient In (FPI)*:	~ June 2016
Last Patient In (LPI)*:	~ July 2017
Enrollment period:	~ 14 months
Last Patient Out (LPO)*:	~ January 2018
Total study duration:	~ 20 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

9 STUDY PROCEDURES

9.1 Overview

Table 7 provides an overview of the study procedures.

Tab. 7: Time schedule and procedures for all patients. Group specific procedures of group A are displayed in blue, and group specific procedures of group B are displayed in green.

Investigations	Enroll-ment	Implan-tation	Pre-hospital discharge	Month 3 ± 30 days	Month 6 ± 30 days
Patient informed consent	x				
Verification of in- and exclusion criteria	x				
Demographic data	x				
Indication for ICD or CRT-D therapy	x				
ECG diagnostics (if available)	x				
NYHA class (if available)	x				X (CRT-D only)
Heart Failure Parameters (LVEF) (if available)	x				
Physicians evaluation responders/non-responders (CRT-D only)					x
Co-morbidities	x				
Cardiovascular medication	x				
Decision on group participation		x			
ICD/CRT-D system implantation		x			
Information / Measurements on DX devices (only if DX is implanted)		x	x	x	x
Device statistics CRT pacing, atrial burden (CRT-D only)			x	x	x
Programming/Handling/Change of programming of MPP		(x)	x	x	x
Programming of device settings		(x)	x		
Programming / Information on Early ATP one-shot		x			
Lead measurements with PSA		x			

Document the handling of Plexa ICD lead		x			
IEGMs of pacing and sensing test / Evaluation of appropriate sensing/pacing				x	
IEGMs / evaluation of ATP one shot success		x	x	x	x
IEGMs and documentation of ventricular tachycardia therapy episodes		x	x	x	x
IEGMs and documentation of the last 3 episodes with fast ventricular rhythm (e.g. SVTs. nVTs) prior to a follow-up		x	x	x	x
Lead measurements		x	x	x	x
IEGMs of all medical episodes (ventricular and atrial episodes, non-sustained VTs and fast intervals)		x	x	x	x
Documentation of MRI examinations, if applicable		x	x	x	x
Adverse event reporting	x	x	x	x	x
Device deficiency reporting		x	x	x	x
Regular study termination					x

9.2 Enrollment

Prior to enrollment into the clinical investigation, all patients will be evaluated by their physician for fulfilling the inclusion criteria. For valid enrollment the informed consent form has to be signed and dated by the patient and also signed and dated by the investigator. The informed consent process has to be documented in the patient record. In case date of enrollment is identical with date of implantation, the exact time of informed consent shall be entered in the patient record to document that informed consent has been obtained prior to any study-specific procedure.

The signed informed consent will be verified by the monitor. The date of enrollment is defined by the patients` signature date of the informed consent. The investigator has to check whether all inclusion criteria are met and the absence of all exclusion criteria is confirmed.

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's demographics
- Indication for ICD or CRT-D therapy
- 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

9.3 Implantation

All patients will be **either** implanted with one of the Ilivia ICDs (**group A**) **and/or** the Plexa ICD lead (**group B**). If both devices are implanted patients will participate in both groups as long as enrollment in both groups is still ongoing. Implantation shall be performed within 30 days after enrollment of the patient to the study.

Patients with planned pacemaker or ICD upgrade to ICD or CRT-D or exchange can also be included in the study (**group A** only).

The specific requirements of the implantation procedures are listed below:

1. Perform lead measurements prior to connection to the device. For patients in **group B** only measurements of the RV lead are required. Pacing thresholds for RA and RV lead have to be measured at a pulse width of 0.4ms. For CRT patients in **group A**, threshold measurements of at least the 6 recommended LV vectors is recommended to ensure availability of a suitable vector combination for MPP programming.
2. After lead connection to the ICD or CRT-D device, the following data have to be recorded during this follow-up:
   - Pacing thresholds measured manually or triggered automatically. In the RA and RV the pulse width must be 0.4 ms, in the LV any pulse width can be chosen. For patients in **group B** only measurement of the RV lead is required. For CRT-D patients in **group A** pacing thresholds in all 12 available LV vectors have to be measured, if MPP programming is already planned at this point in time.
   - P/R-wave sensing amplitude (mean value) of all channels (or RV lead only (**group B**)) including also atrial sensing amplitude in DX leads.
   - Pacing impedance of all channels (or RV lead only (**group B**)). For the LV channel, measurement of the pacing threshold automatically also provides impedance measurement values.
   - Painless shock impedance Pacing polarities of the LV channels (CRT-D only (**group A**))
3. **Group A:** Program and document settings for MPP and evaluate handling of the programming function of the programmer. For programming follow the recommendations provided in section 8.5.6. Document all information on the eCRF "MultiPole Pacing". MPP programming can be delayed but has to be finalized latest at Pre-hospital discharge.

Group B: Collect information on implant procedure regarding incision to suture time final position of RV lead, etc., and evaluate the Plexa ICD lead handling during the implant procedure (x-ray visibility (if routinely available), stability of the lead etc. as described in section 8.5.13). Document all data on the eCRF "Plexa lead handling".

4. Program the following mandatory device settings:
   - Home Monitoring "ON"
   - Capture control "ON" or "ATM" in all channels (**group A**) or RV only (**group B**)
   - Recording episode IEGMs (event-triggered) "ON" (see specifics of programming in section 8.5.7)

     Group A:

   -
   - For CRT-D only: MPP "ON" (see specifics of programming in section 8.5.6)
   - ATP one-shot in VF zone "ON" (see specifics of programming in section 8.5.5)
   - Early ATP one-shot "ON" (recommended)

   Programming can be delayed but has to be finalized until pre-hospital discharge.
5. Register to Home Monitoring Service Center.
6. Complete the electronic Case Report Form (eCRF) immediately.
7. Report all adverse events. In case of a serious adverse event, or adverse device effect (ADE), please provide the information to BIOTRONIK and inform the ethical committee, if required. If the Ilivia ICD or Plexa ICD lead is exchanged or repositioned the follow-up schedule is adapted as described in section 9.8 "Interim Intervention". Report adverse events within the indicated timelines (see section 18.9).

