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Clinical Investigation Plan

for the

BIO|CONCEPT.Amvia Study

First in Human study for the Amvia/Solvia pacemaker family

Reference number:	BA115
Version:	1-0
Date of CIP:	May 30, 2022
Investigational devices:	Amvia Sky pacemakers
	Programmer software: NEO 2204.A/S
	Remote monitoring system – medical device software: Home Monitoring Service Center plugin for Amvia/Solvia family

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

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

Signature of the Principal Investigator

Name: _____

Institution: _____

_____

Street: _____

ZIP code / City: _____

Country: _____

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

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

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

_____	_____
City, date	Signature of Principal Investigator

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1 LIST OF ABBREVIATIONS

aATP	Atrial Antitachycardia Pacing
ACC	American College of Cardiology
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Heart Association
AIMD	Active Implantable Medical Device (Directive 90/385/EEC)
ASADE	Anticipated Serious Adverse Device Effect
AT	Atrial Tachycardia
ATM	Automatic Threshold Monitoring
ATP	Antitachycardia Pacing
AV	Atrio-Ventricular
BiV	Bi-Ventricular
BP	Bipolar
bpm	Beats Per Minute
CA	Competent Authority
CCR	Center for Clinical Research; BIOTRONIK SE & CO. KG study department
CDMP	Clinical Data Management Plan
CDMS	Clinical Data Management System
CDW	Clinical Data Warehouse
CE	CE mark, a stylized "CE" (Conformité Européenne) placed on products to signify conformance with European Union regulations
CI	Coordinating Investigator
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CLS	Closed Loop Stimulation
CM	CardioMessenger (BIOTRONIK device for transmission of HomeMonitoring data)
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy Defibrillator
CRT-P	Cardiac Resynchronization Therapy Pacemaker
DAL	Device Accountability Log
DD	Device Deficiency
DDDR	Dual chamber rate-adaptive pacemaker
DDDRP	Atrial preventive pacing and atrial antitachycardia pacing
DDI	Dual chamber pacing and sensing, but inhibitory mode
DGK	German Cardiac Society (Deutsche Gesellschat für Kardiologie, www.dgk.org)
DR-T	Dual chamber rate-adaptive device with Home Monitoring functionaility

DX	Diagnostics capabilities
EC	Ethics Committee
ECG	Electrocardiogram
EP	Electrophysiology
ERI	Elective Replacement Indicator for batteries
ESC	European Society of Cardiology
EU	European Union
FDA	US Food and Drug Administration (www.fda.gov)
FPI	First Patient In
FSR	Functional System Risk Analysis
FU	Follow-up visit
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HF	Heart Failure
HF-T	Triple chamber ICD with Home Monitoring functionaility
HM	Home Monitoring
HMSC	Home Monitoring Service Center
HRS	Heart Rhythm Society
IB	Investigator's Brochure
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (www.ich.org)
ICM	Implantable Cardiac Monitor
ID	Identification Number
IEGM	Intracardiac Electrocardiogram
IFU	Instructions For Use (user manual)
iMedNet	Web-based electronic data capture (EDC) system for clinical trials provided by MedNet Solutions Inc.
IPG	Implantable Pulse Generator
ISO	International Organization for Standardization (www.iso.org)
ISO14155	International Standard (Clinical investigation of medical devices for human subjects — Good clinical practice) no. 14155
LBB	Left Bundle Branch
LBBP	Left Bundle Branch Pacing
LI	Lead Introducer
LPI	Last Patient In
LPO	Last Patient Out
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction

LVVO	LV VectorOpt
MDCG	Medical Device Coordination Group
MDR	Medical Device Regulation
MedNet	Supplier of Clinical Trial Software (MedNet Solutions, Inc. www.mednetstudy.com)
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MVP	Managed Ventricular Pacing
NA	Not applicable
NCT	National Clinical Trial number (identification number assigned by ClinicalTrials.gov for registered studies)
NHMRC	National Health and Medical Research Council
NSW	New South Wales
NYHA	New York Heart Association
PGH	Programmer Head
PHD	Pre-hospital Discharge
PI	Principal Investigator
PM	Pacemaker
PMCF	Post Market Clinical Follow-up
PNS	Phrenic Nerve Stimulation
PSA	Pacing System Analyzer
PVC	Premature Ventricular Contraction
QM	Quality Management
QP	Quadripolar
QRS	Electrical complex on an ECG related to the depolarization of the ventricles
RA	Right Atrium
RF	Radio Frequency
RV	Right Ventricle
SaaS	Software as a Service
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Statistical Analysis Report
SND	Sinus Node Dysfunction
SOP	Standard Operating Procedure
SR	Single chamber and rate-adaptive
SR-T	Single chamber rate-adaptive device with Home Monitoring funcionality
TACT	Tachos Atrial Conversion Therapy (clinical study)
TGA	Therapeutic Goods Administration (Australia)
TRUST	The Lumos-T Reduces Routine Office Device Follow-Up Study

USA	United States of America
USADE	Unanticipated Serious Adverse Device Effect
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
VV delay	Timespan between the activation of right and left ventricle
ZIP	Zone Improvement Plan (postal code)

2 SYNOPSIS

BIO|CONCEPT.Amvia	
Patient population	Patients with bradycardia and indication for pacemaker or CRT-P implantation; a subset of patients with known history of atrial arrhythmia (except permanent AF)
Design	Exploratory, open, prospective, bi-national, multi-center, non-randomized; 50 patients
Investigational device(s)	Pacemakers: Amvia Sky SR-T, DR-T, HF-T QP Programmer software: NEO 2204.A/S and subsequent versions Home Monitoring Service Center (HMSC) plugin for Amvia/Solvia family and subsequent releases
Objectives	To determine preliminary safety and product performance of the new Amvia/Solvia pacemaker family To support regulatory approvals, promotional claims and future study activities
Primary endpoint	No primary endpoints are defined.
Secondary endpoint(s)	No secondary endpoints are defined.
Data of interest	Baseline data, (S)ADE, electrical pacing parameters, programming, usage and appraisal of new features
Inclusion criteria	• Standard indication for pacemaker or cardiac resynchronization therapy pacemaker (CRT-P) implantation, including de novo, upgrade or replacement implantations • Ability to understand the nature of the study • Willingness to provide written informed consent • Ability and willingness to perform all follow-up visits at the study site • Ability and willingness to use the CardioMessenger and acceptance of the BIOTRONIK Home Monitoring concept
Exclusion criteria	• Planned for conduction system pacing • Planned for activation of aATP without known history of atrial arrhythmia, or with permanent AF • Planned cardiac surgical procedures or interventional measures other than the study procedure within the next 12 months • Pregnant or breast feeding • Age less than 18 years • Participation in another interventional clinical investigation • Life-expectancy less than 12 months
Study duration	~ November 2022 – May 2024 (~ 19 months)

BIO|CONCEPT.Amvia	
Sample size	50, thereof: • 10-15 single-chamber • Min. 10 dual-chamber • Min. 10 triple-chamber • Min. 10 with aATP ‚ON' • Min. 5 with CRT AutoAdapt ‚ON'
Number of investigational sites	~ 8
Number of follow-ups per patient	6
Follow-up scheme	Enrollment; Implantation; Pre-hospital discharge; 1-month follow-up (HM data acceptable); 3-month follow-up; 12-month follow-up.
Coordinating investigator	[redacted]
Sponsor	BIOTRONIK Australia Pty. Ltd.

In this investigational study the term 'patient' is identical with the term 'subject' as defined in ISO 14155, because all study participants are patients treated by physicians at the investigational sites.

3 INTRODUCTION

Permanent cardiac pacemaker devices, including cardiac resynchronization therapy pacemaker devices, are an integral part for the treatment of symptomatic bradycardia and heart block[1]. Today's state-of-the-art pacemakers feature a large number of automatic functions that enable (a) therapies individually adjusted to the patient, (b) remote patient management, and (c) diagnostic capabilities[2]. BIOTRONIKs newest generation of pacemakers Amvia Sky, Amvia Edge, Amvia Stellar and Solvia Rise, hereinafter Amvia/Solvia family, includes all beforementioned features as well as a wide range of functions to help in the therapeutic decisions. The Amvia/Solvia family is based on the BIOTRONIK Edora family pacemakers, which were CE approved in 2016, and TGA approved in 2017. The Amvia/Solvia family extends its predecessor by an improved cyber security of RF telemetry and novel software features. New features include among others atrial antitachycardia pacing (aATP), which aims to reduce the risk of persistent AF, CRT AutoAdapt for the beat-to-beat adaption of cardiac resynchronization therapy (CRT), and EarlyCheck/QuickCheck as a feature for remote patient management.

Among these, atrial ATP is the most interesting new feature of the Amvia/Solvia family, and is therefore described in more detail in the following paragraph.

Atrial ATP

In patients with bradycardia, atrial tachycardia is a frequent comorbidity. Particularly atrial fibrillation (AF) is often observed in these patients[3–5]. According to a systematic review by Chugh et al. in 2010, the global estimated incidence of individuals suffering from AF was approximately at 33.5 million[6]. Considering the risk of concomitant diseases and poor quality of life associated with atrial fibrillation, the need for appropriate therapies becomes apparent[7]. With the release of the 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy (CRT) optimal pacing modes and algorithm selection in sinus node dysfunction (SND) and atrioventricular block (AV block) have been described. However, the choice of the optimal pacing algorithms to prevent AF is still debated controversially[8,9]. In a recent study, a new algorithm for atrial antitachycardia pacing (aATP) has been investigated[10,11]. In this randomized, multicenter, international trial it was shown, that patients with standard indications for permanent pacemaker and previous atrial tachyarrhythmias had a considerably lower risk of progression to permanent or persistent AF when assigned to the atrial preventive pacing, aATP and managed ventricular pacing (DDDRP + MVP) group than in the control group with standard dual-chamber (DDDR) pacing[11,12]. Accordingly, the feature aATP of the Amvia/Solvia family is designated to prevent progression from atrial tachyarrhythmias (AT) to permanent or persistent AF by detecting and terminating stable atrial tachyarrhythmia episodes.

The study is designed as an explorative, open, prospective, bi-national, multicenter, non-randomized study and aims to determine preliminary safety and product performance of the Amvia/Solvia family, including the aATP, CRT AutoAdapt and Early Check features in the setting of a pre-market clinical study.

4 INVESTIGATIONAL DEVICE

4.1 Summary description of the device

The investigational devices in this study are the Amvia Sky pacemakers in combination with the related programmer software ('NEO 2204.A/S') and the remote monitoring software ('HMSC Plugin') to be used in conjunction with the Amvia/Solvia family.

Further information is provided in the following sections as well as in the Investigator's Brochure (IB). Furthermore, a technical manual will be provided by the time of study start.

4.2 Manufacturer

The manufacturer of the investigational devices is:
BIOTRONIK SE & Co. KG
Woermannkehre 1
12359 Berlin
Germany
www.biotronik.com

4.3 Model name including software version and accessories

Table 1 lists the model names and numbers of all investigational devices used within this study.

Table 1: Investigational Devices

Model Name	Catalogue Number
Amvia Sky SR-T	[redacted]
Amvia Sky DR-T	
Amvia Sky HF-T QP	
NEO 2204.A/S	
HMSC plugin for Amvia/Solvia family	

4.4 Description of traceability

Every Amvia Sky pacemaker can be identified by its unique 10-digit serial number. The programmer software is identifiable by its version number. The traceability is assured by recording the serial numbers in the device accountability log (DAL, see section 16) of the clinical data management system (CDMS). This documents the shipment, receipt, transfer and/or return to the sponsor of used, unused or malfunctional investigational devices. Device information as model name, serial number, date of shipment or return and shipment destination is entered in the DAL.

Moreover, serial numbers of investigational devices and patient ID are documented in the corresponding electronic case report form (CRF) in the CDMS at implantation.

Investigational devices have to be visibly labeled as investigational devices. Only trained BIOTRONIK personnel or trained site personnel is authorized to have access and to handle investigational devices.

It is strongly recommended to perform any explantation in the presence of a BIOTRONIK technical support employee. Explanted or malfunctioning investigational devices shall be sent back to the manufacturer. The investigator shall contact the respective sales representative in order to organize shipment.

After study termination all unused investigational devices have to be returned to the sponsor. The programming devices with the investigational device software have to be returned to the sponsor when the programmer software has obtained regulatory approval.

4.5 Intended purpose of the device in the study

Amvia Sky devices are implantable pacemakers (PM; SR-T and DR-T) and implantable cardiac resynchronization pacemakers (CRT-P; HF-T and HF-T QP). A pacemaker is part of an implantable system comprising a pacemaker and leads. The primary function of the system is the ability, first, to sense the intrinsic heart rhythm/rate and, second, to provide pacing by electrical pulses of low energy, as well as to provide antitachycardia pacing by electrical pulses of low energy when necessary to ensure a stable heart rate or to support the intrinsic heart rate when needed. CRT-P systems share all mentioned functions and in addition provide permanent sensing and pacing of the left ventricle.

The implantation of a pacemaker is a symptomatic therapy with the following objectives:

- Sensing and recording the heart rhythm and automatically detecting bradycardia and atrial tachyarrhythmia (PMs and CRT-Ps)
- Compensation of bradycardia through atrial or ventricular, or AV sequential pacing (PMs and CRT-Ps)
- Physiological pacing (LBB(A)P) by stimulating the conduction system (PMs and CRT-Ps) (excluded in this study)
- Termination of atrial tachycardia (AT/AF) through antitachycardia pacing (ATP) in the atrium (PMs and CRT-Ps)
- Cardiac resynchronization through multisite ventricular pacing or through physiological pacing (CRT-Ps, e.g. biventricular pacing).

