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BIO|CONCEPT.BIOMONITOR III

Clinical Investigation Report

CCR CENTER FOR CLINICAL RESEARCH

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Clinical Investigation Report

for the

BIO|CONCEPT.BIOMONITOR III Study

Reference Number:	RD020
Version:	1.0
Date of Report:	18 Oct 2019
Investigational devices:	BIOMONITOR III Remote Assistant III Programmer Software

This is a single arm, first-in-human study investigating patients with an indication for an implantable cardiac monitor. It was done according to ISO14155.

Latest CIP identification: 1.0 from 13 Nov 2018

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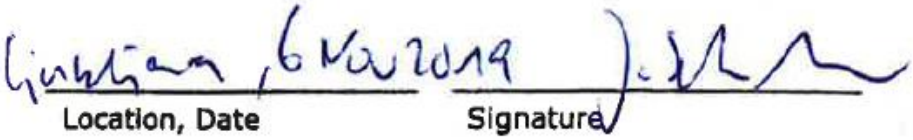

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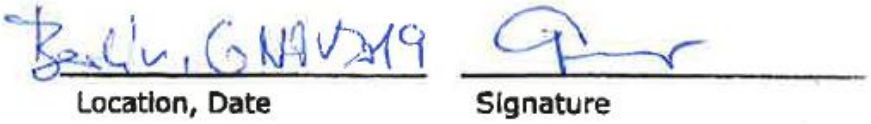

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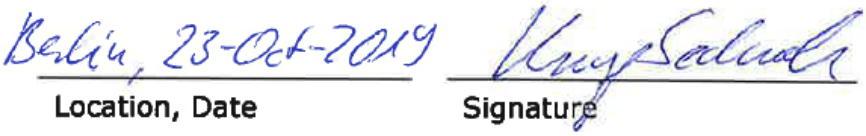

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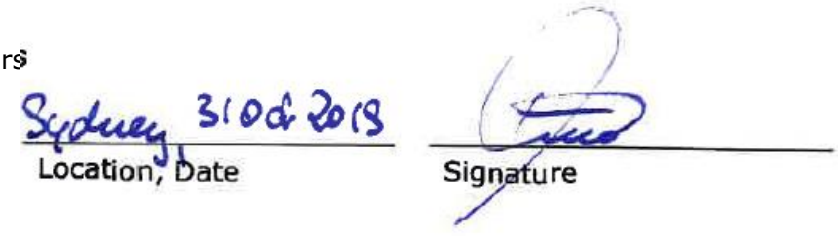

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1 SUMMARY

This is the final report of the BIO|CONCEPT.BIOMONITOR III Study.

1.1 Introduction

This study investigates the Implantable Cardiac Monitor 'BIOMONITOR III' of Biotronik. These devices are permanently implanted to allow long-term cardiac rhythm monitoring.

1.2 Objectives

The objective of this study is to investigate the safety and efficacy of the insertion procedure and the use and handling of the incision and insertion tools. Additionally, the sensing quality of the BIOMONITOR III is investigated.

1.3 Patients

Patients of this study require long-term cardiac rhythm monitoring for diagnostic purposes.

1.4 Methods

This study is designed as a first-in-human study, to allow for a controlled assessment of the implantation procedure and the principal function in the first weeks after insertion.

A sample size of 45 patients has been defined. Investigators from 10 investigational sites were allowed to insert up to 5 study devices each.

Patients are seen in office one week after insertion. One month after insertion, they are contacted by telephone and remote monitoring data are evaluated.

The study follows the rules defined in the declaration of Helsinki and those given in ISO 14155.

1.5 Results

Between March 8 and May 14, 2019, 48 patients were enrolled. Sixteen investigators inserted study devices in 47 patients. Nine patients had an early termination for the following reasons: In 4 patients, an indication for a permanent pacemaker was found based on device data. In 2 patients, the devices protruded shortly after insertion because of a combination of a challenging patient anatomy and possibly suboptimal handling / wound closure. Each one patient did not receive a device, had the device damaged by a cardioversion shock, and was lost to follow-up.

The patients were on average 64 years old and 48% were women.

The insertion procedure lasted a median time of 39 seconds until removal of the insertion tool and 5 minutes until wound closure including cleaning. The investigators rated the insertion tools and most aspects of the procedure as 'good' or 'excellent' in 98% of all cases. 'Force needed for tunnelling' was assessed as 'good' or 'excellent' in 91.5% and 'fair' in 8.5% of all cases.

The mean highest and lowest R-wave amplitudes were 1.0 and 0.8 mV, the range was between 0.2 and 2.0 mV.