9.4 Pre-hospital discharge

At pre-hospital discharge follow-up (PHD) the following procedures are required.

Prior to the patient's 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 PHD visit have to be recorded on the respective eCRF.

1. Perform a regular follow-up procedure as described in the next section "3-month follow-up procedure" with exception of the evaluation of sensing and pacing performance and documentation of MRI examination.
2. If MPP programming has not been done before, measure pacing threshold of all 12 available LV pacing vectors in CRT patients of **group A** to determine best suited vectors for MPP programming. Afterwards program MultiPole Pacing following programming recommendations in section 8.5.6 (CRT-D patients in group A only)
3. If not done before, activate the following features or rather ensure that the features are activated:
   - Home Monitoring "ON"

- Capture Control "ON" or "ATM" in all channels (**group A**) or the RV channel only (**group B**)Recording episodes (Event-triggered) IEGMs "ON" (see specifics of programming in section 8.5.7)

  Group A:

- For CRT-D only: MPP "ON" (see specifics of programming in section 8.5.6)
- ATP one-shot in VF zone "ON" (see specifics of programming in section 8.5.5)
- Early ATP one-shot "ON" (recommended)

The activation of these features is mandatory (recommended: Early ATP) during the entire course of the study.

4. Check if registration to Home Monitoring Service Center is completed, 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.

5. Complete the electronic Case Report Form (eCRF) immediately.

6. 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). If the Ilivia ICD or Plexa ICD lead is exchanged or repositioned the follow-up schedule is adapted as described in section 9.8 "Interim Intervention". Report adverse events within the indicated timelines (see section 18.9).

9.5 3-month follow-up

Three months (± 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 functions. The requirements of this procedure are listed below:

1. Reprogramm ICD settings as applicable to optimize ICD/CRT-D functions
2. The following data have to be measured at the end of the follow-up (same as during implantation) with the final programmed ICD settings:

   - Pacing thresholds measured manually or triggered automatically in all channels (**group A**) or RV only (**group B**). For patients in **group A** with MPP activated, both LV vectors have to be measured accordingly. In all channels the pulse width must be 0.4 ms.
   - P/R-wave sensing amplitude (mean value) of all channels (or RV lead only (**group B**), including also atrial sensing amplitude in DX leads.

- Pacing impedance of all channels (or RV lead only (**group B**)). For the LV channel, measurement of the pacing threshold automatically also provides impedance measurement values.
- Painless shock impedance
- Pacing polarities of the LV channel (CRT-D devices only (**group A**))
- Evaluate the system performance at end of follow-up for all channels (**group A**) or the RV channel and for DX lead also atrial sensing channel (**group B**). It is recommended to record 10 consecutive intrinsic beats (sensing test) and 10 consecutive pulses (threshold test) with markers on the IEGM. Press the "freeze" button to store the IEGM electronically.

3. Document device statistics for CRT-D patients (CRT-D patients only).
4. Document changes in programming of MPP settings, if applicable (**group A**, CRT-D patients only).
5. Evaluate ventricular ICD therapy/therapy attempt episodes: open and store IEGMs of all episodes; all VF and VT episodes according to device detection. Evaluate each episode on the Tachyarrhythmia episode form. Furthermore, evaluate the last 3 episodes with fast ventricular rhythm (SVT, nsVT) prior to the follow-up, if available (**group A**).
6. Open and store IEGMs of all event-triggered episodes: therapies, non-sustained VTs, fast intervals and atrial episodes (**group A** and **B**).
7. Document MRI examinations since last follow-up in eCRF "MRI AutoDetect form", if applicable (**group A**).
8. 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. If the ICD or lead is exchanged or repositioned the follow-up schedule is adapted as described in section 9.8 "Interim Intervention". Report adverse events within the indicated timelines (see 18.9).
9. Complete the electronic Case Report Form (eCRF) immediately.

9.6 6-month follow-up

Patients have to return for a final follow-up visit, six months (± 30 days) after the implantation procedure. The study procedures performed at this visit are identical with the procedures for the 3-month follow-up with exception of the evaluation of sensing and pacing performance.

In addition for patients in **group A** the following assessments have to be performed:

- Determine NYHA class of the patient (CRT-D only)
- Define if patient is considered a responder or non-responder to CRT-D therapy (CRT-D only)

After this follow-up procedure the patients will officially terminate the BIO|MASTER.Ilivia Family / Plexa Study.

9.7 Termination

The patients terminate the study regularly after the completion of the 6-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.

9.8 Interim Intervention: Lead / Device Revision

For all revisions, an interim intervention eCRF has to be completed. Information has to be provided on the nature of the event, the affected device and any newly implanted devices. If the ICD is repositioned or the LV lead is revised and a Sentus QP lead remains active after the revision (**group A**), lead measurements have to be performed at the end of the revision as defined in the 3-month follow-up. Furthermore in case of CRT-D, changes on MPP programming have to be documented (**group A**), if applicable.

An Adverse Event Report has to be completed for every interim intervention.