The programmer Renamic Neo provides communication with BIOTRONIK implantable pacemakers, ICDs, or implantable cardiac monitors (ICMs) during the implantation procedure or patient follow-up. The programmer is intended to enable the intended use of the implantable products by supplying the user interface to the device functions. Therefore, the programmer is used:

- to verify and optimize the therapy delivered by the devices.
- to support diagnosis of the patient status through data delivered by the devices.

The PSA (pacing system analyzer) of the programmer supports lead implantations during the implantation procedure. Therefore, the PSA is used:

- to support lead implantations with intraoperative measurements of electrophysiological parameters.

The software NEO 2204.A/S is the programmer software specific for the programmming and interrogation of the pacemakers of the Amvia/Solvia family.

The intended use of the Home Monitoring Service Center (HMSC) is to monitor and support diagnosis of cardiac arrhythmias and in the prediction of worsening heart failure (HF) in patients with implanted BIOTRONIK cardiac pacemakers, cardioverter-defibrillators (ICDs), cardiac resynchronization therapy devices (CRTs) and cardiac monitors. In addition, the HMSC is used to monitor the status of the active implant and the connected leads. The HMSC plugin for Amvia/Solvia family is part of the software release required for the processing and display of data from pacemakers of the Amvia/Solvia family.

All investigational devices are used within their intended purpose in this study.

4.6 Intended patient population and indications

Single- and dual-chamber pacemakers are indicated to treat symptomatic bradycardia with antibradycardia pacing.

Triple-chamber pacemakers are indicated for patients

- who suffer from chronic heart failure with reduced left ventricular ejection fraction (LVEF ≤ 35%) and dyssynchrony (defined as QRS duration ≥130 ms)

- with heart failure and reduced LVEF (< 40%) who have a high-degree atrioventricular (AV) block with high ventricular pacing demand.
- with chronic heart failure and symptomatic atrial fibrillation with uncontrolled heart rate who are candidates for AV junctional ablation (irrespective of the QRS duration).

The most common indications for permanent pacemaker implantation are sinus node dysfunction (SND) and symptomatic high-grade atrioventricular (AV) block. Beside the most common indications mentioned above the following conditions are included but are not limited to:

- Chronic bifascicular block
- Neurocardiogenic syncope and hypersensitive carotid sinus syndrome
- Hypertrophic cardiomyopathy
- Pacing to detect and terminate tachycardia
- Patients with congenital heart disease

Patients who demonstrate hemodynamic benefit through maintenance of AV synchrony should be considered for dual chamber pacing modes. Dual chamber modes are specifically indicated for treatment of conduction disorders that require both restoration of heart rate and AV synchrony such as AV nodal disease, diminished cardiac output or congestive heart failure associated with conduction disturbances, and tachyarrhythmias that are suppressed by chronic pacing.

In patients with bradycardia-tachycardia variant of SND programming of atrial ATP may be considered.

Rate-adaptive pacing with pacemakers is indicated for patients exhibiting chronotropic incompetence and who would benefit from increased pacing rates concurrent with physical activity.

Physiological pacing (e.g. LBB(A)P) is indicated to maintain or improve the cardiac hemodynamic function by optimizing the physiological cardiac contraction pattern in particular for patients with increased pacing demand.

Generally approved differential diagnostic methods, indications, and recommendations for pacemaker therapy apply to BIOTRONIK devices. See the current guidelines of cardiology associations for guidance. We recommend observing the indications published by the European Society of Cardiology (ESC)[1]. This also applies to the guidelines published by the Heart Rhythm Society (HRS), the American College of Cardiology (ACC), the American Heart Association (AHA)[13], the German Cardiac Society (Deutsche Gesellschaft für Kardiologie, Herz- und Kreislaufforschung, (DGK)) and other national cardiology associations.

Depending on patient anatomy, the pacemakers are implanted in the pectoral or abdominal region.

The pacemakers are intended for adults (including immuno-compromised or elderly patients). The pacemakers are intended for pregnant patients but the need to limit fluoroscopy in pregnant women may complicate device implantation or the patient should be resorted to another imaging method. The pacemakers are intended for children who are suited to bear an implant of the physical dimensions of a pacemaker. Significant technical challenges may arise due to the growth of the patient and the size of the used leads. The pacemakers are not intended for neonates or infants.

As there are no randomized clinical trials of bradycardia pacing in pediatric or pregnant patients, the level of evidence for guideline recommendations is consensus based.

Although covered by the intended population, the enrollment of pregnant or pediatric patients into this study is precluded by the exclusion criteria.

4.7 Description of the investigational device

4.7.1 Amvia Sky pacemakers

The Amvia Sky pacemakers are part of the Amvia/Solvia family of cardiac pacemakers and CRT devices, which are classified as single use, active, implantable medical devices of Class III.

Results gained in this clinical study with Amvia Sky pacemakers are also attributable to the following other brands pertaining to the Amvia/Solvia pacemaker family, as these share the same characteristics and properties: Amvia Edge, Amvia Stellar, Solvia Rise.

However, only the following models will be used within this study (see Figure 1):

- Amvia Sky SR-T
- Amvia Sky DR-T
- Amvia Sky HF-T QP,

whereby single chamber devices have the suffix 'SR-T', dual-chamber devices have the suffix 'DR-T' and triple chamber devices that support the IS4 standard for the quadrupolar left ventricular (LV) lead have the suffix 'HF-T QP'. Product variants with '[…]-T' as suffix are equipped with BIOTRONIK Home Monitoring· Amvia/Solvia family models constitute an MR (magnetic resonance) conditional system together with the corresponding MR conditional leads.

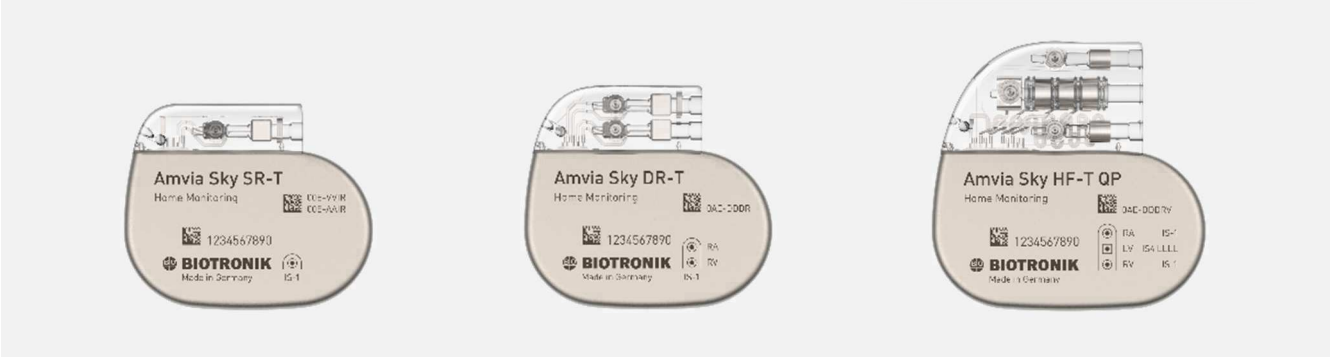

Figure 1: Amvia Sky models used in the BIO|CONCEPT.Amvia study

Amvia/Solvia pacemakers use the following materials in contact with human tissue or body fluids:

- Titanium
- Epoxy resin
- Silicone
- Polysulfone

The Amvia/Solvia family is based on the electromechanical platform of its predecessor, the 'Edora' pacemaker family (Edora /Evity/ Enitra / Enticos), and inherits its entire feature set.

In addition, the Amvia/Solvia family provides the following new features:

- CRT AutoAdapt: provide optimal AV delay with an ambulatory algorithm by adapting AV delays and adjusting ventricular pacing configurations. The latter will reduce unnecessary RV pacing and increase system longevity for patients with normal AV conduction (see 4.7.1.1)
- Atrial Anti-Tachycardia Pacing (aATP): Reduction of permanent AT/AF occurrence due to atrial ATP treatment (see 4.7.1.2)
- MRI Guard 24/7: Optimized workflow of MR-examinations by single activation of an appropriate MRI mode and pacing rate when detecting an MRI, and mandatory monitoring of system-related MRI conditions (see 4.7.1.3)

- QuickCheck / EarlyCheck: Current patient status immediately remotely available via BIOTRONIK Home Monitoring (see 4.7.1.4)
- Additional LV pacing polarities with HF-T QP devices (up to 20 polarities, i.e. 7 more than in the predecessor device) (see 4.7.1.5)
- Automatic LV VectorOpt (Auto LVVO) test during FU: Automated measurements of up to 20 LV polarities in a clinical acceptable time (see 4.7.1.6)

[redacted]

- Leadless ECG: Surface ECG-like signal at the programmer without the need for attaching the skin electrodes to the patients
- Closed loop stimulation (CLS) enhancements: CLS in combination with DDI in dual and triple chamber devcies and with VV delay up to 30 ms in triple chamber devices
- Physiological pacing, i.e. LBB (area) pacing – LBB(A)P
- His Bundle Pacing: Optimized hardware and software solutions to support physiological pacing e.g. His Bundle Pacing (only brand 'Amvia Stellar', not relevant for this study)

The new features that are relevant for this study are further described in the following sections.

4.7.1.1 CRT AutoAdapt

Automatic parameter adaptations are crucial for providing an optimal therapy to the patient, especially under varying living conditions. Since the introduction of BIOTRONIK's latest ICD family (Cor-Neo devices), the CRT AutoAdapt algorithm has been implemented in the CRT devices to adapt AV delays and adjust ventricular pacing configurations automatically while the patient is ambulatory. These adjustments are based on periodic measurements of AV intervals. This functionality is also newly implemented in the HF-T (QP) devices of the Amvia/Solvia family. It includes the option to either adapt AV delays only or adapt AV delays and switch between BiV and LV-only pacing. To adapt the AV delays and ventricular pacing, the CRT AutoAdapt feature will measure the intrinsic AV conduction to RV and LV on a regular basis. The system will provide information about the last measured AV conductions, the optimized AV delays, date and status of the last optimization.

4.7.1.2 Atrial ATP

The atrial ATP feature is available in DR-T, HF-T and HF-T QP devices. Sustained atrial arrhythmia can be treated among others with atrial ATP. The intention of atrial therapy treatments is to interrupt the atrial tachyarrhythmia and restore the patient's normal sinus rhythm. Accordingly, the pacemaker needs to be able to detect an AT or AF episode and to deliver atrial ATP. However, during an AT/AF episode there may be changes in the atrial rhythm or in the underlying substrate. These changes might make it possible to terminate the episode with a therapy that has been unsuccessful before. A repetitive atrial ATP therapy will thus be advantageous compared to conventional atrial ATP.

Up to two aATP modules are programmable. If enabled, aATP is delivered for AT/AF episodes classified as stable. The device provides a programmable 'therapy delay before atrial therapy' and the atrial therapy is only delivered if the atrial episode does not self-terminate within this programmed time. An atrial lead position check is performed before delivery of the atrial therapy to confirm the atrial position of the lead. If the lead position cannot be confirmed, the atrial therapy is disabled until it is released by the physician.

The device can be programmed to repeat aATP in case of a change in atrial rhythm during an unterminated episode. It can also be programmed to repeat aATP after a specified, programmable time during unterminated episodes.

A safety measure is implemented that prevents the device from applying atrial therapies to treat episodes that last longer than 48 h, as AF lasting longer than 48 h might cause atrial thrombi which would require anticoagulation before termination of the episode.

4.7.1.3 MRI Guard 24/7

The 'MRI Guard 24/7' feature is an extension of the MRI AutoDetect feature available in the predecessor devices, which could be used to prepare/pre-program a ProMRI system for a maximum of 14 days so that a patient could be examined in a suitable MRI during this period.

With MRI AutoDetect, the MRI detection mode can be activated subsequently to an MRI system check, for a period of 14 days, in which the implant system uses a magnetic field strength sensor to detect the MRI. If the magnetic field of the MRI machine is detected, the implant is programmed automatically into the pre-defined MRI program during the MRI examination, and is reset automatically to the permanent program after the examination. After the MRI scan the patient's cardiologist is notified via Home Monitoring that the patient underwent an MRI scan. The remotely transmitted follow-up data can be analyzed without additional burden for the patient to visit the cardiologist.

The Amvia/Solvia family aims to further improve the workflow for MRI examinations by allowing patients to go for an MRI examination at any time within two consecutive follow-up examinations if the implantable pulse generator (IPG) is part of an approved ProMRI system. The MRI system check was improved to better support the workflow, and the MRI suitability certificate was redesigned. With MRI Guard 24/7, the system reminds the cardiologist to perform the MRI system check on a regular basis. The MRI detection mode of a ProMRI system, once it has been declared as a ProMRI system, is always active and the patient can go to the MRI examination whenever required.

It is therefore no longer necessary to consult a cardiologist shortly before every MRI examination in order to activate the MRI detection mode, but only approximately once per year to confirm the MRI conditions. The underlying functional principle (detection of magnetic field and subsequent switch to MRI mode; reset to normal pacing mode at the end of the examination) and the hardware remain the same as with MRI AutoDetect.

The system only switches to the MRI brady mode when the patient is in MRI environment. This MRI brady mode is pre-programmed by the physician or automatically chosen based on the permanent pacing mode. The latter AUTO mode is new for MRI Guard 24/7. Furthermore, also new, the pacing rate will be adapted automatically with MRI Guard 24/7 based on the last pacing rate of the patient before he goes into the MRI machine with an offset safety margin of +15 bpm.