Eighty-nine percent of all heart cycles on subcutaneous ECGs, which showed a regular sinus rhythm, had visible P-waves.

The wearing comfort after four weeks was described as 'good' or 'excellent' in a majority of patients (85%). However, in one patient (2.5%), the device has caused significant pain and discomfort, and 7 patients (17.5%) were often or very often aware of the device's presence.

The 'Patient App', a smartphone application to allow communication with the treating physician, was used by 8 patients (20%). The limited amount of data does not allow a meaningful assessment of the application.

1.6 Conclusion

The insertions of the BIOMONITOR III can be concluded in a short period of time and the 16 investigators, who performed between one and 5 procedures, assessed all aspects as good or excellent in 98% of the cases.

The R-wave amplitudes are high and P-waves are visible in most ECGs, which is expected to increase the clinical value of the ECGs that the devices stores and transmits.

Overall, the study device has shown a good performance.

2 INTRODUCTION

The BIOMONITOR III, which is the subject of this investigational study, is the third generation Implantable Cardiac Monitor (ICM) of Biotronik.

ICMs are devices which are permanently implanted under a patient's skin to allow cardiac rhythm monitoring for a long time-period of month to years. Their principal function is to detect rare arrhythmias which are suspected in a patient, and thereby establish evidence that is suited to guide further therapy. ICMs have a retrospective loop memory, which continuously records the most recent minutes of a patient's subcutaneous electrocardiogram (sECG). The device can automatically capture arrhythmic events and freeze the sECG in a permanent memory. State-of-the-art devices as the BIOMONITOR III additionally transmit these ECG snapshots by remote monitoring to notify the physician.

The most common application of ICMs is the diagnosis of unexplained recurrent syncope. The devices are also used in the evaluation of unclear palpitations. A further application of ICMs is in the detection and management of atrial fibrillation.

The immediate predecessor of the BIOMONITOR III was the BioMonitor 2, which is market approved in many markets worldwide. While the BIOMONITOR III maintained many functional aspects of its predecessor, the device was miniaturized and the implantation, or insertion, procedure was simplified.

This study was designed as a first-in-human study, to allow for a controlled assessment of the insertion procedure and the principal function in the first weeks after insertion. It follows the rules defined in the declaration of Helsinki and those given in ISO 14155. The study was reported to the Australian Competent Authority (Therapeutic Goods Administration).

3 INVESTIGATIONAL DEVICE

BIOMONITOR III is an ICM for the monitoring and automatic recording of the heart rhythm. Its primary purpose is to provide early detection and diagnostics of symptoms of arrhythmias, such as atrial tachycardias and the causes of syncopes, which can be clinically manifested. Like all ICMs, it does not deliver any therapy.

BIOMONITOR III is BIOTRONIK's third generation of ICM.

The housing consists of biocompatible titanium, with a shape to facilitate the subcutaneous insertion. It has automatic detection algorithms for asystole, bradycardia, high ventricular rate, atrial fibrillation and sudden rate drop. The settings for sensing of heartbeats and for detection of arrhythmias can be adjusted by the physician with a programmer device. It can store up to 55 subcutaneous ECG (sECG) snapshots. Once per day, it can transmit a message by remote monitoring that can contain up to 6 sECGs. The responsible physician can assess these messages on a secure internet site.

It is, in most aspects, similar to its predecessor device, the BioMonitor 2, which is a market available and accepted device. There are two major differences, when compared to the BioMonitor 2. First, the BIOMONITOR III has a simplified insertion procedure. An Incision Tool is used to make an incision through the skin. The 'FIT OneStep' insertion tool allows the forming a device tunnel and the positioning of the implant in a single step. Second, it is smaller. For reliable sensing of the heart rhythm, large ECG signal amplitudes are preferred. They correlate approximately linearly with distance between the ECG electrodes, which are on the ends of the device. To achieve a compromise between patient comfort (which calls for a smaller device) and reliable sensing (which calls for a larger device), these two opposing goals were realized in the BioMonitor 2 through the combination of a rigid body and a flexible 'antenna', which can follow the body's curvature and movements. The BIOMONITOR III maintains this approach, but the total length incl. antenna has been reduced from 88 (BioMonitor 2) to 77 mm.

4 CLINICAL INVESTIGATION PLAN (CIP)

4.1 Objectives

The objective of this study is to investigate the safety and efficacy of the new insertion procedure and the use and handling of the incision and insertion tools. Additionally, the sensing quality of the BIOMONITOR III will be investigated.