In case of any revision with invasive corrective action, the following follow-up schedule applies:

- Patients are drop-outs in case of Ilivia and/or Plexa explantation or exchange and/or Plexa repositioning after initial implantation. In case patients participate in both groups A and B, drop-out is only applicable for the respective group.
- In case of Ilivia repositioning at any time after implantation, the initial follow-up schedule remains unchanged. The data will be used for further analysis.
- In case of unsuccessful implantation of Ilivia and/or Plexa, the patient is a drop-out patient. No further follow-ups are performed. Patients participating in both groups A and B are only considered drop-out patients in the respective group.
- In case of revision of a non-investigational device at any time after implantation, the initial follow-up schedule remains unchanged. The data will be used for further analysis.

9.9 Description of activities performed by sponsor representatives

9.9.1 Sponsor

The sponsor of the BIO|MASTER.Ilivia Family / Plexa Study is:

BIOTRONIK SE & Co. KG
Woermannkehre 1
D-12359 Berlin
Phone: +49 (0) 30 68905 0

The sponsor ensures that all documents, information and necessary human resources in regards to the sponsors` responsibilities are made available for initiation, conduct and termination of the study.

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

- Contracting of an adequate insurance coverage for all participating patients
- Contracting of investigational sites and investigators
- Selection of suitable investigational sites, investigators and clinical monitors
- Support in obtaining of a favourable ethics vote(s) for conduct of the clinical study
- Obtaining approval of the involved competent authorities (if applicable)
- Ensure funding of the clinical trial
- Supervision of study conduct according to the legal regulatory requirements and the requirements of the CIP.
- Fulfil reporting duties of the sponsor to ethic committees and regulatory authorities.
- Data analysis and data management.

9.9.2 Clinical Project Manager

The clinical project manager is responsible for the following (selected 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 research associates, data assistants, data base managers).

9.9.3 Data Management

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

- Development and maintenance of the electronic data capture (edc) system (iMedNet of the company MedNet Solutions Inc, Minnetonka, MN 55305 USA)
- Development of the data management plan
- Development of the eCRF Userguide
- Data management

9.9.4 Statistician

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.

9.9.5 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.

9.10 Responsibilities of the investigator

9.10.1 Coordinating Clinical Investigator (CCI)

The BIO|MASTER.Ilivia Family / Plexa study is coordinated by:

Prof. Dr. Christian Sticherling
Universitätsspital Basel
Abteilung für Kardiologie/Elektrophysiologie
Petersgraben 4
CH-4031 Basel
Email : christian.sticherling@ubs.ch

Responsibilities of the Coordinating Clinical Investigator are listed in the following:

- Medical review of the clinical investigation plan
- Medical evaluation of adverse events during the study time course, if necessary
- Supervision of study progress and conduct of the clinical study
- Continuous assessment of the risk/benefit ratio if necessary
- If necessary, decision on premature termination of the study after consultation of the sponsor
- Giving advice to all investigators to medical questions related to the study or study conduct

The Coordinating Clinical Investigator is supported by the clinical project manager and other staff members of the sponsor.

In addition, the Coordinating Clinical Investigator has the same rights and duties as other principal investigators.

9.10.2 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 Principle Investigator retains the main responsibility for proper study conduct with respect to the following responsibilities:

- 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 and requirements of the Ethics Committee, if applicable

- Provide adequately trained staff including Co-Investigators and study nurses
- 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 medical devices
- 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 activities: The investigators are obliged to provide adequate access to the original patient files and other relevant source data related to the clinical study. Adequate manned and spatial resources have to be provided for all monitoring activities. The investigational sites need to collaborate closely with the clinical monitor. The investigational sites are obliged to keep the source data (e.g. patient files) and eCRF-entries up-to-date to ensure efficient and time-saving monitoring.
- Confidential treatment of all study-related documents and information

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

9.11 Essential documents

Prior to initiation of the study at the respective investigational site, the following documents have to be provided to the sponsor (copies of the documents shall be stored in the investigator's file[k]):

- Ethic vote of the local ethic committee (if applicable)
- Dated and signed CVs of all investigators involved in the clinical study.
- ISO certificate or training documentation of all investigators
- Dated and signed financial disclosure forms of the investigator involved in the clinical study at the time of initiation.
- Investigator statement signed and dated by all involved investigators.
- Study contract signed by the principle investigator and clinic's administrative department (if applicable).

The following documents will be provided to the investigational sites by the sponsor prior to initiation of the study:

- Approval by the competent authorities (if applicable)

[k] Exceptions can be made for the signed study contract during conduct of the clinical trial.

- All study related documents and material (this includes e.g. the clinical investigation plan, patient informed consent form, medical device information, eCRFs and log sheets)
- Valid certificate of patient insurance coverage including insurance terms and conditions

9.12 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 study protocol, applicable laws, and FDA and/or local regulations (e.g. CFR 21, parts 50, 54, 56, and 812, ISO 14155:2011, Declaration of Helsinki) and any conditions of approval imposed by the reviewing IRB/EC.

The entries in the eCRF will be reviewed and source data verified at the investigational site by monitors (authorized BIOTRONIK personnel, Clinical Research Associates-CRAs, or by authorized BIOTRONIK designees) to ensure that the investigator and the clinical investigation team conducts the clinical investigation in accordance with the CIP, The Declaration of Helsinki, ISO 14155:2011, and applicable FDA and local laws and regulations to ensure adequate protection of the rights, safety and wellbeing of subjects and the quality and integrity of the resulting data.

A monitor will visit the study site periodically during the study. All 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/IRB/CA has been informed about approved CIP changes as required, that records on study conduct and data collection are complete and present, that appropriate and timely reports have been made to the sponsor and the authorities, and that the investigator is carrying out all agreed activities.