4.7.1.4 QuickCheck / EarlyCheck

The QuickCheck feature, is a multi-system feature (IPG, CardioMessenger, and HMSC) and can be triggered by the clinician via the Home Monitoring Service Center. Since the introduction of BIOTRONIK's latest ICD family (Cor-Neo devices) this feature is implemented in BIOTRONIK ICDs and it will now also be used in the pacemakers of the Amvia/Solvia family. If the medical status of a patient who is connected to Home Monitoring needs to be checked, the physician can remotely check the current state of the implant within a few minutes (see Figure 2): 1. Patient has to be close to their CardioMessenger (triggered maybe by a phone call), 2. Physician triggers the interrogation via the HMSC, 3. HMSC instructs the CardioMessenger to wake-up and interrogate the implant, 4. CardioMessenger relays the data to HMSC, 5. Physician checks the data. The reaction time between initiating the interrogation on demand and receiving the data in the HMSC platform will not be more than 15 minutes but is typically between 3-6 minutes if the patient is in the vicinity of the switched on CardioMessenger at the time of triggering and the communication can be established between IPG and CardioMessenger as well as between CardioMessenger and HMSC. On the basis of the transmitted data, the patient can be advised on possible next steps. QuickCheck helps to decrease the follow-up burden for patients and physicians, as many patients can be treated remotely and will not need to go to the ER.

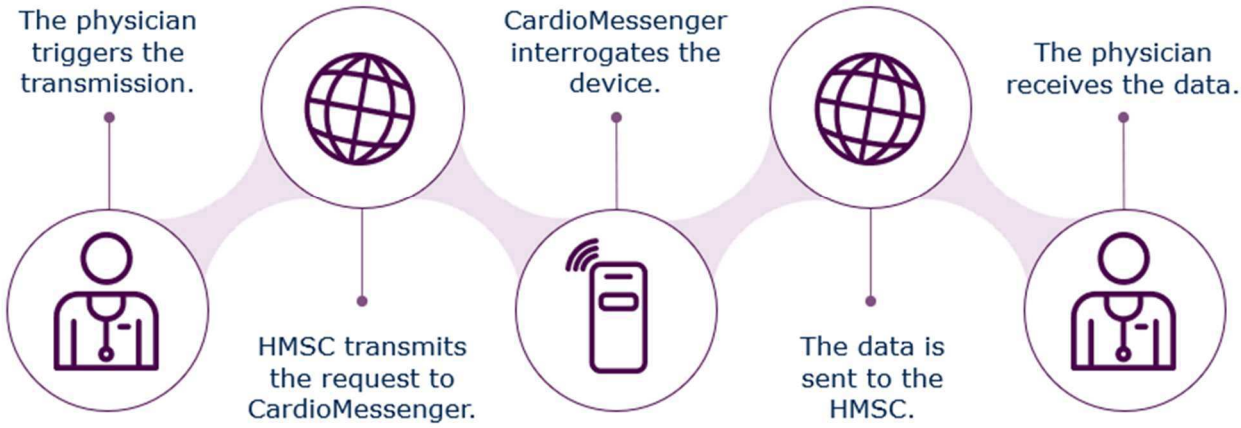

Figure 2: QuickCheck workflow

EarlyCheck, as a newly introduced subfunction of QuickCheck, allows a data transmission as described for QuickCheck for the first time shortly after implantation detection via any QuickCheck-compatible CardioMessenger. With this system, a pre-hospital discharge (PHD) can be supported remotely via the HMSC. To support a PHD, sensing, impedance, threshold measurements and an IEGM are available in the EarlyCheck HM message.

4.7.1.5 Additional LV pacing polarities

The HF-T QP models of the predeceding pacemaker family (Edora) offer an IS-4 connector with 13 different pacing polarities for the LV. In BIOTRONIK's latest ICD systems of the Cor-Neo family the number of available pacing polarities was increased to 20. This improvement is now also implemented in the Amvia/Solvia pacemakers, providing more options for electronic repositioning and thus optimization of cardiac resynchronization therapy.

In order to facilitate the workflow of measuring all pacing configurations and determining the electrically most suitable one, the programmer interface was adapted to support the workflow during the follow-up procedure (see 4.7.1.6).

4.7.1.6 Automatic LV VectorOpt

Along with the increased number of LV pacing polarities, HF-T and HF-T QP variants of Amvia/Solvia offer Auto LV VectorOpt (Auto LVVO), a feature that allows automatic measurement of the LV thresholds.

The test of the LV threshold can be conducted both manually and automatically (the latter being new for Amvia/Solvia). The most important values to be shown are: LV pacing thresholds with resulting relative service times[1] (expected ERI), phrenic nerve stimulation (PNS) thresholds (only manually), and LV impedances (always automatically). Besides those measurements, the conduction delays from paced and sensed RV events to all of the LV poles will support the physician to choose the 'best vector', as the point of latest activation in the LV is supposed to be the best site for resynchronization pacing. The conduction delay between RVsense and LVsense events is new for Amvia/Solvia, taken over from the Cor-Neo device family.

1 The service time calculations will be done with the measured LV threshold plus a programmed safety margin for every LV polarity respectively. The delta for each polarity shall be given related to the polarity with the longest lifetime, which is labeled as 'Best'. Thus the service time difference is based on the different LV lead impedance values and pacing output and pulse width only.

4.7.2 Programmer software NEO 2204.A/S

Renamic Neo is a portable programmer and monitoring device with an integrated pacing system analyzer (PSA), which is used at implantations and for the follow-ups of BIOTRONIK implantable pacemakers, ICDs, CRT-devices and ICMs. The programmers are operated via a touch sensitive display, and interrogating the implant is achieved through a programming head (PGH) or via wandless RF telemetry.

The programmer devices provide communication with BIOTRONIK implantable pacemakers, ICDs, CRT-devices and ICMs during the implantation procedure and device follow-up. Thereby, they enable normal use of the implantable products by providing a user interface for the functions of the device.

The programmer software is an integral and essential component of the programmer system. Compared to previous, already approved software versions, the main novelty of NEO 2204.A/S is the support of the new Amvia/Solvia pacemaker family. Subsequent software versions might be included in the study upon notification of the EC and/or authority, if applicable.

4.7.3 Home Monitoring Service Center plugin for Amvia/Solvia family

The BIOTRONIK Home Monitoring Service Center (HMSC) is a remote monitoring software intended to be used for patients with cardiac implanted electronic devices of BIOTRONIK that are equipped with the Home Monitoring function (i.e. the "T-option"). Together with other devices, BIOTRONIK's Home Monitoring Service Center forms the BIOTRONIK Home Monitoring System, which allows automatic transmission of diagnostic information to the patients' physician.

The HMSC supports patient care among others with

- automatic daily transmission from the implanted devices,
- automatic detection of events with notification to the physician,
- Home Monitoring-supported follow-ups,
- the option to export data to electronic health record systems.

The HMSC plugin for Amvia/Solvia family is the software that is necessary to receive, process and display data transmitted from pacemakers of the Amvia/Solvia family.

4.8 Summary of training and experience needed

The Amvia Sky pacemakers are medical implants intended for physicians who are familiar with the implantation of pacemakers and CRT-P devices and their leads. The handling and implantation instructions will be described in the respective Technical Manuals, that will be provided before study start. The physician must be familiar with the associated risks and complications. The interrogation and programming of the pacemakers shall only be done by appropriately trained personnel using the BIOTRONIK programmer.

All investigators need to be trained by BIOTRONIK personnel on the use of the Amvia Sky pacemaker, the related programmer software and the HMSC prior to study start.

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

All investigators must dispose of adequate research training and experience. Training on ISO 14155 and/or several years of experience in conducting clinical trials are generally required. Investigators with responsibilities including CRF completion, CRF sign-off, and/or obtaining informed consent require a documented assessment of appropriate training and experience on ISO 14155 and applicable regulations by qualified BIOTRONIK personnel before they can be authorized for any such activities.

4.9 Description of medical and surgical procedures

The Amvia Sky pacemakers have to be implanted by a physician according to the standard implantation procedure. Specific information pertaining to procedures will be provided in the respective Technical Manuals. The device measurements should be regularly observed via Home Monitoring by the investigator. During the onsite visits, the measurements will be performed via the BIOTRONIK programmer.

5 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

5.1 Pre-clinical data

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

5.2 Clinical data

The following clinical studies contribute to the evaluation of clinical data:

- BIO|MASTER.Edora Family Study (Master study for the predecessor pacemaker family) (NCT 03091322)
- BIO|MASTER.Cor Family Study (Master study for the current ICD family which includes several features that are now implemented in the Amvia/Solvia family) (NCT 03891329)
- TACT Study (Tachos Atrial Conversion Therapy Study; BIOTRONIK ICD study investigating i.a. the effectiveness of atrial ATP)
- Minerva study (MINimizeE Right Ventricular pacing to prevent Atrial fibrillation and heart failure; Study investigating i.a. the influence of atrial ATP on clinical outcomes) (NCT00262119)

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

5.2.1 BIO|MASTER.Edora Family Study[14]

Objectives and methods:

This study was designed as post market clinical follow-up study with the Edora family pacemakers (CE-marked products) to evaluate the new features AV Opt and LV VectorOpt under clinical routine conditions. Furthermore, Adverse Events were evaluated to identify residual risks associated with the use of the study product. No hypotheses have been defined.

Patients with standard indication for their respective device were enrolled. Initially, follow-up evaluations were planned before discharge, and at 1 and 6 months after implantation. Following an amendment, patients were asked to agree to an extension of the study period until an additional follow-up visit taking place between 11 and 19 months after implantation (the 'extended follow-up').

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

Results:

One hundred and twenty patients were enrolled between February 12, 2017 and March 13, 2018 at 11 investigational sites. The last-patient-out date was September 12, 2019. The data base was closed on December 2, 2019.

Of 96 patients asked to take part in the extension of the follow-up period, 53 (55.2%) agreed and 43 (44.8%) declined.

Of the 120 enrolled patients, ten (8.3%) terminated the study prematurely and 110 (91.7%) regularly: 57 after 6 months of follow-up and 53 after extended follow-up. The single follow-up visit in the extended period took place on average 15 months after implantation.

- The first study endpoint was related to the new AV Opt feature, which was designed to support the selection of appropriate AV delay values. The algorithm suggested AV delay values in 91.9% ('sensed' AV delays) and 93.2% ('paced' AV delays) of the 74 patients in whom the test was done according to protocol. The investigators used the AV delay values suggested by the algorithm, or considered them clinically acceptable, in 66 (95.7%) of 69 patients contributing to this endpoint.
- The second study endpoint was related to the new LV VectorOpt feature, which was designed to simplify the programming of LV stimulation vectors. The feature was used in 32 of 37 patients (86.5%) with appropriate devices. The test procedure and the

programmer's test page were assessed as excellent or good in 71.9% and 78.1% of the cases, respectively.

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

Conclusion:

The study has been executed and evaluated as planned. No unexpected safety issues or performance deficiencies have been identified in the study devices, neither during the initially planned, nor during the extended follow-up until up to ca. 18 months after implantation. The new algorithms intended to support the programming of the device have been assessed as 'good' or 'excellent' in most cases.

Thus, the results show the expected performance and support safety and efficacy of the Edora pacemaker family.

5.2.2 BIO|MASTER.Cor Family Study[15]

Objectives and methods:

The BIO|MASTER.Cor Family study was designed to provide post-market data and supporting evidence for the clinical safety and performance of the new family of ICD and CRT-D devices and the Plexa ProMRI S DX ICD lead for regulatory purposes.

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

The primary endpoint was the number of Serious Adverse Device Effects possibly or securely related to the Cor family devices (SADE-d) until the 3-month follow-up. Kaplan-Meier estimates for the SADE-d free rate at 3 and 12 months were collected as secondary endpoint. Two further secondary endpoints were related to the automatic LV VectorOpt test and to the CRT AutoAdapt feature.

Only patients with ICD or CRT-D indication who were planned to be implanted with a Cor family device according to the investigators' decision were enrolled into the BIO|MASTER.Cor Family study. Further in- and exclusion criteria were mainly for formal reasons and did not confine the patient population to specific clinical characteristics.

During the study, all clinical procedures were performed according to clinical routine. Follow-up visits were scheduled prior to hospital discharge and at 3, 6, and 12 months after implantation. The Automatic LV VectorOpt test for LV vector selection and the AV Opt test were mandatory in the respective devices at the 3-month follow-up at latest. The CRT AutoAdapt feature had to be activated in the respective devices at least from pre-hospital discharge visit to the 3-month follow-up unless contraindicated.

Results:

The clinical investigation was initiated with the first patient in on April 30, 2019. The last patient was enrolled on September 10, 2020, and the last patient terminated study participation on September 24, 2021. A total of 130 patients were enrolled. 127 of them successfully received an investigational device – 127 patients were implanted with a Cor Family device and 30 patients with a Plexa ProMRI S DX. The total follow-up period per patient was 340 ± 94 days after implantation.

Primary endpoint

One SADE-d has occurred. This was a case of death which had to be rated as possibly related to the investigational device due to insufficient information on the cause of death. The resulting SADE-d free rate until the 3-month follow-up was 99.2% (122/123) with a 95% confidence interval of 95.6%-100.0%. The SADE-d free rate for the Cor family devices until the 3-month follow-up is significantly higher than 90%. The endpoint was met.

Secondary endpoints

The Kaplan-Meier estimates for the SADE-d free rate at 3 months (92 days) and 12 months were 99.2% with a 95% confidence interval of 94.5%-99.9%.