4.2 Design

This is an open, prospective, single-arm, multi-site, non-randomized, explorative study, which is conducted at Australian sites.

The study is conducted according to BIOTRONIK CCR Standard Operating Procedures which describe in detail measures and actions to minimize bias.

To avoid undue influence of single investigators of the evaluation of the insertion procedure, a high number of investigators (up to 15) shall take part in the insertions and contribute to a comprehensive assessment of the new insertion procedure. The maximum number of insertions per investigator is limited to 5.

No statistical endpoints are defined. For the assessment of the insertion, insertion success, adverse events and the investigators subjective assessment are evaluated. For the sensing quality, the R-wave amplitude is measured and the visibility of P-waves is assessed. Further data of interest comprise demographics, indication for device therapy, medical history and all diagnostics stored by the device.

4.3 Ethical Aspects

The clinical study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (current version). Ethics committee opinions were obtained prior to each site's participation in this clinical investigation. Patient enrolment was not allowed to begin until the ethics committee had given favourable opinion and BIOTRONIK had granted their approval for the investigation site.

The benefit of the use of ICMs has been proven in various studies. Patients benefit from the continuous patient monitoring during the in-office follow-ups (FUs), and from continuous observation via Home Monitoring (HM), which is above the average level of routine care. By participating in this study, patients contribute to medical progress which may benefit other patients in the future.

The insertion procedure of the BIOMONITOR III was carefully investigated in pre-clinical tests, during which no safety issues were revealed.

For this reason, no additional risks were anticipated with the participation in the study.

4.4 Monitoring and Quality Measures

The sponsor implements and maintains written clinical quality procedures. These procedures ensure that the clinical investigation is designed, conducted and monitored, and that data are generated, documented, recorded and reported in compliance with ISO14155:2011 and any other applicable standard and regulatory requirements.

Data recorded on the electronic case report forms (eCRFs) have been reviewed against source data by clinical monitors during periodic monitoring visits with regard to accuracy, completeness and verifiability from source documents (e. g. patient files, examination results). For recording of the clinical data, a validated clinical data management system has been used (iMedNet).

The electronic clinical databases are stored on a dedicated database server with daily backup. Only authorized users have access to the clinical databases. Every access is logged and changes of the clinical data are stored in independent audit trails.

After data entry, the clinical data are automatically checked with programmed quality checks. Errors, discrepancies, missing data, and entries out of range are resolved by either automatic (CDMS) or manual (clinical monitor, data manager) generation of data queries.

The system supported detailed tracking of the query process. Corrections to eCRF can only be done by the designated site personnel and requires approval of an investigator by signing electronically.

4.5 Target Patient Population

The patient population consists of patients in whom long-term cardiac rhythm monitoring may be required for diagnostic purposes. To be eligible for participation in the study, patients must fulfil at least one of the following four inclusion criteria:

- Patient is at high risk of developing a clinically important cardiac arrhythmia; or
- Patient is undergoing investigation for symptoms such as palpitations, pre-syncope or syncope, that are suggestive of an underlying cardiac arrhythmia; or
- Patient is undergoing investigation for the detection of atrial fibrillation following cryptogenic stroke; or
- Patient is planned for AF ablative procedure or has already undergone an AF ablative procedure.

Additionally, the patient must be able to understand the nature of study, provide written informed consent, be willing to perform all follow up visits use Home Monitoring. Further, the patients must not be implanted with ICD or pacemaker, be pregnant or breast feeding, be less than 18 years old, participate in another interventional clinical investigation or have a life-expectancy of less than 6 months.

The sample size of 45 patients has been defined based on the rationale that it would allow with 95% confidence to observe at least one event of a certain type of events if this type of events would occur with 15% probability in the respective population.

4.6 Treatment Schedule

Patients were implanted with a BIOMONITOR III using the FIT OneStep insertion tool. After insertion, all patients received a CardioMessenger® device for remote transmissions via HM and were registered on the Home Monitoring® Service Center. After one week, one on-site follow-up was conducted, during which the devices were interrogated through a BIOTRONIK Renamic programmer, device based measurements and device data read-outs were performed and collected. All detected or reported adverse events were recorded. After one month, a Home Monitoring observation follow-up with telephone interview was conducted.
The study participation was terminated automatically after this last follow-up.

4.7 Follow-up Duration

The patients' participation in the clinical investigation was one month during the regular study conduct.

4.8 Statistical Plan

This study has no hypotheses. The analysis and summary of the results is purely descriptive.

4.9 Planned Interim Analyses

There were no interim analyses.

5 RESULTS

5.1 Study Realization

Between March 8 and May 14, 2019, 48 patients were enrolled. The study participation of the last patient ended on August 6, 2019.