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 14155:2011 and applicable FDA and local regulations and laws

If a monitor becomes aware that an investigator is not complying with the requirements mentioned above, the monitor is obliged to notify BIOTRONIK study management. BIOTRONIK will evaluate the non-compliance and issue corrective actions, discontinue enrollment or as a last measure close the clinical investigation site (see section 14 and 20).

11 STATISTICAL CONSIDERATIONS

11.1 Statistical design, method and analytical procedures

The BIO|MASTER.Ilivia Family / Plexa study is a prospective, single-arm, non-randomized, open clinical study.

For both primary hypotheses exact binomial tests are carried out. All endpoints are analyzed per-protocol (PP), whereby the analysis sets are defined for each hypothesis separately. Patients without written informed consent are not included in any analysis set. More details as already presented in section 8.3 will be presented in the Statistical Analysis Plan, which will be completed after finalizing this CIP.

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

11.2 Sample size

Sample sizes were calculated for each primary hypothesis separately. A correction for multiple testing is considered by adjusting the significance level. The global Null hypothesis and global Alternative hypothesis is given by the following combinations

H0: H01 AND H02

HA: HA1 OR HA2

Primary hypothesis 1 group A Ilivia family

The sample size for primary hypothesis 1 (safety of Ilivia ICD family) calculated for an exact test for binomial proportions resulted in 94 patients without drop-outs and 105 patients including 10% drop-outs. Thereby a SADE-free rate of 98% was assumed in the population.

Primary hypothesis 2 group B Plexa

The sample size for primary hypothesis 2 (safety of Plexa ICD lead) calculated for an exact test for binomial proportions resulted in 166 patients without drop-outs and 185 patients including 10% drop-outs. Thereby a SADE-free rate of 97% was assumed in the population.

11.3 Level of significance and the power of the study

The 2-sided level of significance is alpha = 2.5% for each alternative hypothesis (1-sided 1.25% significance level). Thus, the 2-sided significance level of the global hypothesis of 5% (1-sided 2.5% significance level) is maintained.

A minimum statistical power for primary hypothesis 1 of 80% and a minimum power of 90% for primary hypothesis 2 were used for sample size calculation.

11.4 Expected drop-out rate

It is expected that approximately 10% of the enrolled patients cannot be included in the analysis set for each primary hypothesis, e.g. due to lost-to follow-up or withdrawal of patient consent, respectively. This was considered in the sample size calculation.

11.5 Pass/fail criteria

The clinical investigation is deemed to be passed, if the primary Alternative hypothesis 1 or the primary Alternative hypothesis 2, or both primary Alternative hypotheses can be accepted.

11.6 Provision for an interim analysis

In the BIO|MASTER.Ilivia Family / Plexa study no interim analysis is planned to accept the primary alternative hypothesis, e.g. like in a group-sequential design.

However, in case of a significant discrepancy of the enrollment periods between both groups, the first group may be analyzed prior to the overall final analysis.

This kind of preliminary analysis would not bias the analysis of the other group, as the hypotheses of both groups are analyzed independently. The preliminary analysis of one group (after completion of data collection for this group) would not constitute a multiple interim testing and therefore does not necessitate further statistical adjustment.

Additionally, specific data[l] will be provided to the Australian competent authorities based on a database-freeze planned Q2/Q3 2017. This kind of preliminary analysis would not bias the further data because no investigator except the Coordination 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 the preliminary analysis.

11.7 Termination criteria

Group A of the clinical investigation will be terminated after confirmed knowledge of at least 4 patients with one or more Ilivia-endpoint-related SADEs (see 18.11), because it would be impossible to accept the primary Alternative hypothesis 1 for the planned sample size.

Group B of the clinical investigation will be terminated after confirmed knowledge of at least 9 (or at least 10 in case of a low dropout rate) patients with one or more Plexa-endpoint-related SADEs (see 18.11), because it would be impossible to accept the primary Alternative hypothesis 2 for the planned sample size.

11.8 Procedures for reporting of deviations to the statistical plan

Deviations from the statistical plan described in this Clinical Investigation Plan and the Statistical Analysis Plan (latest version finalized before database closure) will be documented in the Clinical Investigation Report.

[l] A detailed description of all variables will be provided in the Statistical Analysis Plan.

11.9 Specification of subgroups

Results of the Ilivia ICD family and the Plexa ICD lead are analysed separately. No further subgroup analysis is planned.

11.10 Procedure for accounting of all data for analysis

Due to the required strict adherence to the monitoring plan, the data acquisition of all data is ensured. In certain circumstances, the following data handling requirements need to be considered:

1) In case of lead explant/repositioning/exchange, additional lead implantation, or ICD repositioning at any time, the data will be used for further analysis. The corresponding follow-up schedule is described in section 9.8 Interim Intervention: Lead / Device Revision.
2) If a patient belongs to both groups A and B, the data will be used for the analysis of groups A and for the analysis of group B.

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

If the patient has atrial fibrillation during the device based measurements, the P-wave amplitude and the atrial threshold are not included in the analysis.

Protocol deviations in regard to the follow-up schedule will not result in an exclusion of data in the analysis but will be subject to query management. Detailed information will be provided in the Statistical Analysis Plan.

Further exclusion of data are defined in section 8.1

11.13 Minimum and maximum number of patients per site

To minimize site-specific bias, the maximum number of patients per center will be n= 40. Each center should implant at least 10 patients (including drop-outs).

12 DATA MANAGEMENT

The Clinical Data Management is conducted to assess compliance with accepted current external standards (ISO 14155:2011, FDA 21 CFR Part 11, ICH GCP, GCDMP) as well as compliance with BIOTRONIK internal standards.