The LV VectorOpt test was performed in 52 patients. The automatic LV threshold measurements took a mean of 1.3 min ± 1.6 min less than the manual measurement which corresponds to a time saving of about 50%. The different aspects of the test performance were assessed very positive or positive in 86.5% (intuitiveness) to 92.3% (overall handling) of patients. Investigators strongly or somewhat agreed with positive statements on the usability and clinical benefit of the LV VectorOpt in 98.1% to 100% of patients.

The CRT AutoAdapt feature was activated in 21 patients. Between pre-hospital discharge and 3-month follow-up a mean of 39.9% ± 36.6% of heart beats were paced in the left ventricle only. Programmability, clinical acceptability of the algorithm decisions, and the overall feature were assessed as 'very good/very easy' or 'good/easy' in 70% to 85% of patients at the 3-month follow-up. There were no 'poor' or 'very poor' assessments.

Other data of interest

- The different aspects of size and shape of the Cor Family ICD/CRT-D device were assessed as 'very good' or 'good' in 86.6% (required length of incision) to 93.7% (lead connection) of cases.
- Mean values for right atrial (ventricular) sensing were 4.6 mV - 5.1 mV (16.9 mV - 17.2 mV) and mean values for the atrial (ventricular) pacing threshold were 0.7 V - 0.9 V (0.5 V - 0.7 V). In accordance with these measured lead parameters, sensing and pacing were assessed as adequate in all cases.
- Mean values for left ventricular sensing were 13.6- 17.1 mV and mean values for the pacing threshold were 1.2-1.3 V. In accordance with these measured lead parameters, sensing and pacing were assessed as adequate in all cases except of one case of lead fracture reported at the 12-month follow-up that resulted in oversensing and exit block. A 'new' pacing vector that was not available in previous device families was programmed in 23.4% (at implantation) to 30.4% (at 3-month follow-up) of patients.
- Plexa S DX lead implantation was successful in 30/31 patients. The failed implantation was due to a device deficiency (broken connector detected during implantation without medical occurrence). The different aspects of lead handling were assessed as 'very good' or 'good' in 86.7% (flexibility) to 100% (X-ray visibility) of cases. No adverse events related to the Plexa S DX lead occurred.
- The AV Opt test for automatic optimization of the AV delay was performed in 53 patients. Finally programmed AV-delays were slightly shorter than the suggested AV delays with a mean difference for the AV delay after pace of 11.1 ms (p=0.008) and a mean difference for the AV delay after sense of 8.3 ms (p=0.12).
- 66 episodes of ventricular arrhythmia (VT or VF) occurring in 16 patients were correctly detected. Only one episode of VT/VF was falsely detected as supra-ventricular tachycardia. Thus, the sensitivity for VT/VF detection per episode was 98.5%. Inappropriate detection of supra-ventricular or non-sustained ventricular arrhythmia detected in the VT or VF zone occurred for 11 episodes in 9 patients. The overall specificity of VT/VF-detection was 91.7%.
- ATP therapy for termination of VT episodes was successful in 94.6% of episodes. ATP-one-shot therapy for terminating potential fast VTs detected in the VF zone had an efficacy of 51.9%. Shock efficacy was 100%. Thus finally, all detected VT/VF episodes were successfully terminated by any kind of ICD therapy.
- A total of 5 serious adverse events and 9 serious adverse device effects occurred. Five SADEs were related to the implantation procedure (e.g. pocket hematoma, pneumothorax), two SADEs were related to the RV lead (not the Plexa S DX lead) and one SADE was possibly related to the CRT AutoAdapt feature. The internal adjudication board however assessed this event as not relevant for the primary endpoint. According to the board, the event was primarily related to the LV-electrode because of its

positioning with CRT-stimulation probably being delivered on scar tissue. A causal relation with the CRT AutoAdapt was ruled out because the feature has minimal influence on the timing of LV stimuli. Apart from the death from unknown cause that was considered for the primary endpoint analysis, there were no further SADEs related to the Cor family devices.

Conclusion:

The results obtained in the BIO|MASTER.Cor Family study comprising data from 127 patients implanted with an investigational device and followed up for a mean period of 340 days support safety and clinical performance of the new ICD/CRT-P family and of the Plexa S DX ICD lead.

Only one SADE was reported that had to be rated as possibly related to the investigational device due to insufficient information on the cause of death and therefore the primary safety endpoint was met with an SADE-d free rate of 99.2% at 3 months. Data collected for the secondary endpoints underline the clinical benefit and a good performance of the LV VectorOpt and the CRT AutoAdapt feature.

Lead parameters were in the expected and clinically acceptable range at all follow-ups. Sensitivity and specificity of ventricular arrhythmia detection and ICD therapy success rates were also well in line with clinical literature.

5.2.3 TACT study[16]

Objectives and methods:

The purpose of the 'Tachos Atrial Conversion Therapy' (TACT) study was to demonstrate the ability of the Tachos DR Atrial Tx ICD to detect and convert atrial tachyarrhythmias in patients that require standard ICD therapy and that have a history or significant risk of atrial tachyarrhythmias. All patients were implanted with the Tachos DR Atrial Tx and then had both atrial and ventricular detection and therapy features enabled. All patients still received standard antiarrhythmic drug therapy as deemed appropriate by the investigator.

Eligible patients signed an informed consent and were then enrolled into the study. Induction and conversion of induced atrial and ventricular tachyarrhythmias was required after enrollment (or implant of the device). Stored data that documents the detection and conversion of spontaneous and induced atrial tachyarrhythmia episodes were retrieved from the implanted device. The atrial therapy features should be enabled throughout the duration of the study because assessment of atrial detection and conversion was a secondary endpoint of the study. However, atrial therapy could be deactivated at the discretion of the investigator if written justification was provided to document the specific rationale for deactivating these investigational features. Though not the primary goal of this study, data were also collected regarding quality of life specific to the presence of atrial tachyarrhythmias.

Results:

179 patients were included in the study. The following results cover the period form December 21, 2000 (first implantation) through September 11, 2002.

- Nearly 67% of the enrolled patients had a history of atrial tachyarrhythmias prior to enrollment into the study. Of those patients with a prior history of AT/AF, 76.7% of the patients had prior documented atrial fibrillation, 33.3% of the patients had prior documented atrial flutter, and 17.5% of the patients had prior documented atrial tachycardia.
- The cumulative implant duration is 1922 months with an average duration of 10.7 months. A total of 163 (91.1%) patients have an implant duration greater than three months and 135 (75.4%) of the patients have an implant duration greater than six months.
- Atrial tachyarrhythmias were successfully induced in 149 (83.2%) of the patients at the implant procedure. The mean lowest converting energy for atrial fibrillation was 5.9 joules.

- No ventricular tachyarrhythmias were induced by automatic atrial therapy. There were 2 manual shocks out of 304 shocks delivered during supervised testing that were unsynchronized which induced VT/VF, however, the device appropriately detected and converted the rhythm.
- There have been 291 anticipated adverse events (253 observations in 122 patients and 38 complications in 34 patients). There have been no unanticipated adverse device effects reported.
- The overall protocol compliance rate was 98.0%. The overall followup compliance rate for the clinical study to date was 94.9%.
- There have been 16 patient deaths reported. The clinical investigators judged all 16 deaths as unrelated to the implanted device.

Primary Endpoints:

- The AT/AF detection sensitivity of the ICD was evaluated based on the review of stored electrograms following induction of AT/AF during supervised testing performed at implant and subsequent followups. Based on the testing completed during the study, there were 362 episodes of AT/AF in 156 patients, of which 353 episodes resulted in appropriate detection. Therefore the effectiveness of the atrial detection algorithm to appropriately detect atrial tachyarrhythmias is 97.5%. This outcome supports the ability of the atrial detection algorithm to appropriately detect AT/AF.
- There were 38 complications in 34 patients. This results in a complicationfree rate at 6months of 85.9%. There were no complications reported related to atrial therapy, which supports the safety of the atrial detection and therapy features of the ICD.

Secondary Endpoints:

- The overall atrial therapy conversion rate was 55.7%. There were 1148 episodes of detected atrial tachyarrhythmias in 79 patients. Of these 1148 episodes, 542 episodes received therapy in 66 patients.
- The overall atrial shock conversion rate was 77.8%. The atrial shock conversion rate was 77.4% for episodes in the AF zone, 79.2% for episodes in the AT1/AT2 zones. There were a total of 84 successful conversions out of the 108 episodes in 42 patients that received atrial shock therapy.
- The overall atrial HF Burst conversion rate was 38.2%. The atrial HF Burst conversion rate was 38.4% for episodes in the AF zone and 27.5% for episodes in the AT2 zone. There were at total of 156 successful conversions out of the 408 episodes in 49 patients that received atrial HF Burst therapy.
- **The overall atrial ATP conversion rate was 43.6%. The atrial ATP conversion rate was 43.6% for episodes in the AT1/AT2 zone. There were at total of 62 successful conversions out of the 142 episodes in 29 patients that received atrial ATP therapy.**
- The quality of life survey demonstrated an improvement in both the Symptom Frequency and Severity Scores in 116 patients. The average Symptom Frequency Score was 18.0 at the preenrollment procedure and 11.1 at the threemonth followup, which demonstrates a 6.9-point (38.3%) improvement in the Frequency Score. The Symptom Severity Score was 14.1 at the preenrollment procedure and 8.4 at the threemonth followup, which demonstrates a 5.7point (40.4%) improvement in the Severity Score.

The data received and analyzed demonstrate the general safety and effectiveness of the Tachos DR Atrial Tx ICD System.

5.2.4 Minerva study[10,11]

Objectives and methods:

The MINERVA study investigated whether atrial preventive pacing and atrial antitachycardia pacing (DDDRP) plus managed ventricular pacing (MVP) reduces mortality, morbidity or permanent AF compared to standard dual chamber pacing.

1,166 patients with bradycardia and previous atrial tachyarrhythmias, and no history of permanent AF or third-degree AV block, were randomized to standard dual-chamber pacing (control, DDDR), DDDRP + MVP, or MVP after a run-in period of 1 month. Follow-up examinations were performed 3 and 6 months after implantation and thereafter every 6 months until 24 months after inplantation. Endpoints were adjudicated by an independent Event Adjudication Committee.

The study was conducted in 63 investigational sites in 15 countries.

Results:

The primary outcome, the 2-year incidence of the combined endpoint consisting of death, cardiovascular hospitalization or permanent AF, showed a 26 % relative reduction between the DDRP+MVP group and the DDDR control group. In the same period a relative risk reduction of 61 % could be shown for the development of permanent AF, associated with a 52 % relative reduction in AF-related hospitalizations and ER visits. The relative risk reduction in AF episodes >7 days was 48%, and 34 % in AF longer than 1 day.

Conclusion:

DDDRP + MVP was shown to be superior to standard dual-chamber pacing in the study population of patients with bradycardia and atrial tachyarrhythmias. The reduction of progression of atrial tachyarrhythmias to permanent AF significantly contributed to the primary endpoint, the efficacy of atrial antitachycardia pacing being a predictor of permanent or persistent AF reduction.

5.3 Justification

The above mentioned studies indicate the safety and efficacy of the predecessor devices of the Amvia/Solvia family, as well as the safety and efficacy of the features that were taken over from ICDs. Regulatory approval of the Amvia/Solvia family (except Amvia Stellar) is expected to be obtained based on equivalence with the predecessor pacemaker (5.2.1) and the features which are already available in marketed ICDs and supported with clinical data (5.2.2).

The BIO|CONCEPT.Amvia study is a pre-market study to determine preliminary safety and product performance before the new product family is placed on the market . Its objectives are the monitoring of product performance, the support of regulatory approvals in other regions, the validation of promotional claims, and the support of future study activities in a controlled setting.

No endpoints or hypotheses are required since this study is only a first observation of the device performance, which will be based on descriptive statistics of the data of 50 enrolled patients. Any safety issues will be analyzed in detail based on all available data until the interim or final analysis. The distribution of device models (single, dual and triple chamber devices) was chosen in such a way that all device types are covered and thus contribute to the analysis, especially to the SADE-free rate. The number of single-chamber devices is limited, so that more devices providing data for the features of interest aATP and CRT AutoAdapt can be included.

Although the interim analysis is planned when enrollment is completed and at least 10 patients have had their 3-month follow-up performed, the follow-up duration is extended to 12 months. Firstly, this follow-up duration is chosen so that patients remain in the study until the expected time of regulatory approval, until which the devices need to be interrogated with the study programmer software. Secondly, it is considered ethically justifiable to collect data over a longer period in patients already participating in a clinical study. These data might be used for regulatory purposes, if the need arises, instead of enrolling more patients into another study.

Furthermore, the patients benefit from a potentially more intensive monitoring of device functionalities.

The lifetime of the device is nevertheless not covered by the study duration. It is planned to conduct a PMCF study with the Amvia/Solvia family devices after regulatory approval.

The data of interest include the performance of the device system, as well as the documentation of usage and assessment of features inherent to the Amvia/Solvia family.

The use of the features atrial ATP and CRT AutoAdapt is not mandatory for every study patient. However, it is required that atrial ATP is turned ON in at least 10 patients, and CRT AutoAdapt in at least 5 patients within the study population, so that every feature is adequately represented in the analysis.

While CRT AutoAdapt aims at improving hemodynamics, it is not expected that significant effects on hemodynamics can be detected due to the small sample size and relatively short duration of this investigation. Effects on patient outcome are currently being investigated in the BIO|Adapt study. However, data on the functionality, behavior and acceptance of the feature will be collected within BIO|CONCEPT.Amvia that will help to gain first insight into the clinical use of this feature in the CRT-P population.