All patients fulfilled all inclusion criteria and none fulfilled any exclusion criterion.

Of the 48 enrolled patients, 47 had a study device inserted. Ten investigational sites included between 2 and 8 patients. At the 10 investigational sites, 16 investigators each inserted between 1 and 5 study devices. In accordance with the CIP, no investigator inserted more than 5 study devices (Table 25, page 25).

The mean and cumulative study duration was 35.2 ± 18.5 days and 1689 patient-days or 4.6 patient-years, respectively.

Thirty-seven patients had a regular study termination.

Eleven patients did not have a regular study termination:

- One patient was terminated before insertion. When the insertion was to start, there was confusion within the hospital staff as to whether a valid consent existed. So, the patient did not receive a study device. Since, however, the consent had in fact been valid, the baseline data are included in this report.
- In two patients from one investigational site, the devices protruded shortly after insertion (few hours and 6 days). These cases were followed up by a Biotronik product specialist and discussed with the investigator. The investigator concluded that the cases were caused by a combination of challenging patient anatomy (excessive subcutaneous fatty tissue) and possibly suboptimal handling / wound closure.
- Four patients have been diagnosed with a pause or bradycardia during the study. They received a permanent pacemaker implantation after explantation of the study device.
- One study device was damaged by a 200 joule electrical cardioversion with one shock electrode directly over the device. It was replaced with a new ICM but the patient was excluded from the study in accordance with the CIP.
- One patient was lost to follow-up after the 1-week FU. It was impossible to contact the patient for the 1-month follow-up.
- In two patients, the termination was later than suggested by the protocol (at 3 months instead of 1 month). Although all study procedures were completed in those patients, the termination was not reported as ‘regular’.

5.2 Summary of all –planned or unplanned- interim analyses

No formal interim analyses have been done.

5.3 Basic Data

Baseline conditions

Patients were on average 64 years old and slightly overweight (Table 1). 23 of the 48 patients (47.8%) were female.

Patient demographics	N	Mean	SD	Min	Lower quartile	Median	Upper quartile	Max
Age [years]	48	64.0	14.0	20.0	55.5	67.5	74.0	87.0
Height [cm]	45	170.9	10.5	150.0	164.0	171.0	179.0	189.0
Weight [kg]	44	78.7	15.3	48.5	68.0	79.7	89.1	106.0
Body mass index [kg/m2]	44	26.8	4.6	16.0	24.5	26.0	28.5	37.0

Table 1: Patient demographics

More than one half of the patients (58.3 %) have received the device after a syncopal event, and 12.5 % due to suspected AF after cryptogenic stroke (Table 2). 14 patients (29.2 %) were inserted with a device for AF management. In the patients designated 'other AF monitoring', the device was inserted to decide on the future AF therapy, but an ablation had neither been done nor had been already planned.

Primary type of ICM indication, N = 48	Absolute frequency	Relative frequency [%]
Syncope/Pre-syncope	28	58.3
AF Monitoring	14	29.2
AF ablation has been done	5	10.4
AF ablation is planned	5	10.4
Other	4	8.3
Cryptogenic stroke	6	12.5
Sum	48	100.0

Table 2: Details of the ICM indication

The medical history and the disease burden of the included patients are summarized in Table 3. One of the three patients with heart failure was in NYHA functional class I, for the other two this item is not reported.

Medical history, N = 48	N	Yes: N (%)
History of heart failure	48	3 (6.3%)
History of coronary artery disease	48	7 (14.6%)
Prior myocardial infarction	7	2 (28.6%)
Prior revascularization (PCI or CABG)	7	5 (71.4%)
History of sick sinus syndrome	48	1 (2.1%)
History of atrioventricular block (all AV-block 1°)	48	4 (8.3%)
History of bundle branch block (all right BBB)	48	2 (4.2%)
History of atrial fibrillation	48	15 (31.3%)
Paroxysmal	15	9 (60%)
Persistent	15	5 (33.3%)
Long-standing persistent	15	1 (6.7%)
History of other atrial/ supraventricular arrhythmias	48	8 (16.7%)
History of ventricular arrhythmia	48	1 (2.1%)
Hypertension (including well-controlled)	48	24 (50.0%)
Valvular heart disease	48	5 (10.4%)
History of cerebrovascular disease (e.g. TIA / Stroke)	48	10 (20.8%)
Peripheral vascular/arterial disease	48	1 (2.1%)
Asthma or other chronic lung disease (except COPD)	48	2 (4.2%)
Chronic obstructive pulmonary disease (COPD)	48	3 (6.3%)
Chronic renal insufficiency / chronic kidney disease (i.e. eGFR < 60)	48	1 (2.1%)
Sleep apnoea	48	4 (8.3%)
Chronic liver disease	48	1 (2.1%)
Diabetes mellitus	48	3 (6.3%)
Anaemia	48	1 (2.1%)
Cancer	48	3 (6.3%)
Hyperlipidaemia	48	23 (47.9%)
Other comorbidities	48	20 (41.7%)

Table 3: Medical history at enrolment

The medication that was reported at enrollment is presented in Table 4.