By signing the informed consent form, the patient agrees with the collection of specified data during the study performance and transmission of this data to BIOTRONIK and also to national and foreign authorities, if required. All clinical data collected is pseudonymized, without using patient initials, to ensure traceability of data, but preventing unauthorized identification of individual patients. Applicable national and international requirements pertaining to data protection of the subjects is respected during the study and until the end of the archiving period.

At the investigational sites, the Principal Investigator is responsible for the confidentiality of subject data and protection of all study related data against unauthorized access. At BIOTRONIK, these duties are followed by all staff in contact with clinical study data. This includes, but is not limited to the clinical data management team, the clinical monitoring team, and the responsible Clinical Project Manager.

All raw-data will be entered in the adequate documentation sheets and will be collected in adequate files (e.g. patient files, depending on the organizational structure of the investigational site). The clinical data have to be stored and shall be made available upon request in order to allow source data verification.

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

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

All incoming clinical data will be checked for correctness, completeness and consistency.
Incorrect, incomplete or inconsistent data will be scrutinized via query.

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

Data recorded in the eCRFs are checked against source data by clinical monitors during periodic monitoring visits as described in the Monitoring Plan. Furthermore, eCRF entries of device data will be checked against provided source data (e.g. programmer exports) by the in-house monitor. If corrections are necessary, entries have to be corrected accordingly by the designated site personnel in the eCRF and have to be signed by the investigator.

Queries will be used to clarify incorrect, incomplete or inconsistent data. Queries will be originated by the clinical data manager, the monitor or the in-house clinical research associate

on behalf of the sponsor after review of incoming data and will be submitted to the respective investigational site directly in the eCRF.

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

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

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

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

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

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

12.3 Procedures for data retention

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

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

12.4 Specified retention period

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

13 AMENDMENT PROCEDURES

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

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

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

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

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

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, as well as applicable amendments. Deviations that are likely to seriously affect or that actually have seriously affected the rights or safety or wellbeing of subjects or the scientific integrity of the clinical investigation are **major** deviations. Otherwise they are **minor** deviations.

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

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

14.2 Recording, reporting and analyzing deviations

14.2.1 Site specific deviations

Investigational sites inform the monitor immediately about any deviation as they become aware of it. In addition, compliance to the CIP is verified by the sponsor through monitoring visits. Each site specific deviation is recorded in the EDC system and will be assessed by the monitor for the need of corrective or preventive actions. All information from EDC system is consolidated by the sponsor in one overall **study deviation log**.

14.2.2 Other deviations

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

14.2.3 Reporting

Deviations are reported in the interim and final Clinical Investigation Reports.

14.3 Notification requirements and timelines

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

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 log to identify the need of general preventive actions.

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

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

15 DEVICE ACCOUNTABILITY

All medical 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 in all countries accepting CE mark. However, the implanted Ilivia ICDs and Plexa ICD leads are identifiable by a unique serial number. This number will be recorded on **the implantation eCRF form**. By need or at least at the end of the study, a list with all used devices will be created.

For participating countries outside of the CE region, the sponsor keeps records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until usage, disposal or return. An electronic device accountability log is used via access on the EDC system for the documentation of the whole process.

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

The Principal Investigator or an authorized designee shall keep records documenting the receipt, usage, return and disposal of the investigational devices.

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

The information of the device accountability log will be verified by the responsible BIOTRONIK personnel during the clinical investigation. After the closure of the study, the summary of this log will be used for the Clinical Investigation Report.

16 STATEMENT OF COMPLIANCE

16.1 Applicable ethical standards

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

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

16.2 Applicable international and national standards

The study will be conducted in compliance with the international standard ISO 14155:2011 "Clinical investigation of medical devices for human subjects – Good clinical practice".

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

However an Investigator´s Brochure will be provided for investigational sites outside the CE region if required by the respective national regulations.

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

16.3 Ethics committee and competent authority

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

16.4 Statement of adherence to additional requirements

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

16.5 Statement on subject insurance

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

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

17 INFORMED CONSENT PROCESS

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

17.1 General considerations

The informed consent procedure is performed by the Principal Investigator or any investigator designated for this task as recorded in the delegation of duties log. The investigator has to fully inform the patient of all pertinent aspects of the clinical investigation in language and terms she/he is able to understand. When the patient agrees in the study participation, the patient as well as the investigator who performed the informed consent discussion both personally write the date and sign on the informed consent form. Date 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. If the implantation is performed on the same day, also the time of patient´s signature has to be documented. A copy of the signed and dated written informed consent form is provided to the patient.

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

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

17.2 Special circumstances for informed consent

Inclusion of subjects unable to read or write:

Informed consent will be obtained through a supervised oral process if a subject is unable to read or write. An independent witness will be present throughout the process. The written informed consent form and any other information will be read aloud and explained to the prospective subject and, whenever possible, either will sign and personally date the informed consent form. The independent witness also signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given.

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 with exception of those listed in section 18.1 and all DDs of the investigational devices shall be assessed by the investigator and shall be documented and reported throughout the clinical investigation within the timelines defined below.

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

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

18.1 Definition of adverse events

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

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

*see ISO14155:2011 3.2

Exceptions:

Phrenic nerve stimulation occurring during implantation or MPP tests are only considered Adverse Events and have to be reported in case it results in a serious medical condition.

Tachyarrhythmia episodes in a patient with ICD /CRT-D indication are not considered as Adverse Events as they are part of his underlying condition. However, tachyarrhythmia episode have to be reported as Adverse Event in case the episode resulted in a serious medical condition.

Recurrent inappropriate therapies resulting from the same origin and detected within a 3 months' time period may be summarized in one Adverse Event Report.