Data collection related to aATP will be limited to the documentation of and reasoning for the choice of programmed parameters, and the confirmation of the delivery of atrial therapies as programmed in case of occurrence of atrial arrhythmias. An evaluation of the effectiveness of the therapy by the investigator will not be possible due to the shortness of the pre-termination IEGM recording that will not display the therapy delivery in most cases. However, the termination of an atrial episode within 30 seconds of therapy delivery might be considered as a hint for therapy effectiveness. In order to account for safety, the potential relation between aATP delivery and SAEs will be assessed. However, only few atrial episodes are expected to occur in this limited number of patients.

The MRI system check as part of MRI Guard 24/7, EarlyCheck, the evaluation of leadless ECG and of Auto LVVO are required for every patient with a corresponding device, as these features are used during in-office follow-ups (preferably at pre-hospital discharge) only, and do not affect the actual device therapy. MRI examinations and the performance of MRI Guard 24/7, however, will only be documented in case of MRI scans that become necessary for medical reasons independently of study participation.

[redacted]

An investigator questionnaire will be issued at the end of the enrollment/implantation phase in order to collect feedback to these and other features for the validation of promotional claims that are not based on the treatment of an individual patient, but on the overall user experience with the feature, and its evaluation by the user.

6 BENEFITS AND RISKS OF THE DEVICE, CLINICAL PROCEDURE, AND CLINICAL INVESTIGATION

6.1 Anticipated clinical benefits

The clinical benefits for the patients inherent to the use of the implantable pacemakers are the detection of an unphysiological low heart rate (bradycardia) of a patient and subsequently the restoration of a physiological heart rate.

Triple-chamber pacemakers provide the additional clinical benefit to improve the ejection fraction and/or cardiac output in patients with heart failure and interventricular dyssynchrony.

The Amvia/Solvia family pacemakers meet the current state of medical science and technology and are used within their intended purpose. In addition to the general benefit of pacemaker therapy, the patient may benefit from the features implemented in this new generation of pacemakers, i.e. improved remote monitoring options through EarlyCheck/QuickCheck, easier access to MR examinations through MRI Guard 24/7, and the potential optimization of CRT therapy through CRT AutoAdapt and additional LV pacing vectors. Furthermore, atrial therapy provides the additional clinical benefit of terminating atrial stable tachyarrhythmia after detection.

The integrated Home Monitoring functionality (including QuickCheck) 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[17]. The QuickCheck feature offers the additional advantage of providing a 'real-time' report including a current periodic IEGM typically within 5-6 minutes of triggering it, e.g. if the patient experiences symptoms.

The individual patient does not benefit directly from study participation besides the implantation of an Amvia Sky pacemaker with the implemented new functionalities. The patient receives an intensive monitoring of the device functionalities and an optimization of device settings during study conduct.

6.2 Anticipated adverse device effects

A definition of adverse device effects is given in section 19.2. Anticipated adverse events that are associated with the implantation and use of a pacemaker system are described in section 19.8 of this clinical investigation plan. The indicated frequency is based on published clinical data. In addition, please refer to the Investigator's Brochure, especially the section 'Risk management of the investigational device'. Furthermore, the technical manual will provide information under 'Possible Complications' and 'Possible Risks'.

6.3 Risk associated with participation in the clinical investigation

Patients included in the BIO|CONCEPT.Amvia Study have an indication for pacemaker or cardiac resynchronization therapy and will receive an implantation irrespective of their study participation. As the implantation of an Amvia Sky pacemaker does not differ from the standard implantation procedure, no study specific risks are associated with the implantation procedure.

However, the investigational devices under investigation in this study are not yet routinely available. The risk management process according to BIOTRONIK's quality management system has identified and analyzed all foreseeable risks related to the investigational devices. This includes the likelihood of the chain of events leading to their occurrence in the Functional System Risk Analyses (FSR).

Residual risks, e.g. technical failures in the implant due to component failures, or other events that could compromise functioning, cannot be completely ruled out; they are expected to occur, however, very rarely. Instructions for use will inform the users about hazardous usage conditions, but user errors cannot be prevented completely. There may be other risks associated with the devices that are currently unforeseeable.

The conducted examinations, like device interrogation and measurement of the leads' electrical parameters, are part of clinical routine. Depending on the specific routine of an investigation site and on the actual tests performed on the devices, the duration of in-office follow-ups might slightly increase from the routine. This is not considered to be a risk. However, due to the investigational status of the pacemaker and the programmer software, device interrogations can only be performed at investigational sites equipped with a Renamic Neo programming device with the corresponding study software, and not in any standard health care institution. This restriction will persist until regulatory approval of the devices and/or software under investigation is granted.

In the circumstance of a pandemic situation, in-office follow-up visits might pose an additional infection risk to the patient if the follow-up windows mandated by the study deviate from the site's routine follow-up scheme.

In the course of the study, event-triggered or physician-triggered (QuickCheck) IEGMs will be transmitted via BIOTRONIK Home Monitoring. The transfer of these data will result in a reduction of battery lifetime. The use of QuickCheck is assumed to reduce the battery lifetime by 2-3 weeks per year. However, these transmissions are not expected to be more frequent than in routine care using Home Monitoring, and they provide physicians with more information on patient status and might therefore be beneficial for the treatment of the patient. The benefit of Home Monitoring has been shown in different trials[17–19] 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.

Inadequate parameter adjustment was identified as a possible hazard of the CRT AutoAdapt algorithm. To account for this, the LV only mode is deactivated under certain conditions, like loss of capture or in the presence of tachycardia events. Possible effects of erroneous measurements, i.e. due to premature ventricular contractions (PVCs), are minimized by always using averages of three measurements. The small impact on battery life caused by the algorithm may be compensated when LV only pacing is possible.

Potential risks associated with the atrial ATP feature include 1) premature battery discharge and insufficient power supply due to repetitive aATP delivery that might lead to cardiac arrest in pacemaker-dependent patients; mitigated by a limitation of the number of delivered aATP, the selection of an appropriate battery technology and design of the electronic circuit; 2) tracking of the atrial therapy through to the ventricle, or delivery of aATP to the ventricle in case of instability of atrial lead, leading to a non-physiologic fast ventricular rhythm; mitigated by atrial therapy conduction protection (including 'stable rhythm check' and 'lead position check') and corresponding warning notices in the technical manual; 3) a general risk in all devices that provide atrial therapies related to embolism caused by coagulation thrombi after the atrial episode has been terminated; mitigated by suppressing atrial therapies in case of atrial fibrillation episodes whose duration exceeds a specified value. The residual risk remains that thrombi may still occur.

The risks associated with QuickCheck, CRT AutoAdapt and atrial ATP are the same within the study as if the feature is activated in routine care. However, they account as study-specific, as the activation of these features is mandatory for a subset of patients in this study, and the features are not yet routinely available in pacemakers outside the study.

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

No further burden for the patient due to study participation is expected.

6.4 Possible interactions with concomitant medical treatments

For pacemaker and CRT-P therapy, no interactions with concomitant medication and medical treatment are expected.

6.5 Steps to control or mitigate the risk

The investigational devices meet the current state of medical science and technology and are used according to their intended use.

For all risks identified in the FSRs, appropriate risk control measures have been applied (see also 6.3). The defined measures derived from the different aspects of risk assessments are documented, implemented and their effectiveness is reviewed. This process is in compliance with the ISO 14971 standard.

The risks can be further 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.

Study patients will be provided with an Implant Card including information on the participation in the study, the need to use a specific programmer for device interrogation, and the contact details of the investigational site, so that other treating healthcare institutions can be adequately informed.

In case of a pandemic situation, study related follow-up visits that otherwise would have been canceled or postponed to avoid the risk of infection, should not be conducted only for protocol compliance reasons. In such cases, the sponsor needs to be informed upfront, so that a planned and justified CIP deviation can be documented. Depending on the situation, the follow-up should be postponed or performed remotely.

6.6 Rationale for benefit-risk ratio

Patients in this study are provided with the newest available BIOTRONIK pacemaker or CRT-P technology. The implantation procedure does not differ from other comparable pacemaker/CRT-P system implantations, thus resulting in no additional risk for the patient.

The Amvia/Solvia family pacemakers are technically and functionally based on the predecessor and well-established Edora family. Furthermore, most of the new features are based on features already established in market approved BIOTRONIK ICDs. Appropriate risk control measures have been applied for all risks identified in the respective FSRs.

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

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

The mandatory use of Home Monitoring, the transmission of IEGMs and the potential use of QuickCheck decrease battery lifetime. On the other hand, the transmitted data provide physicians with more information on patient status and might therefore be beneficial for the treatment of the patient. Thus, physicians might choose these options for their patients also if not participating in the study, as recommended by current guidelines[20].

The individual benefit for the patient from participation in the clinical study is limited to the intensified clinical care in the controlled setting of the study, including the testing of the available features. The general benefit of the study is to monitor the product performance of the new Amvia/Solvia pacemaker family, and to collect data to support the decision for market release and regulatory approvals. Thus, the results of this study will make this new generation of pacemakers available for a greater patient population.

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

7 OBJECTIVES AND HYPOTHESES

7.1 Purpose of the clinical investigation and claims

7.1.1 Purpose of the clinical investigation

The purpose of the clinical investigation is to determine preliminary safety and product performance of the new Amvia/Solvia pacemaker family and its new features. The data collected within this study will be used as a basis for decision for market release, potential support of product approval, validation of promotional claims, and the support of future study activities.

7.1.2 Claims for clinical performance, effectiveness or safety

The promotional claims related to the Amvia/Solvia pacemakers and their features that will be considered within this study are summarized in Table 2. For the evaluation of claims that rely on the overall experience with a feature rather than on patient-individual outcomes an investigator questionnaire will be used (see 8.1.4.20).

Table 2: Promotional Claims to be assessed within the BIO|CONCEPT.Amvia study

Feature	Promotional Claim	Method of assessment
Atrial ATP	[redacted]	
CRT AutoAdapt		
QuickCheck		
EarlyCheck		
MRI Guard 24/7		

Feature	Promotional Claim	Method of assessment
	[redacted]	
Leadless ECG		
HM always ON		

7.2 Objectives

The primary objective of this study is to determine preliminary safety and product performance of the new Amvia /Solvia pacemaker family, and to collect data to support the decision for market release in regions where regulatory approval is already granted.

Secondary objectives comprise the potential support of product approval in other regions, the validation of promotional claims, and the support of future study activities.

7.3 Hypotheses

Due to the explorative nature of this first-in-man study, and the variety of models and features that are covered, no pre-specified statistical hypotheses are defined. The small number of patients allows for a descriptive explorative analysis and generation of case reports, but not for a statistically significant analysis of hypotheses.

7.3.1 Scientific justification and clinical relevance

Not applicable, as no hypotheses, effects sizes or non-inferiority margins are defined.

7.4 Risks and anticipated adverse device effects

There will be assessments of risks and anticipated adverse device effects throughout the clinical investigation as described in section 19.

Anticipated adverse device effects and risks associated with participation in the clinical investigation are described in subchapters 6.2 and 6.3.

8 DESIGN OF THE CLINICAL INVESTIGATION

8.1 General considerations

8.1.1 Design type of clinical investigation

The study is designed as an explorative, open-label, prospective, non-randomized, multi-center, bi-national study.

Blinding e.g. by performing sham operations or using dummy devices is ethically not justifiable in the field of standard pacemaker therapy. In the absence of comparators or subgroups, randomization is not appropriate.

8.1.2 Measures taken to minimize or avoid bias

It is planned to run this study in about 8 sites where more than one physician per site are expected to participate. It is intended to get an adequate level of heterogeneity of sites and investigators to obtain representative results. A maximum number of 17 patients per investigational site is defined in order to avoid a center effect (see section 12.9).

Furthermore, the study is conducted according to BIOTRONIK Center for Clinical Research´s (CCR) Standard Operating Procedures (SOPs), which describe in more detail further measures for the avoidance of bias.

8.1.3 Endpoints

No primary or secondary endpoints are defined. All data required for the monitoring of device performance in this relatively small group of patients are described as 'further data of interest'. For information on descriptive statistics and further analytical procedures see chapters 12.2 and 12.3.

8.1.3.1 Primary endpoints

As no hypothesis has been defined, no primary endpoint is defined either.

8.1.3.2 Secondary endpoints

Due to the low number of use cases per feature, no secondary endpoints are defined.

8.1.3.3 Further data of interest

The following data of interest will be collected and assessed:

- Baseline characteristics and medical history
- IPG-related SADE-free rate (see definition below)
- Lead measurements (sensing amplitude, pacing threshold, pacing impedance at implantation and at each follow-up and/or via Home Monitoring)
- Evaluation of appropriate sensing and pacing performance for all available channels (RA, RV, LV)
- Implantation and device details
- Device programming settings
- Home Monitoring data, e.g. programmed parameters, automatically measured device data, EarlyCheck/QuickCheck transmissions
- Home Monitoring transmission performance
- Usage and assessment or CRT AutoAdapt ('ON' in at least 5 patients; HF-T QP only)
- Usage and assessment of Auto LV VectorOpt

- Usage and assessment of atrial ATP (aATP 'ON' in at least 10 pts.; DR-T or HF-T QP only)
- [redacted]
- Adverse Events
- Device deficiencies
- Usage and assessment of MRI Guard 24/7
- Usage and assessment of EarlyCheck and QuickCheck
- Usage and assessment of leadless ECG
- Usage of CLS enhancements (DDI-CLS, VV delay with CLS)
- Usage of additional LV pacing vectors (HF-T QP only)
- [redacted]
- Occurrence of additional events in HM (early lead failure detection, high average heart rate)

Definition of SADEs to be taken into account for the calculation of the SADE-free rate:

SADEs will be adjudicated internally, whereby the seriousness and device relatedness will be re-examined. If any amply documented external physical influence (e.g. accident, sport, twiddling) or other causative AE led to the SADE, the SADE does not contribute to the calculation of the SADE-free rate. Only SADEs directly related to the investigational device (SADE-d) will be included in the analysis. SADEs which are securely related to the implantation procedure (SADE-p) (e.g. pocket infection, etc.) will not be considered for the analysis. Furthermore Twiddler`s syndrome will not be considered for the analysis either.