Drug category, N = 48	N (%)
Angiotensin receptor blocker	14 (29.2%)
Beta-blocker (excluding sotalol)	14 (29.2%)
Antiplatelets	15 (31.3%)
Anticoagulation	14 (29.2%)
Antiarrhythmics	8 (16.7%)
Calcium channel blocker	8 (16.7%)
Aldosterone blocker	3 (6.3%)
Diuretics (other than Aldosterone blocker)	3 (6.3%)
Statins	24 (50.5%)
Other cardiovascular medication	5 (10.4%)
Non-cardiovascular medication	31 (64.6%)

Table 4: Medication at baseline (analysis not according to SAP)[1]

5.4 CIP Compliance

Thirty-two minor protocol deviations were recorded. Classifications are presented in Table 5.

Category	Minor events	N
Protocol implementation	Participant seen outside visit window	6
Protocol implementation	Missed visit	3
Protocol implementation	Measurement/Examination not done	5
Protocol implementation	Measurement/Examination too early/delayed	6
Protocol implementation	Setting (e.g. Home Monitoring) wrong or not activated	3
Protocol implementation	Remote assistant not handed out	2
Other	Remote assistant not handed out	2
Other	Measurement/Examination not done	5

Table 5: Protocol deviations (analysis not according to SAP)

[1] The CRF for medication contained an incorrect label which resulted in underreporting of baseline medication with standard statistical analysis (as reported in the SAR).

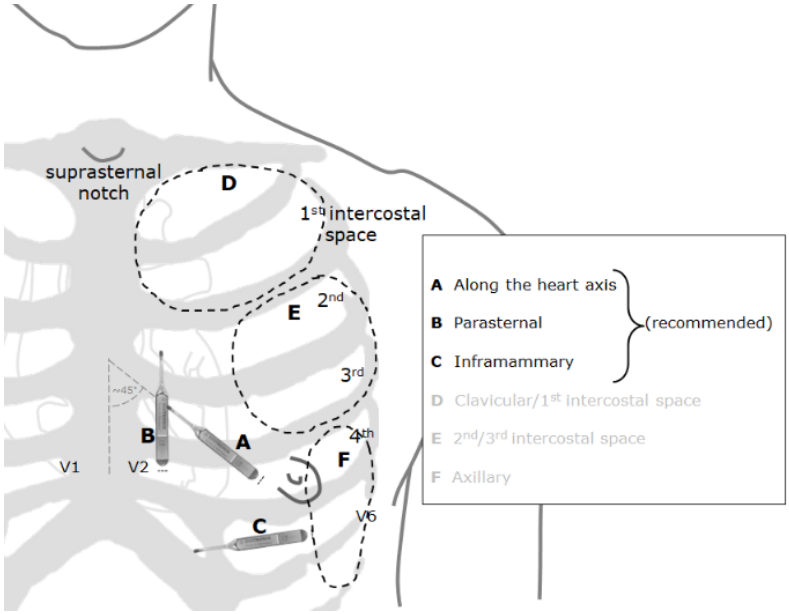
5.5 Data Analysis

The following analysis is purely descriptive. Missing data were not replaced.

5.5.1 Insertion results

Forty-seven attempted insertions were successfully completed (100%). One enrolled patient did not undergo insertion.

The positions of the device are reported in Table 6. The letters A trough F refer to the graph below. For positions D through F, investigators were asked in which direction the antenna points, expressed by the positions of a clock. Implants in positions D and F were inserted horizontally, in position E pointing roughly 45° down to the right (4 to 5 o'clock position).



Insertion site, N = 47	Absolute frequency	Relative frequency [%]
A – Along the heart axis	22	46.8
B – Parasternal	15	31.9
C – Inframammary	0	0.0
D – Clavicular/1st intercostal space (pointing to 3 o'clock)	1	2.1
E – 2nd/3rd intercostal space (pointing to 4 & 5 o'clock)	6	12.8
F – Axillary (pointing to 3 o'clock)	3	6.4
Sum	47	100.0

Table 6: Positions of the insertion

The duration of the procedure is summarized in Table 7. The pure device insertion took a median time of 39 seconds.