18.2 Definition of adverse device effects

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

*see ISO14155:2011 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/treatment, the natural history of the underlying disease, other concurrent illness or risk factors. Each SAE will be classified according to five different levels of causality. Based on MEDDEV 2.7/3 rev 3, the investigator will use the following categories to assess the relationship of the serious adverse event to the investigational medical device or procedures and the sponsor will review the investigator's 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 were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

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

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

The investigators will distinguish between the serious adverse events related to the investigational device and those related to the device procedures (i.e. procedure related to the application of the investigational medical device only and therefore not to any other procedure for other devices or treatments applied later throughout the clinical investigation, for instance to treat adverse events). Replacement procedures of the investigational device are considered as an application of a new investigational device and shall be assessed accordingly. The sponsor will review the investigator's assessment of device or procedure relatedness.

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

18.3 Definition of device deficiency

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

*see ISO14155:2011 3.15

DDs of the investigational devices 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 a 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 ISO14155:2011 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 pseudomized copy of the death records, an autopsy report (if performed) and a doctors 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, as detailed as possible:

- Cause and circumstances of the 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 ISO14155:2011 3.6

18.6 Definition of unanticipated serious adverse device effects

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

*see ISO14155:2011 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 Adverse Events may possibly occur as medical complications of an ICD or CRT system implantation. The most common adverse events related to the ICD or CRT therapy are listed in Tables 8a-e. All references used for this chapter refer to the list at the end of this section.

Tab.8a: Expected peri-operative events based on literature research

Frequency	**Percentage** (%)	**Risk**
Very frequent >1 out of 10 patients	7-19[45]	LV lead exchange due to unsuccessful positioning
	3-27[32]	Atelectasis (when thoracotomy necessary)
	3-27[32]	Pleural effusion (when thoracotomy necessary)
	3-27[32]	Pneumonia (when thoracotomy necessary)
	Up to 17[32]	VT/VF exacerbation[8,32]
Frequent 1 to 10 patients out of 100	1-7[32]	Infection (general)
	5.2[55,56] - 6[32]	Lead perforation
	3-4[32]	Pericarditis (when patch lead placement necessary)
	Up to 3[32]	Embolism
	Up to 3[49]	Phrenic nerve stimulation
	0.6 – 2.0[49]	Infection requiring reoperation

	0.07*-3[32,54]	Pericardial tamponade (2-3% during patch lead placement)
	0.93[31]-10.6[2,49]	Lead dislodgement
	0.12[31]–3.4[49]	Coronary sinus dissection
	0.42[31] -1.1[68]	Pneumothorax
	1.2[68]	Hematoma
Occasionally 1 to 10 patients out of 1.000	0.7[54]	Loosening of set screw
	0.02[31] -1[30]	Myocardial infarction
	0.06[31]-2[32]	Cerebrovascular accident, stroke (1-2% during thoracotomy)
	0.6[30]	Lead dysfunction
	0.5[30] – 0.7[57]	Mortality
	0.5[30]	Severe pocket hematoma
	0.5[54]	Pericardial tamponade (2-3% during patch lead placement)
	0.3[31] – 0.4[49]	Cardiac arrest
	0.2[30]	Arrhythmia
	0.2 – 0.3[49]	Respiratory arrest
	0.2[49]	Tamponade
	0.1 - 0.4[51]	Allergic reaction to ionic contrast material
	0.14[50]	Air embolism
	0.1[49]	Lead fracture/ insulation failure
	0.1[59]	Ventricular fibrillation
Rare 1 to 10 patients out of 10.000	0.09[31]	Drug reaction
	0.08[31]	Hemothorax
	0.07[31]	Cardiac perforation
	0.04[31]	Phlebitis, superficial
	0.03[31]	Conduction block
	0.03[31]	Infection related to device
	0.03[31]	Peripheral embolus
	0.02[52]– 0.04[53]	Allergic reaction to non-ionic contrast material
	0.02[31]	Phlebitis, deep
	0.02[31]	Transient ischemic attack
Very rare <1 patient out of 10.000	<0.01[31]	Cardiac valve injury
	<0.01[31]	Peripheral nerve injury
	<0.01[31]	AV-fistula
Not known		Allergic reaction to dexamethasone acetate, bleeding[32], brachial plexus injury[32], device migration[30,41],

Frequency not assessable on the basis of the available data		diaphragmatic stimulation[32], discomfort, erosion, exit block[32], failure to insulate set screw[32], hemoptysis[32], injury to vagus nerve[32], lead malpositioning[32], lead micro-dislodgement[32], local tissue reaction[30], muscle stimulation[30], nerve stimulation (general) [30], myocardial lesion[30], pocket seroma[32], subclavian artery puncture[32], higher x-ray load due to extended fluoroscopy times[34], failing of shock test[40], injury due to implantation accessories[42,44]