8.1.4 Methods

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 are documented on the corresponding electronic case report forms (CRFs). The investigator is required to use an electronic signature to approve the content of the data reported in the CRFs. BIOTRONIK will audit and monitor the content of the CRFs as described in section 10.1.4. The corresponding time schedule is described in section 9.1.

Data will be recorded at the following points in time:

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

The following events can be documented at any time

- Adverse Event
- Device Deficiency
- Deviation (patient / site related)

The investigator questionnaire will be completed after the end of overall study enrollment.

Source data, e.g. medical records, has to be available for all data entered in the CRFs, unless specified differently by this CIP (compare sections below). CRFs will be verified at monitoring visits by the sponsor's representative.

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

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

8.1.4.1 Examination of eligibility criteria

The inclusion and exclusion criteria (see sections 8.3.1 and 8.3.2) must be assessed before the subject is enrolled by signing the informed consent form.

The CRF is accepted as source if the patient record does not contain information about the following inclusion criteria:

- Ability to understand the nature of the study
- Willingness to provide written informed consent
- Ability and willingness to perform all follow-up visits at the study site
- Ability and willingness to use the CardioMessenger and acceptance of the BIOTRONIK Home Monitoring concept.

The CRF is accepted as source document if the patient record does not contain information about the following exclusion criteria:

- Life expectancy of less than 12 months
- Pregnant or breast-feeding
- Participation in another interventional clinical investigation

8.1.4.2 Patient demographics and medical history

Demographic information including age, gender, height and weight will be collected for all subjects on the Baseline CRF. Furthermore, information on the medical condition of the patient and the indication for the pacemaker are documented. Further collected information comprises the medical history of the patient, current cardiovascular medication and NYHA class; ECG diagnostics and left ventricular ejection fraction (LVEF) within 3 months prior enrollment are documented, if routinely available.

8.1.4.3 Implantation information

The implantation of the Amvia/Solvia family pacemakers is performed according to standard procedures as will be described in the technical manual. Any lead delivery system can be used. However, BIOTRONIK accessories are recommended.

The following implantation information has to be collected:

- Implanted device system (IPG and leads) – to be entered on Device Log, see 8.1.4.4
- Type of implantation (first pacemaker/CRT-P implantation, pacemaker upgrade, pacemaker replacement)
- X-ray time, procedure time
- Optional: Device-based measurements of the sensing amplitudes and pacing thresholds (manually measured or automatically triggered) and recording of pacing impedance

8.1.4.4 Device Log

All elements of the implanted system that were part of an implantation process shall be entered into the device log. Therefore, also information on unsuccessful implantations of investigational medical devices shall be entered into the log. In case a new device or a new lead is added or exchanged, the new information on the device system shall be added to device log and an AE CRF shall be filled out by the study team. The implantation or exchange of devices follows the clinical routine procedures.

The following information shall be recorded in the device log:

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

8.1.4.5 Device-based measurements

At implantation (optional), PHD, 1- , 3- and 12-month follow-up, the measurements of the mean sensing amplitude, the pacing threshold and the pacing impedance have to be documented for all available channels (RA, RV, LV). Threshold tests can be performed either manually or triggered automatically (as available). If no manual measurements were performed during the on-site follow-up, or in case of a remote follow-up, the values which were automatically measured by the pacemaker the previous day are acceptable. In the RA and RV the pulse width must be 0.4 ms, in the LV any pulse width can be chosen. For CRT-P patients measurement of LV pacing vectors with the Automatic LV VectorOpt feature is recommended (see 8.1.4.8). Pacing polarities of the LV channel must be documented.

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

8.1.4.6 Evaluation of system performance

The investigator is asked to assess the system performance, i.e. appropriate sensing and pacing performance at the end of the implantation procedure (optional) and **at the end** of each follow-up (including storing of an IEGM snapshot):

Pacing/sensing performance will be assessed as adequate or inadequate. If the assessment is not possible, e.g due to absence of an intrinsic rhythm/signal or due to inability to perform overpacing, this shall not be considered as inadequate. Reasons for an assessment as inadequate shall be specified.

While relying on device-based measurements and IEGM snapshots, the evaluation of system performance is based on the investigator´s subjective but professional judgment.

8.1.4.7 EarlyCheck / QuickCheck

The use of EarlyCheck is mandatory after implantation, whereas the use of QuickCheck is optional. The feature needs to be programmed 'ON' (default setting) in order to enable data transmissions.

For the use of EarlyCheck for the transmission of post-implantation data, the pacemaker needs to be registered in HMSC before the implantation, or at latest within 2 hours after the begin of the implantation procedure. To enable the transmission the patient needs to be provided with a CardioMessenger shortly after the end of the implantation procedure, e.g. while they are in the recovery room. The data will then be automatically transmitted to the HMSC, and can be viewed there, typically between 2 and 6 hours after the implantation.

The following data related to the use of EarlyCheck will be documented in the CRF at PHD:

- When was the CardioMessenger placed in the patient's vicinity?
- Where was the CardioMessenger positioned for the EarlyCheck transmission?
- Completeness and reliability of data (Score: 'Very good/good/adequate/poor/very poor')
- Potential for replacement of PHD visit (Investigator assessment: Is the data transmitted via EarlyCheck sufficient to replace a PHD visit? (Score: 'Yes/no/cannot judge'; Comment))

For the use of QuickCheck, the investigator needs to trigger a data transmission via the HMSC, and the patient needs to be in the vicinity of their CardioMessenger to enable the transmission. The data can then be viewed in the HMSC, typically within 5-6 minutes. (Prerequisite is at least one HM message received at HMSC before QuickCheck is triggered.)

The following data related to the use of QuickCheck will be documented in the follow-up CRF:

- Reason for activation of QuickCheck
- Potential avoidance of patient in-office visit
- Overall assessment of QuickCheck (Score: 'Very good/good/adequate/poor/very poor')

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

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

8.1.4.8 Automatic LV VectorOpt test

The automatic LV VectorOpt (LVVO) test has to be perfomed once for every CRT-P patient during the study. It is recommended to perform the test at pre-hospital discharge, but testing at implantation, 1- or 3-month follow-up is also acceptable.

It is recommended to perform the measurement of RV/LV conduction times at the beginning of the test to facilitate the selection of vectors that are to be measured. The automatic LV VectorOpt test should be performed for all 20 available vectors. Alternatively, a subset of at least three vectors at the investigator's discretion may be chosen. Finally, the PNS thresholds shall be measured manually for a selection of vectors at the investigator's discretion.

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

- Time needed to perform the LV threshold measurement automatically (using all 20 vectors or for selected vectors)
- Listing of pacing vectors that were tested during the automatic procedure [Multiple choice]
- Values for pacing threshold, pacing impedance, and PNS threshold of the finally programmed pacing vector
- Overall handling assessment of Auto LV VectorOpt feature (Score: 'Very good/good/ adequate/poor/very poor')

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

8.1.4.9 Assessment of CRT AutoAdapt

CRT AutoAdapt shall be programmed 'ON' in at least five patients with CRT-P devices in the study. However, its use is recommended for all CRT-P patients, with the exception of patients with AV block, for whom this feature is contraindicated. Furthermore, CRT AutoAdapt cannot be programmed at the same time as atrial ATP.

CRT AutoAdapt should be programmed at implantation or pre-hospital discharge. A later activation of the feature is possible.

The following data will be recorded at 3-month follow-up:

- Percentage of CRT pacing since last follow-up
- Percentage of adaptive BiV pacing since last follow-up
- Percentage of programmed BiV pacing since last follow-up
- Percentage of adaptive LV pacing since last follow-up
- Mean adapted AV delay after pace/sense
- Reason for deactivation, if applicable

- Overall assessment of the CRT AutoAdapt feature (Score: 'Very good/good/adequate/ poor/very poor')

At 12-month follow-up the following data will be recorded again:

- Reason for deactivation, if applicable
- Overall assessment of the CRT AutoAdapt feature (Score: 'Very good/good/adequate/ poor/very poor')

The CRF may be accepted as source document for the overall assessment at both follow-ups. The use of a site-specific source data sheet is recommended.

8.1.4.10 Assessment of atrial ATP

It is required that atrial ATP is programmed 'ON' in at least 10 patients with dual or triple chamber devices and a known history of atrial arrhythmias except permanent atrial fibrillation.

Atrial ATP should be programmed at 1-month follow-up, when a a reliable stable fixation of the atrial lead is ensured. An earlier or later activation of the feature is possible if a reliable stable position of the lead is achieved earlier (e.g. in case of device exchange) or later. However, atrial ATP cannot be programmed at the same time as CRT AutoAdapt. The programming of parameters is left at the investigator´s discretion. An example is shown in Figure 3 and Figure 4.

Figure 3: Example for programming of aATP – Tachycardia tab

Figure 4: Example for programming of aATP – Dialogue for AT/AF therapy programming

The following data will be recorded at 3- and 12-month follow-up:

- Programmed parameters (e.g. burst/ramp, repetition, delay, ventricular back-up pacing)
- Reasons for activation (study-related, prevention of permanent/persistent AF, prevention of stroke, other)
- Reasons for programming of ventricular back-up pacing
- Occurrence of atrial arrhythmia episodes
- Was aATP delivered as programmed?
- Termination of atrial arrhythmia episode within 30 seconds of aATP delivery?

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

8.1.4.11 Assessment of Leadless ECG

The use of leadless ECG is mandatory at pre-hospital discharge and optional at any subsequent in-office follow-up. No specific action is required, as the feature is 'ON' per default.

The following data will be recorded at pre-hospital discharge:

- Assessment of legibility of leadless ECG (Score: 'Very good/good/adequate/poor/very poor')

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

8.1.4.12 Assessment of MRI Guard 24/7

During the first follow-up after implantation (generally pre-hospital discharge) the investigator is prompted by the programmer to perform an MRI system check for every patient.

Figure 5: Screenshot of programmer interface for MRI system check

The following data related to the MRI system check and the MRI Guard 24/7 workflow will be recorded when the leads are implanted for more than 42 days (i.e. at pre-hospital discharge in case of device exchange, or at 3-month follow-up for de novo implantations). Please ignore the prompt for MRI system check until the leads are implanted for more than 42 days, unless they are not MR conditional per se.

- Is the patient approved for MRI scans? If no, why not?
- Was a printout of the MRI suitability certificate performed and handed out to the patient?
- Programmed MRI mode
- Reason for not using 'Auto' mode

If an MRI examination was performed during the course of the study (independently from the study), the following data related to MRI Guard 24/7 will be recorded at the subsequent follow-up:

- Activation of MRI Guard 24/7
- Assessment of the information flow via Home Montioring after the scan
- Adverse Events/Device Deficiencies related to the MRI procedure or use of MRI Guard 24/7.

The CRF may be accepted as source document for the assessment of MRI Guard 24/7. However, the use of a site-specific source data sheet is recommended.

8.1.4.13 Documentation of usage of CLS Enhancements

The use of CLS is optional within the study. CLS may be programmed at any time. The following data related to the CLS enhancements (DDI-CLS and CLS with programmable VV-delay) will be recorded at 3- and 12- month follow-ups:

- Was DDI-CLS programmed?
- Was CLS with VV delay programmed?

- Rationale for programming
- Assessment of benefit for the patient (Score: 'Very good/good/adequate/poor/very poor')

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

[redacted]

8.1.4.16 Medication Log

The concomitant cardiovascular medication shall be documented in the medication log at baseline. In case of adverse events changes or additions during study participation shall be entered in this log as well. The following data shall be entered in the log:

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

8.1.4.17 Adverse Events and Device Deficiencies

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 19.9). All adverse events will be classified according to their seriousness, the relation to the investigational devices and to the procedure. Furthermore, relation to atrial ATP or MRI Guard 24/7 will be documented. Reporting of adverse events is required starting from the time of signature on the patient informed consent form until study termination. Serious adverse device effects (SADE) that are not solved at patient´s study termination will be followed until local last-patient-out of the respective investigation site, but for a minimum of 4 weeks after study termination of the individual patient.

The definition of event classification is described in section 19.

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

Investigational devices which are related to a device deficiency or an adverse device effect must be returned to BIOTRONIK unless they remain implanted or in use. All explanted investigational devices must be returned to BIOTRONIK regardless of whether the explantation was related to an ADE or not.

8.1.4.18 BIOTRONIK Home Monitoring Data

The sponsor will collect the patient data obtained by telemetry over the period of study participation. This will include P- and R-wave sensing, pacing thresholds and impedance, periodic

IEGMs and recording episodes IEGMs and further data. The observation of Home Monitoring data by the sponsor cannot be used as an emergency system. The investigator is responsible to follow-up the patients via Home Monitoring and during in-office follow-ups.

8.1.4.19 ReportShare (Provision of Programmer Data)

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

The programmer data and IEGMs shall be provided to the sponsor via the ReportShare function to the Home Monitoring Service Center. Files exported via ReportShare are automatically pseudonymized. The export can be performed automatically or manually.