Time from start of insertion to ..	N	Mean	SD	Min	Lower quartile	Median	Upper quartile	Max
.. removal of insertion tool [sec]	47	52.4	42.4	7.0	19.0	39.0	65.0	200.0
.. to wound closure [min]	47	4.1	2.4	0.0	2.0	3.0	5.0	10.0
.. to wound closure cleaning completed [min]	47	5.5	3.1	1.0	3.0	5.0	8.0	13.0

Table 7: Insertion times

In 33 insertions (70.2%), the wound was closed in a single layer, i.e. only superficially; in 13 cases (37.0%), it was sutured below in a single layer and closed superficially with an additional adhesive strip, and in one case, it was sutured in two layers and additionally closed with adhesive strip (Table 8).

Please note that in a single patient, a description of the kind of wound closure is missing.

Type of pocket closure, N = 47	Absolute frequency	Relative frequency [%]
Steri Strip (3M) (single layer)	17 (5 sites)	36.9
Stitches (single layer)	10 (5 sites)	21.7
Dermabond (Ethicon) (single layer)	5 (1 site)	10.9
Stitches & Steri strip (double/triple layers)	14 (4 sites)	30.4
Sum	46	100

Table 8: Pocket closure

All wound closures were done by the investigator (i.e. none by an assisting nurse) (Table 9). In 19 %, general anaesthesia was used, and in 49 %, systemic antibiotics were used (local antibiotics were not used).

The device was not repositioned in any case.

In one case (2.1 %), the insertion site was surgically modified. Some more details about this case are reported in the following section 'Insertion: Assessment'.

Insertion details, N = 47	N	N (%)
Pocket closure performed by Investigator/Study Physician	47	47 (100.0%)
General anaesthesia applied before the insertion	47	9 (19.1%)
Local anaesthesia applied before the insertion	47	43 (91.5%)
Local antibiotics used in the perioperative period	47	0 (0.0%)
Systemic antibiotics used in the perioperative period	47	23 (48.9%)
BIOMONITOR III was repositioned	47	0 (0.0%)
Surgical modification of insertion site necessary	47	1 (2.1%)
BIOMONITOR III insertion was in conflict with patient's anatomy	47	0 (0.0%)

Table 9: Further insertion procedure details

5.5.2 Insertion: Assessment

The assessment of the insertion tools is given in Table 10. 'Sharpness of the incision blade', 'Grip on the incision tool' and 'Overall rating of the incision tool' were rated in 83 to 89% 'excellent' and in 8.5 to 15% as 'good'. In one single case, the sharpness and the overall rating were 'fair'.

Incision tool assessment, N = 47	Excellent N (%)	Good N (%)	Fair N (%)	Poor N (%)	Very poor N (%)
Sharpness of the incision blade	42 (89.4%)	4 (8.5%)	1 (2.1%)	0 (0.0%)	0 (0.0%)
Grip on the incision tool	41 (87.2%)	6 (12.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Overall rating of the incision tool	39 (83.0%)	7 (14.9%)	1 (2.1%)	0 (0.0%)	0 (0.0%)

Table 10: Incision tool assessment

In one single case, the investigator reported that the incision width and depth were not satisfactory (Table 11). In a comment the investigator stated 'used size 11 scalpel blade and create a pocket.' The patient was male, 54 years, 182 cm high and had a BMI of 29 (96 kg). The insertion site was 'A – along the heart axis'. In this case, the rating of the sharpness was 'excellent' and the grip 'good', only the 'Incision width and depth' were not satisfactory.

Incision length and depth, N = 47	Yes N (%)	No N (%)
Incision width and depth satisfactory	46 (97.9%)	1 (2.1%)

Table 11: Assessment of the incision width and depth

The assessment of the force needed for tunnelling was rated in 57% as 'excellent' and in 34% as 'good' (Table 12). The unlocking was assessed as excellent or good in 81% and 17% of the cases. Overall, the incision tool was rated in 85% as 'excellent' and in 15% as 'good', and the handling was described as 'very easy' or 'easy to use' in 91% and 9% of the cases.

The investigators answered the question whether the 'BIOMONITOR III [was] well-placed with respect to the intended target position' with yes in all cases.