Tab. 8b: Expected post-operative events based on literature research

Frequency	**Percentage** (%)	**Risk**
	9.7[20] -37[23]	Lead failure[20,22,23]
Very frequent >1 out of 10 patients	2.9[7]–25.4[24]	Inappropriate shocks[7,24,25,54]
	Up to 13[29]	Device explantation (manufacturers` advisory: 4%[29], electronic failure: 2%[29], housing defects: 1%[29])
	0.3[1] – 13.6[4]	Phrenic nerve stimulation
	12[6,21]	Lead dysfunction
	1.2[19] –10.6[2]	Lead dislodgement
Frequent 1 to 10 patients out of 100	1.7[2] – 9.5[2]	Formation of clinical significant hematomas
	7.6[15] – 9.5[1]	Hematoma[1,3,15,16,17]
	7[46]	Subclavian vein occlusion ≥ 75%
	0.1[5] - 7[1]	Infections[1,5,14] (CRT-D related: 1.9[1,4,13] - 1.9%[1,4]; in-hospital infections: 0.7%[12]; infections after replacement: 1.9%[13])
	0.1 – 4.2[60]	Lead fracture
	1.6[7] – 3.9[4]	Elevated pacing threshold/ loss of capture/ failure to capture
	2.4[30]	Aggregate perforation
	3.4[30]	Pocket erosion
	0[2] – 1.5[7]	Mortality within 30 days after implant (0.4% related to implant procedure[7])
	1.5[30]	Premature depletion of battery
	1.4[7]	Diaphragmatic muscular stimulation
	0.3[2] – 1.3[5]	Lead perforation
	1.3[1]	Pericarditis requiring anti-inflammatory agents
	0.05[7] – 1,2[12,57,61]	Pneumothorax
	0.9[1]	High LV threshold
	0.7[5]	Oversensing
	0.6[7]	Discomfort
	0.6[7]	Pain at device pocket

	0.6[1]	Pericardial effusion requiring intervention
	0.6[7]	Seroma
	0.6[7]	Shoulder pain
	0.5[4]	Lead conductor fracture
	0.5[30]	M. pectoralis tremor
	0.3[5] – 0.5[18]	Post-operative perforation
	0.7[54]	Thrombosis of brachial, subclavian or jugular veins
	0.3[12]	Acute renal failure requiring hemodialysis
	0.3[1]	Ipsilateral venous thrombosis
	0.3[7]	System- or lead-related arrhythmia
	0.2[4]	Elevated lead impedance
	0.2[63]	Site pain
	0.2[54]	Thrombosis of deep femoral vein
Rare 1 to 10 patients out of 10.000	0.09[35]	Fluid accumulation due to heart perforation
	0.1[7]	Cardiac/ cardiac vein/ coronary sinus dissection
	0.1[7]	Hypotension
	0.07[39]	Twiddlers syndrome
Not known Frequency not assessable on the basis of the available data		Farfield sensing or crosstalk leading to pacemaker malfunction[30], Pacemaker Mediated Tachycardia[30], isolation deficiency[30], connector deficiency[30], undersensing[30], chronic nerve damage[30], fibrotic tissue formation[30], keloid formation[30], formation of cysts[30], sensing of myopotentials[30], pulse generator failures[26], device extrusion[36, 43], vein occlusion[37], occlusion of coronary sinus[38]

Tab. 8c: Expected psychological events based on literature research

Frequency	**Percentage** (%)	**Risk**
Very frequent >1 out of 10 patients	25[9,10] - 50[9]	Anxiety or depression[9,10,11,27]
Occasionally 1 to 10 patients out of 1.000	Up to 1[6]	Psychological intolerance
		Psychosomatic impairment
Not known Frequency not assessable on the basis of the available data		Decreased energy levels[28], sleep disturbances[28], loss of libido[28], fatigue[28], reduced physical capacity[28], change in body perception[28], decreased activity level[28], sense of impending danger and uncertainty about the future[28], sensation of losing control[28], sensation of isolation[28], cognitive impairment[28], decline in social interaction[28], fear of shock delivery[28], fear of death[28], fear of device malfunction[28], alteration of social relationships[28], obsessive thinking about shocks[28]

Tab. 8d: Expected events deriving from DX functionality based on literature research

Frequency	**Percentage** (%)	**Risk**
Very frequent > 1 out of 10 patients	20[62]	Change of RV lead during implantation with respect to the distance between tip and atrial sensing rings
	40[62]	Undersensing of atrial signals during AF
	36[63]	Atrial undersensing during atrial tachyarrhythmia and R-wave oversensing
Frequent >1 to 10 patients out of 100	3,2[63]	Exchange of device due to dislodgement, high pacing threshold, upgrade or high energy device required
	3[63]	Inappropriate shocks due to misclassification of SVT
Not known Frequency not assessable on the basis of the available data		Additional implantation of atrial lead due to conversion to sinus rhythm[63,64,65] with bradycardia as result of CRT therapy
		Sensing capability inferior to standard atrial lead

Tab. 8e: Expected events deriving from MultiPole Pacing based on literature research

Frequency	**Percentage** (%)	**Risk**
Very frequent > 1 out of 10 patients	32[47]- 41[48]	Phrenic nerve stimulation in 1 or more pacing vectors
	18[66]	Rise in capture threshold
	16[67]	Inability to select a valid pacing vector combination (either > 2.5V or PNS)
	10[66]	Negative responders to CRT
Frequent >1 to 10 patients out of 100	9[66]	Lack of sufficient LV vectors with capture
	1.4[67]	Device software conversion issue
Not known Frequency not assessable on the basis of the available data		Palpitations

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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 CRF pages provided within the EDC system. 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 the current ISO 14155:2011.

For device deficiencies of the investigational device, which did not lead to an Adverse Event, 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 AEs until study termination of the patient. In addition, ongoing SADEs shall be followed up for a maximum of 4 weeks after study termination of the patient.

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

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 (see 18.4.1).

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 ethic committees request reporting of SAEs and DDs with SADE potential during the course of the study. Investigators have to ensure, that they fulfil the reporting obligations of their local competent authorities and EC/IRBs.

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 a SADE potential to the competent authorities depending on the local regulatory requirements.

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

BIOTRONIK SE & Co. KG will inform the investigators about all reported SAEs and DDs that could have led to a SADE on a regular basis. As a proposal, regular listings may be provided

quarterly and unanticipated serious adverse device effects (USADEs) shall be reported immediately.

18.9 Reporting timelines

In Table 9 the reporting timelines for the investigator are displayed. Investigators are bound to adhere to these timelines.