ReportShare export settings (see Figure 6: ReportShare export settings):

- Select 'Preferences' [1] and 'Connectivity' [2]
- Click on 'Remote Services' [3]
- Select 'ReportShare (Upload without name and date of birth)' [4]

- **Manual upload option**: performed by site team member after patient visit by choosing the data set from the data manager of the Renamic Neo programmer
- **Automatic upload option**: by clicking on 'Automatic upload' [5]. Subsequently each data set will be transmitted immediately after data interrogation end

Figure 6: ReportShare export settings

ReportShare manual upload:

- Click on ‘Data manager’ (see Figure 7)

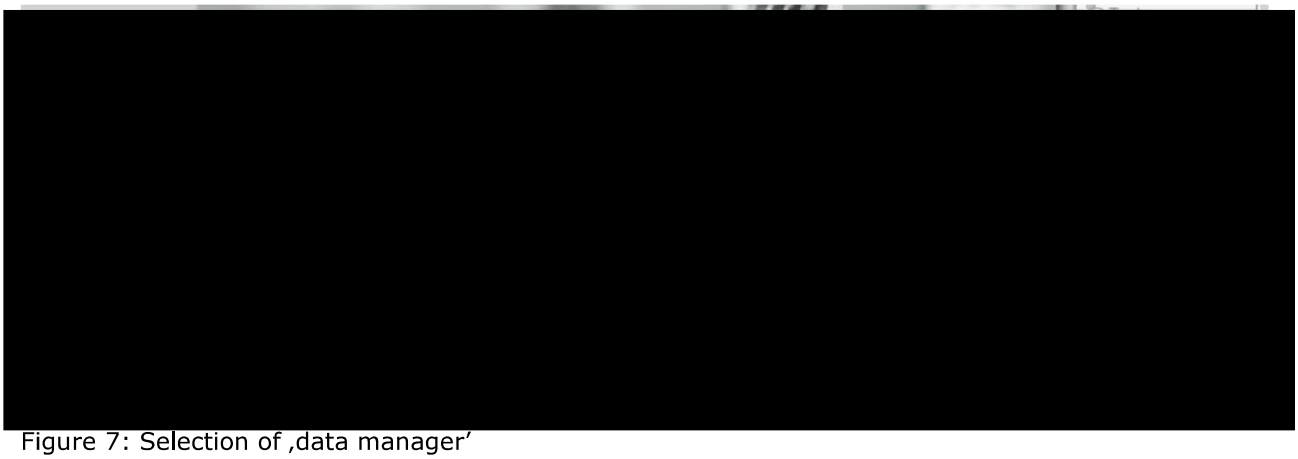

Figure 7: Selection of ‚data manager’

- Select FU data (one or more) [1]
- Click on ‘ReportShare’ [2] (see Figure 8)

Figure 8: Selection of follow-up data

- Click on 'Upload follow-up report' (Figure 9)

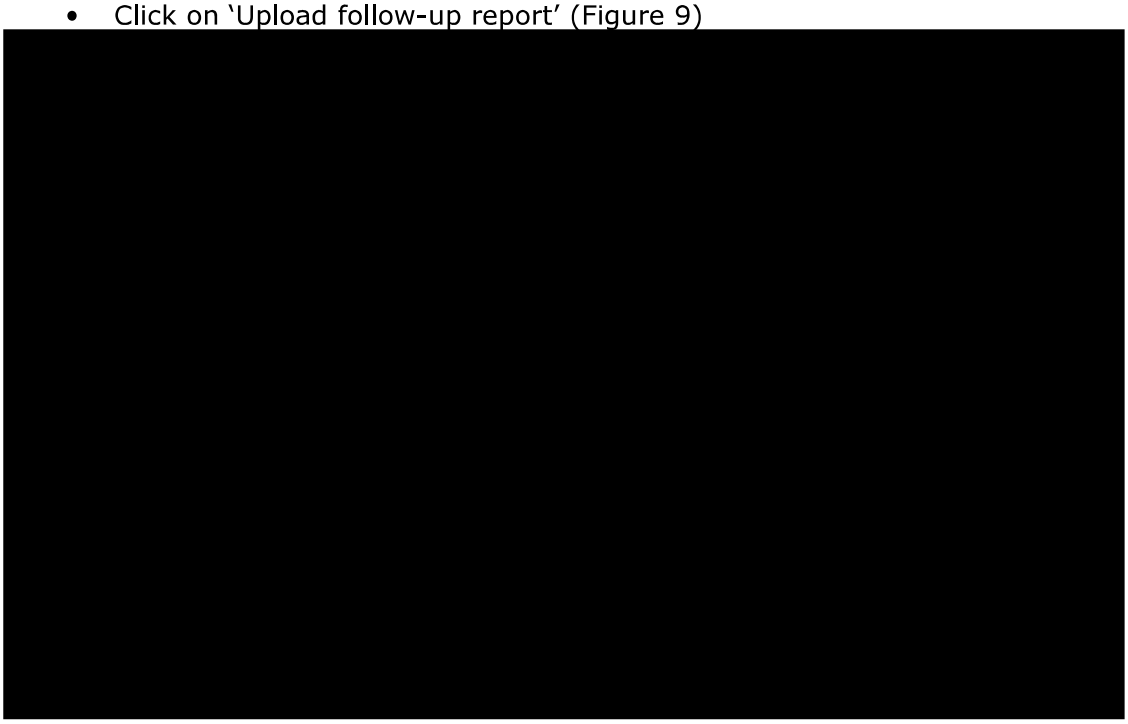

Figure 9: Button 'Upload follow-up report'

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

- Export via USB stick and delivery via email to the responsible clinical monitor

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

8.1.4.20 Investigator Questionnaire

In addition to data collected in patient-related CRFs, an investigator questionnaire will be issued after the completion of enrollment. This questionnaire should be answered by at least one investigator from every actively recruiting site, ideally the investigator who gained the most experience with Amvia Sky pacemakers within the study. Additional (co-)investigators involved in the implantation and/or follow-up of at least one study patient are welcome to complete the questionnaire as well.

The questionnaire will contain questions about the general experience with the Amvia/Solvia family and its features, e.g. related to handling, usability or workflow improvements, and will be used for the validation of promotional claims (see 7.1.2). Features to be covered will likely include atrial ATP, CRT AutoAdapt, EarlyCheck/QuickCheck, MRI Guard 24/7, leadless ECG and HM always ON.

8.1.5 Equipment to be used for the assessment of variables

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

Device:	BIOTRONIK Amvia Sky SR-T, DR-T, HF-T QP
RA-lead:	Free of choice
RV-lead:	Free of choice
LV-lead:	Free of choice
Accessories:	Compatible Introducer Sheath (i.e. LI plus, SafeSheath II)
	BIOTRONIK Selectra Catheters (recommended)
	BIOTRONIK Selectra Accessory Kit (recommended)

	Compatible balloon catheter (i.e. Corodyn P1)
	0.014'' Guidewires (i.e. Streamer, VisionWire for Sentus)
External programming device:	BIOTRONIK Renamic NEO
Programmer software:	NEO 2204.A/S and subsequent versions
Remote monitoring tools:	BIOTRONIK CardioMessenger Smart 4G
Remote monitoring software:	BIOTRONIK HMSC, including plugin for Amvia/Solvia family and subsequent releases
Thermometer:	Ear thermometer; Free of choice

If their regulatory approval is granted before the end of the study, the programmer software version NEO 2204.A and subsequent versions, as well as PSW 2204.A and subsequent versions on programming device BIOTRONIK Renamic, may be used for patient follow-up.

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

8.1.6 Replacement of patients

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

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

Patients that will be lost to follow-up or prematurely terminate the study for any reason after a successful implantation or coming into contact with an investigational device will not be replaced.

8.1.7 Investigation sites

About 8 investigation sites located in Australia and New Zealand are selected for participation in this investigation. All sites are experienced with pacemaker and CRT-P implantation.

8.1.8 Completion of the clinical investigation

The end of the clinical investigation is defined as the date of termination of the last patient (last patient out).

8.2 Used devices and comparators

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

In Europe, the implantable transvenous lead pacemakers belonging to the Amvia/Solvia family are classified as single use, implantable, active medical devices of Class III[2]. In Australia, the Amvia/Solvia family is classified as Class III.

According to the nature of implantable devices, the Amvia Sky 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.

The programmer software NEO 2204.A/S will be installed on Renamic Neo programmers exclusively for use within this study. It will be used for the interrogation and programming of

2 According to article 2, definition no. 1 (medical device), 4 (active device), 5 (implantable device) and 8 (single use device) and Rule 8 of Annex VIII, Chapter III of the MDR

the Amvia Sky devices at implantation and follow-up visits until the investigational devices and programmer software receive regulatory approval.

No comparator is used within this study.

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

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

8.2.3 Number of investigational devices to be used and a justification

It is expected that for each patient one Amvia Sky pacemaker will be used. However, in case of failed implantation attempts, deviations may occur.

Within the 50 patiens to be enrolled, the distribution of the different types of devices is planned as follows:

- 10-15 Amvia Sky SR-T
- Min. 10 Amvia Sky DR-T
- Min. 10 Amvia Sky HF-T QP

8.3 Patients

The patient population consists exclusively of patients with an indication for pacemaker therapy or cardiac resynchronization therapy according to the current clinical practice.

The investigator is responsible for screening all potential patients and selecting those who are appropriate for study inclusion. Patients who will participate in this study should be selected from the investigator's general patient population according to the inclusion and exclusion criteria described in chapters 8.3.1 and 8.3.2.

The decision for implantation of the respective BIOTRONIK devices should be based exclusively on medical reasons and should not be influenced by the enrollment to this clinical trial.

8.3.1 Inclusion criteria

For patient enrollment in the clinical trial all of the following inclusion criteria have to be fulfilled at the time of enrollment, not throughout the time of participation:

- Standard indication for pacemaker or cardiac resynchronization therapy pacemaker (CRT-P) implantation, including de novo, upgrade or replacement implantations
- Ability to understand the nature of the study
- Willingness to provide written informed consent
- Ability and willingness to perform all follow-up visits at the study site
- Ability and willingness to use the CardioMessenger and acceptance of the BIOTRONIK Home Monitoring concept

8.3.2 Exclusion criteria

Enrollment of a patient is not permitted if at least one of the following criteria is fulfilled:

- Planned for conduction system pacing
- Planned for activation of aATP without known history of atrial arrhythmia, or with permanent AF
- Planned cardiac surgical procedures or interventional measures other than the study procedure within the next 12 months
- Pregnant or breast feeding
- Age less than 18 years

- Participation in another interventional clinical investigation according to the definition given below[3,4]
- Life-expectancy less than 12 months

8.3.3 Criteria and procedures for subject withdrawal or lost to follow-up

Efforts to be made to trace subjects

In the case of patients who do not show up for the scheduled 3- or 12-month follow-up, all efforts should be made to contact them and complete the required checks, even if this would be far out of the planned schedule. Equally, all efforts should be made to contact the patient for the 12-month follow-up to assure that no adverse events will remain unnoticed. It should be kept in mind that the study device has no market approval and is implanted only under the condition that the patient is followed in this study.

Withdrawal of patient by investigator

Since no invasive, stressful or risky procedures are planned by this protocol after the implantation, it is not allowed that a patient is excluded from the study by decision of the investigator once an implantation with the investigational device has been performed. This does not infringe on the investigators' right, and obligation, to refrain from any study procedure that may not be medically justified. It is merely intended to assure complete reporting of adverse events from the complete study duration.

Study participation will be terminated for patients who are not implanted with an investigational device and who did not come into contact with any investigational device during implantation attempt (dropout according to protocol).

A breach of an inclusion criterion or fulfilment of an exclusion criterion in the course of the study does not constitute a reason for early study termination.

Withdrawal of patient consent

Patients may withdraw their consent for study participation at any time without stating the reason and without any unfavorable consequences. All data that is collected until the date of withdrawal will be deleted immediately by effective anonymization, unless their further processing is still required as regulated by the legal exceptions to the deletion obligations. This also applies if the patient has requested data erasure. Depending on the patient's decision to delete the data, it will be deleted by effective anonymization as soon as the conditions for the legal exceptions on further retention and processing cease to apply. A withdrawal sheet and a study termination CRF have to be filled in by the investigational site.

8.3.4 Point of enrollment

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

3 According to ISO 14155:2020, an interventional clinical investigation is a pre-or post-market clinical investigation where the assignment of a subject to a particular medical device is decided in advance by a CIP or diagnostic or monitoring procedures requested in the CIP are in addition to those available as normal clinical practice and burden the subject .

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

8.3.5 Total expected duration of the clinical investigation

The enrollment period is expected to last 5-6 months. With a follow-up period of 12 months +/- 30 days, the overall study duration is estimated to be 19 months.

Projected timelines*:

First Patient In (FPI)*:

Last Patient In (LPI)*:

Enrollment period:

Individual study participation:

Last Patient Out (LPO)*:

Total study duration:

*Timelines subject to change without requiring protocol amendments.

8.3.6 Expected duration of each subject's participation

The individual duration of patients' participation is 12 months (+/- 30 days).

8.3.7 Number of subjects required to be included

It is planned to include 50 patients. See also section 12.5.

8.3.8 Estimated time needed to select patients

The estimated time needed to select 50 patients corresponds to the enrollment period, which is expected to last 5-6 months.

8.3.9 Relationship of investigation population to target population

The patient population consists exclusively of patients with an indication for pacemaker therapy or cardiac resynchronization therapy according to the current clinical practice.

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

9 STUDY PROCEDURES

9.1 Overview

Table 3 gives an overview of the study visits and procedures.

The 3-month and 12-month follow-ups shall be performed in-office, whereas for the 1-month follow-up Home Monitoring data are acceptable.