Assessment of the insertion tool	N (%)	N (%)	N (%)	N (%)	N (%)
N = 47	Excellent (very low)	Good	Fair	Poor	Very poor (very high)
Rating of the force needed for tunnelling	27 (57.4%)	16 (34.0%)	4 (8.5%)	0 (0.0%)	0 (0.0%)
	Excellent	Good	Fair	Poor	Very poor
Rating of the unlocking	38 (80.9%)	8 (17.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)
Overall rating of the insertion tool FIT OneStep	40 (85.1%)	7 (14.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Very easy to use	Easy to use	Fair	Somewhat difficult to use	Very difficult to use
How easy or difficult was it to use FIT OneStep	43 (91.5%)	4 (8.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 12: Assessment of the Fit OneStep tool

5.5.3 R-wave amplitude

R-waves were reported after the insertion, as measured by the device and displayed on the programmer screen. The amplitudes of a sequence of beats are displayed and of all displayed amplitudes, the lowest and highest are presented in Table 13.

One single measurement ('lowest amplitude') of 0.0 mV was reported. From the same patient, who had the device inserted in the recommended 'A' position, the highest amplitude 1.0 mV is reported at insertion. In the 40 Home Monitoring messages, which this patient's device sent during the study, the mean R-wave amplitude was 1.28 ± 0.06 mV (median 1.27, IQR 1.23 – 1.32; minimum 1.19)[2].

Furthermore, the device can only measure the amplitude of a signal that exceeds its sensing threshold, i.e. it must be larger than 0.0 mV. Although it cannot be excluded that a single beat (e.g. an extrasystole with a different morphology) was not sensed by the device, and the investigator recorded 0.0 mV to report this, it appears more probable that this entry is an error.

R-wave amplitude, [mV] N = 47	Mean	SD	Min	Lower quartile	Median	Upper quartile	Max
Highest amplitude value	1.01	0.47	0.20	0.60	1.00	1.30	2.00
Lowest amplitude value	0.84	0.45	0.00	0.50	0.89	1.00	2.00

Table 13: Highest and lowest R-wave amplitudes after insertion

5.5.4 Device programming and communication

Programming

At the insertion and at the 1-week FU, the investigators were asked whether the 'Indication based program sets were useful whilst programming the device'. This was answered with 'yes' in all but one case (97.9 %) at the insertion. In the single case where the answer was 'no', a comment reads 'Independently programmed - no reason given'.

The interrogation of the device at the 1-week FU was successful in all 45 cases.

At the 1-week follow-up, the devices were reprogrammed in 11 cases. Mostly, the sensitivity to arrhythmias was reduced. On these occasions, the indication based programmes were rated as useful in 7 cases (63.6%), less often than after insertion. When the device needs to be reprogrammed to optimize the settings to the patient's conditions, a predefined set is less likely to be the correct choice.

None of these results can be reported at the 1-month FU, because the patients did not return to the hospital for this FU as planned in the CIP.

Indication based program sets were useful whilst programming the device	N	Yes: N (%)	No: N (%)
Insertion	47	46 (97.9%)	1 (2.1%)
1-week follow-up	11	7 (63.6%)	4 (36.4%)
Device interrogated successfully	N	Yes: N (%)	No: N (%)
1-week follow-up	45	45 (100.0%)	0 (0.0%)

Table 14: Results concerning device programming

[2] Based on HM data downloaded from 'Clinical Data Warehouse' on 23 Sept 2019.

Remote Assistant III

In 44 of 47 patients who received an insertion, the Remote Assistant III has been handed out to the patient to test its function. In all cases, the patient successfully triggered a recording of the ECG[3]. The 'Remote Assistant success rate' was thus 100%.

Home Monitoring success

Of 47 patients with an inserted study device, two dropped out of the study before discharge (one case of study device damage by external cardioversion and one device protruded after some hours). All 45 patients who were discharged within the study transmitted successfully to the Home Monitoring Service Center.

The percentage of study days with transmission was 98.0 ± 5.5 %, Median (IQR) were 100% (100 % - 100 %). In fact, only 9 of 45 patients (19.1%) did not transmit every day[4].

5.5.5 P-wave visibility

Investigators were asked to check the visibility of P-waves in periodic ECGs downloaded from the Home Monitoring Service Center at the 1-week FU and at the 1-month FU. For this, they were to count the number of heart cycles in the ECG, and the number of 'clearly identifiable' P-waves. At the 1-week FU, they were to check the first and the most recent periodic ECG, and at the 1-month FU the most recent periodic ECG.

At the 1-week-FU, 39 patients had each two periodic ECGs available (none had only one periodic ECG). Of them, the first ECG showed sinus rhythm with 1:1 conduction in 34 and the second ECG in 35 patients. The remaining 9 ECGs showed atrial fibrillation.