Tab. 9: Reporting timelines

Event	Report to	Timeline
Adverse Event (AE) / Adverse Device Effect (ADE)	CCR BIOTRONIK SE & Co. KG: Documentation in the AE-eCRF	Within 2 weeks
Serious Adverse Event (SAE) / Serious Adverse Device Effect (SADE)	1) CCR BIOTRONIK SE & Co. KG: Documentation in AE-eCRF	1) Immediately, latest 24h after detection
Unanticipated Serious Adverse Device Effect (USADE)	1) CCR BIOTRONIK SE & Co. KG: Documentation in AE-eCRF	1) Immediately, latest 24h after detection
Device Deficiencies	CCR BIOTRONIK SE & Co. KG: Documentation in the DD-eCRF	Within 14 days
Device Deficiency with SADE potential	CCR BIOTRONIK SE & Co. KG: Documentation in DD-CRF	Within 24 hours

18.10 Emergency contact

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

18.11 Definition of endpoint-related SADEs

The SADE-free rate calculated for primary endpoint 1 of the Ilivia family and primary endpoint 2 for the Plexa ICD lead will be based on the total number of subjects with at least one SADE related to the respective device.

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 (e.g. lead dislodgement). 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 in question (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 endpoints. Furthermore lead infections

will not be considered for the endpoint as long as the specific event cannot be securely classified as related to the investigational device. Inappropriate ICD therapies which are not related to a device defect (e.g. correct sensing and behavior of the device 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.

All serious adverse device effects that meet these primary endpoint criteria for the respective device will be included in the primary endpoint event analysis, respectively. Adverse events with a device relation of "not related" will not contribute to or be included in the evaluation of the primary safety endpoints of both devices.

The SADEs will be adjudicated by an internal adjudication board, whereby the seriousness and device relatedness will be re-examined.

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 8.8.2 and 8.8.3). 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 MEC/IRB

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.
- Results from other clinical trials indicate a non-tolerable risk for further conduction of this study.
- The number of premature study terminations exceeds the tolerable percentage of drop-outs so that proper completion of the study cannot be expected anymore.
- Insufficient enrollment rates so that proper completion of the study cannot be expected anymore.
- Study data are not required anymore due to change of requirements by the regulatory bodies
- 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 or the enrollment, the sponsor is required to promptly notify the investigator(s) to whom the decision applies. The investigator will inform the MEC/IRB 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 MEC/IRB and all enrolled patients of this decision.

If the MEC/IRB 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 MEC/IRB decision, additional requirements from the MEC/IRB with respect to follow-up and data collection may apply.

Ongoing SADEs of the patient will be followed in a maximum time period of either 4 weeks after pre-mature or regular study termination of the individual patient, if not resolved before, in order to follow the outcome, clarify open questions or for collection of missing information concerning the respective SADE. Both follow-up periods are 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 will be informed on this procedure in written form in the patient informed consent form.

21 PUBLICATION POLICY

21.1 Decision for publication

This section refers to all publications of the study. A publication can be an article in a scientific journal or a contribution to a scientific congress. The decision whether the study results will be published will be made by the Publication Team, consisting of the Coordinating Investigator and a representative of BIOTRONIK. The Publication Team will develop a Publication Plan including details and timelines for all planned publications. All publications 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 point for each enrolled patient
- 1 point for each implanted investigational device
- 1 point for each patient, with complete and 100% compliant data set until study termination according to Clinical Investigational Plan
- -1 point for each Serious-Adverse-Device-Effect (SADE) not reported within the timeline provided by this CIP

If a publication refers only to either the Ilivia ICD or the Plexa ICD lead, the scoring will be done separately for the patients contributing to the publication (group A and AB for Ilivia publications, or group B and AB for Plexa publications).

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 publication, 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 Publication Team.

The Publication Team must approve suggestions for ancillary publications and will ensure that these publications are not in conflict with previously submitted suggestions. Requests for ancillary publications will be evaluated for scientific validity and the ability of BIOTRONIK to provide resources.

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23 APPENDICES

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

Exit block - stimulation threshold exceeds the pacemakers` programmed output

Hematoma – A localized collection of extravasated blood, usually clotted, in an organ, space, or tissue.

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

Infection – An invasion and multiplication of microorganisms in body tissues causing local cellular injury and requiring pharmaceutical and/or surgical treatment.

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

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

Lead Impedance Out of Range – Pacing impedance is considered abnormal if a measurement is ≤ 200 Ohms (low impedance) or ≥ 2000 Ohms (high impedance).

Lead Undersensing – Intermittent failure to sense any intrinsic events that occur outside the programmed refractory periods at programmed sensitivity settings.

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

Loss of Sensing – Complete failure to sense any intrinsic events that occur outside the programmed refractory periods at programmed sensitivity settings.

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

Table 10: Definition of NYHA classes

NYHA Class	Symptoms
I	Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain
II	Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain
III	Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain
IV	Symptoms of cardiac insufficiency or of the anginal syndrome may be

	present even at rest. If any physical activity is undertaken, discomfort is increased.

No Capture (Loss of Capture) – Complete failure to achieve cardiac stimulation at programmed output delivered outside of the cardiac refractory period.

No Output – Pacing pulses are provided by the device but not transferred by the lead

Pneumothorax – Air or fluid in the pleural space surrounding the lung leading to collapse or partial collapse of the lung.

Pocket Pain – Pain in the area of the pulse generator implant that lasts longer than typically associated with the procedure and requires pharmaceutical and/or surgical treatment.

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

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

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

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

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

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

Total Procedure Time – Time (hours and minutes) required to complete implant procedure from initial incision/puncture to last suture.

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

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