In case of a pandemic situation, study related follow-up visits that otherwise would have been canceled or postponed to avoid the risk of infection, should not be conducted only for protocol compliance reasons. In such cases, the sponsor needs to be informed upfront, so that a planned and justified CIP deviation can be documented. Depending on the situation, the follow-up should be postponed or performed remotely.

It is required that Atrial ATP is programmed 'ON' in at least 10 patients throughout the study, and CRT AutoAdapt in at least 5 patients.

Table 3: Overview of study visits and procedures

Investigations	**Enroll-ment**	**Implan-tation**	**PHD** ±4 days	**1-month follow-up** -7 days / +21 days	**3-month follow-up** -28 days / +14 days	**12-month follow-up** ±30 days
Patient informed consent	•					
Verification of in- and exclusion criteria	•					
Doc. of demographics and physical examination	•					
Doc. of cardiac diagnostics	•					
Doc. of therapy indication	•					
Doc. of medical history and co-morbidities	•					
Cardiovascular medication	•					
IPG/CRT-P implantation		•				
HMSC registration, hand-out CardioMessenger		•	•			
Programming of device settings		(•)	•	•	•	(•)
Device-based measurements		(•)	•	•/HM	•	•
Evaluation of system performance		(•)	•	•	•	•
Auto LV VectorOpt assessment		(•)	•	(•)	(•)	
Leadless ECG assessment			•			
[redacted]						
MRI Guard 24/7 assessment			•			
Doc. of MRI examinations				•	•	•
aATP assessment					•	•
CRT AutoAdapt assessment					•	•
EarlyCheck assessment			•			

Investigations	Enroll-ment	Implan-tation	PHD ±4 days	1-month follow-up -7 days / +21 days	3-month follow-up -28 days / +14 days	12-month follow-up ±30 days
QuickCheck assessment				●	●	●
Doc. of CLS enhancements					●	●
AE/DD reporting		●	●	●	●	●
ReportShare upload		(●)	●	●/HM	●	●
CRF completion	●	●	●	●	●	●
Regular study termination						●
Investigator questionnaire		After LPI				

Doc.-Documentation; ● – mandatory; (●) – optional; ● – if applicable; ●/HM – HM data acceptable

9.2 Enrollment

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

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

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

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

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

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

- Patient demographics and physical examination
- Medical history, including information on cardiovascular diseases and co-morbidities
- Indication for pacemaker or CRT-P therapy
- ECG diagnostics (if available within 3 months prior to implantation)
- For CRT-P patients: LVEF and NYHA class evaluated within 3 months prior to implantation (if available)

On the Medication Log the following data have to be recorded:

- Current cardiovascular medication

9.3 Implantation

The implantation can only be performed after enrollment of the patient. The implantation may be performed on the same day as informed consent was given. If the implantation is not performed within 30 days of the informed consent, the patient may be excluded from the study. The implantation procedure will follow the clinical routine. For further details, please refer to section 8.1.4.3 and the Investigator´s Brochure.

In addition to de novo implantations, patients with planned device exchange or upgrade from pacemaker to CRT-P may also be included in the study.

The following procedures have to be performed:

1. For the use of EarlyCheck, register the patient in the Home Monitoring Service Center before or within 2 hours of start of implantation (see 8.1.4.7)

2. Perform lead measurements via pacing sensing analyzer (PSA) (any analyzer can be used but BIOTRONIK device recommended; no documentation in CRF required)
3. Optional: Perform device-based measurements of pacing thresholds, sensing amplitudes and pacing impedances via Renamic Neo programmer (see 8.1.4.5)
4. Optional: Evaluate system performance (sensing and pacing) (see 8.1.4.6)

[redacted]

6. Optional: For CRT-P patients: Perform Automatic LV VectorOpt Test (see 8.1.4.8)
7. Program the following mandatory device settings:
   - Home Monitoring 'ON' (unchanged default setting)
   - Recording episode IEGMs 'ON' for high atrial rate, high ventricular rate and nsT (unchanged default setting)
8. Program the following recommended device settings:
   - Capture Control 'ON' or 'ATM'
9. Program the following optional device settings:
   - For CRT-P patients (with exception of patients with chronic complete AV block): CRT AutoAdapt 'ON'
   - For DR-T or HF-T QP patients with known history of atrial arrhythmia (except permanent AF): aATP 'ON'
10. Register to Home Monitoring Service Center
11. Complete the electronic Case Report Forms (CRF) in a timely manner
12. Provide programmer data, if available (see 8.1.4.19)
13. 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 ethics committee, if required. Report adverse events within the indicated timelines (see section 19.10). [redacted]

9.4 Pre-hospital discharge

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

The following procedures are required.

1. Reprogram pacemaker settings as applicable to optimize pacemaker/CRT-P function
2. Perform device-based measurements of pacing thresholds, sensing amplitudes and pacing impedances via Renamic Neo programmer using leadless ECG (see 8.1.4.5 and 8.1.4.11)
3. Evaluate system performance (sensing and pacing) (see 8.1.4.6)

[redacted]

5. Assess leadless ECG (see 8.1.4.11)
6. For CRT-P patients: Perform Automatic LV VectorOpt Test (see 8.1.4.8) (if not yet done at implantation)
7. Program the following mandatory device settings:
   - Home Monitoring 'ON' (unchanged default setting)
   - Recording episode IEGMs 'ON' for high atrial rate, high ventricular rate and nsT (unchanged default setting)

8. Program the following recommended device setting:
   - Capture Control 'ON' or 'ATM'
9. Program the following optional device settings:
   - For CRT-P patients (with exception of patients with chronic complete AV block): CRT AutoAdapt 'ON'
   - For DR-T or HF-T QP patients with known history of atrial arrhythmia (except permanent AF), if reliable stable atrial lead position is ensured: aATP 'ON'
   - QuickCheck 'ON'

[redacted]

11. Assess EarlyCheck (see 8.1.4.7)
12. If leads are implanted for >42 days: Perform MRI system check and Assess MRI Guard 24/7 (see 8.1.4.12)
13. Document MRI examinations since implantation, if applicable (see 8.1.4.12)
14. Register to Home Monitoring Service Center and hand over the CardioMessenger, if not yet done

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

    In the time between the follow-up visits it is recommended to check the Home Monitoring transmission on a regular basis. If data transmission is missing, the investigator or study nurse has to contact the patient to clarify the reason for non-transmission.
15. Complete the electronic Case Report Forms (CRF) in a timely manner
16. Provide programmer data (see 8.1.4.19)
17. Report all adverse events. In case of a serious adverse event, or adverse device effect (ADE), please provide the information immediately to BIOTRONIK, and inform the ethics committee, if required. Report adverse events within the indicated timelines (see section 19.10). [redacted]

9.5 1-month follow-up

One month (30 days; - 7 days / + 21 days) after the implant procedure, an assessment of the implanted system has to be performed. The assessment should be performed as in-office follow-up visit if this is in accordance with the site´s routine follow-up schedule, or if the patient is planned for activation of aATP. Otherwise, a remote follow-up based on information in the patient file and via Home Monitoring is acceptable as well.

The investigator reviews the system performance and, in case of an in-office visit, adjusts the programmed parameters as necessary to optimize the pacemaker/CRT-P functions. The requirements for an in-office follow-up visit are listed below. The procedures required in case of a remote follow-up are marked in **bold** letters.

1. Reprogram pacemaker settings as applicable to optimize pacemaker/CRT-P function
2. Perform device-based measurements of pacing thresholds, sensing amplitudes and pacing impedances via Renamic Neo programmer (see 8.1.4.5) / **Document automatic pacing thresholds, sensing amplitudes and pacing impedances from HMSC.**
3. **Evaluate system performance (sensing and pacing) (see 8.1.4.6)**
4. For CRT-P patients: Perform Automatic LV VectorOpt Test (see 8.1.4.8) (if not yet done at implantation or PHD)
5. Program the following mandatory device settings:
   - Home Monitoring 'ON' (unchanged default setting)

- Recording episode IEGMs 'ON' for high atrial rate, high ventricular rate and nsT (unchanged default setting)

6. Program the following recommended device setting:
   - Capture Control 'ON' or 'ATM'
7. Program the following optional device settings:
   - For CRT-P patients (with exception of patients with chronic complete AV block): CRT AutoAdapt 'ON'
   - For DR-T or HF-T QP patients with known history of atrial arrhythmia (except permanent AF): aATP 'ON'
   - QuickCheck 'ON'
8. **Document MRI examinations since PHD, if applicable (see 8.1.4.12)**
9. **If QuickCheck was used: Assess QuickCheck (see 8.1.4.7)**
10. **Complete the electronic Case Report Forms (CRF) in a timely manner**
11. Provide programmer data (see 8.1.4.19)
12. **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 ethics committee, if required. Report adverse**

[redacted]

9.6 3-month follow-up

An in-office follow-up visit is performed three months (92 days; -28 days/+14 days) after the implant procedure.

The investigator reviews the system performance and adjusts the programmed parameters as necessary to optimize the pacemaker/CRT-P functions. The requirements for this follow-up visit are listed below:

1. Reprogram pacemaker settings as applicable to optimize pacemaker/CRT-P function
2. Perform device-based measurements of pacing thresholds, sensing amplitudes and pacing impedances via Renamic Neo programmer (see 8.1.4.5)
3. Evaluate system performance (sensing and pacing) (see 8.1.4.6)
4. For CRT-P patients: Perform Automatic LV VectorOpt Test (see 8.1.4.8) (if not yet done at implantation, PHD or 1-month follow-up)
5. Perform MRI system check and assess MRI Guard 24/7 (if not yet done at PHD) (see 8.1.4.12)
6. Assess CRT AutoAdapt, if programmed (see 8.1.4.9)
7. Assess atrial ATP, if programmed (see 8.1.4.10)
8. Document usage of CLS enhancements, if applicable (see 8.1.4.13)
9. Program the following mandatory device settings:
   - Home Monitoring 'ON' (unchanged default setting)
   - Recording episode IEGMs 'ON' for high atrial rate, high ventricular rate and nsT (unchanged default setting)
10. Program the following recommended device setting:
    - Capture Control 'ON' or 'ATM'
11. Program the following optional device settings:
    - For CRT-P patients (with exception of patients with chronic complete AV block): CRT AutoAdapt 'ON'
    - For DR-T or HF-T QP patients with known history of atrial arrhythmia (except permanent AF): aATP 'ON'

- QuickCheck 'ON'

[redacted]

13. Document current medication on the medication log (see 8.1.4.16)
14. Document MRI examinations since 1-month follow-up, if applicable (see 8.1.4.12)
15. If QuickCheck was used: Assess QuickCheck (see 8.1.4.7)
16. Complete the electronic Case Report Forms (CRF) in a timely manner
17. Provide programmer data (see 8.1.4.19)
18. 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 ethics committee, if required. Report adverse events within the indicated timelines (see section 19.10). [redacted]

9.7 12-month follow-up

Twelve months (365 ±30 days) after the implant procedure, the patient has to return to the hospital for an in-office follow-up and study termination. The investigator reviews the system performance and adjusts the programmed parameters as necessary to optimize the pacemaker/CRT-P functions. The requirements of this follow-up visit are listed below:

1. Reprogram pacemaker settings at investigator´s discretion as applicable to optimize pacemaker/CRT-P function
2. Perform device-based measurements of pacing thresholds, sensing amplitudes and pacing impedances via Renamic Neo programmer (see 8.1.4.5)
3. Evaluate system performance (sensing and pacing) (see 8.1.4.6)
4. Assess CRT AutoAdapt, if programmed (see 8.1.4.9)
5. Assess atrial ATP, if programmed (see 8.1.4.10)
6. Document usage of CLS enhancements, if applicable (see 8.1.4.13)
7. Document current medication on the medication log (see 8.1.4.16)
8. Document MRI examinations since 3-month follow-up, if applicable (see 8.1.4.12)
9. If QuickCheck was used: Assess QuickCheck (see 8.1.4.7)
10. Complete the electronic Case Report Forms (CRF) in a timely manner
11. Provide programmer data (see 8.1.4.19)
12. 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 ethics committee, if required. Report adverse events within the indicated timelines (see section 19.11). [redacted]
13. The programming at study termination is at the investigator´s discretion. See also section 9.9.

9.8 Interim follow-up

Interim follow-ups will not be documented.

9.9 Termination and post treatment

The patients terminate the study regularly after the completion of the 12-month follow-up. The CRF 'Study termination' has to be filled in. In case of any premature study termination, the CRF Study Termination has to be completed with the reason for study termination. It is strongly recommended that a final examination is performed in this case, if possible. If the implantation of the investigational devices could not be completed successfully, the reason must be provided. If the patient is lost to follow-up, the attempts to get in contact with the patient or his/her relatives have to be documented in the patient file. The process of consent withdrawal is described in section 8.3.3.

After study termination the patients are treated according to standard routine care, and according to the site´s routine follow-up schedule for pacemakers and CRT-P devices, respectively. The device programming is at the investigator's discretion. Due to the investigational status of the programmer software, device follow-ups and programming can only be performed at investigational sites until regulatory approval is obtained for the programmer software.

In case of a temporary halt or suspension of the site or study, patients will be followed up according to clinical routine using the investigational programmer software, unless the suspension letter describes other measures.

If the device needs to be exchanged after termination of the study, the patient will receive any device model with market approval at that time.

9.10 Description of those activities performed by sponsor representative

The only study-specific activity of sponsor representatives will be to support the site with patient registration to HMSC before or shortly after implantation, and with the hand-over of the CardioMessenger shortly after implantation, so as to ensure the EarlyCheck data transmission, which is not yet part of the clinical routine.

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

Monitoring will be performed by a sponsor representative according to the monitoring plan (see 11).

9.11 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.