Of the 34 and 35 ECGs showing sinus rhythm, 11 did not show a regular 1:1 relationship between P- and R-waves. Reasons were PVCs (premature ventricular contractions), PACs (premature atrial contractions), artefacts, or the comment 'unable to determine appropriately'. As a result, each 29 ECGs from 30 patients could be assessed for the first and the most recent ECG.

At the 1-month FU, 41 patients had a periodic ECG. Four ECGs showed paced rhythm, supraventricular tachycardia or AF, leaving 37 ECG with sinus rhythm. Of them, 32 had a clear 1:1 conduction. Of the 5 without a clear 1:1 conduction, 4 had a comment 'Unable to determine appropriately' and one 'PVC and possible junctional beats'.

The share of heart cycles with clearly visible P-waves in the periodic ECG with sinus rhythm and clear 1:1 conduction is given in Table 15. In the 'pooled' row, the figures of up to 3 ECG of all patients with at least one ECG suited for analysis were taken together as the patient's figure and then summarized for the population.

Share of visible P-waves, N = 29	Mean	SD	Min	Lower quartile	Median	Upper quartile	Max
1 week FU: first ECG	0.88	0.26	0.00	0.93	1.00	1.00	1.00
1 week FU: second ECG	0.89	0.25	0.00	0.90	1.00	1.00	1.00
1-month FU	0.91	0.23	0.15	0.95	1.00	1.00	1.02
Pooled	0.89	0.24	0.00	0.85	1.00	1.00	1.02

Table 15: Share of visible P-waves

5.5.6 Patient comfort

At the 1-month FU, patients were asked questions concerning their comfort with the device. Results are given in Table 16. A clear majority of 70 % to 92.5 % of patients was rarely or never aware of the device, did not think that the device limited daily activities, and considered the wearing comfort good or excellent.

[3] Post-hoc analysis (not predefined in the SAP)

[4] Based on HM data downloaded from 'Clinical Data Warehouse' on 23 Sept 2019

However, a minority feels disturbed by the device. The patient who answered the first two questions in Table 16 with 'very poor' said 'device site sore everyday' and 'every time patient moves it hurts'. The remaining patients, who were often or very often aware of the device reported (verbatim from the eCFR):

- 'Describes it as a discomfort. Nervous when son hugs him tightly so now avoids hugs. Finds carrying the device inconvenient.'
- 'She says she is aware of the device when sitting and when laying down. Discomfort when putting on bra and tops. Also feels discomfort of the device when drying/rubbing with towel.'
- 'Feels device when stretching'
- 'Aware of device everyday'
- 'Dull burning sensation over the top of the device when touching it'
- 'When undressing, taking a shower. More aware of device due to location'

Patient comfort, N = 40	Excellent N (%)	Good N (%)	Fair N (%)	Poor N (%)	Very poor N (%)
Wearing comfort of the newly inserted BIOMONITOR III today	20 (50.0%)	14 (35.0%)	5 (12.5%)	0 (0.0%)	1 (2.5%)
	Not at all N (%)	Rarely N (%)	From time to time N (%)	Often N (%)	Very often all the time N (%)
BIOMONITOR III interfere with patient's daily activities in any way	31 (77.5%)	6 (15.0%)	2 (5.0%)	0 (0.0%)	1 (2.5%)
How often has patient been aware of wearing the BM III in the past few days?	18 (45.0%)	10 (25.0%)	5 (12.5%)	4 (10.0%)	3 (7.5%)

Table 16: Wearing comfort and the patient's awareness of the device

5.5.7 Patient App

Only a minority of 8 patients (20.0% of 40 patients available at the 1-month FU) has been using the patient app. Comments, why patients did not use it are presented in Table 17. Questions and answers of the patient interview are reported in Table 18 to Table 20 .

Patient has been using the Patient App (N = 40)	Absolute frequency	Relative frequency [%]
Yes	8	20.0%
No	32	80.0 %
Patient .. unaware of the App / forgotten	7	17.5 %
.. does not have an appropriate Smartphone.	6	15.0 %
No (yet) approved by ethics committee	5	12.5 %
Patient .. declines	5	12.5 %
.. has a technical issue with installation	6	15.0 %
.. has a language issue (English second language)	1	2.5 %
Unknown	2	5.0 %

Table 17: Usage of the Patient App

Patient App interview N = 8 N (%)	On a daily basis	Several times a week	Weekly	Once every two weeks	Monthly less often
How often did the patient use the APP?	0 (0.0%)	0 (0.0%)	4 (50.0%)	0 (0.0%)	4 (50.0%)
	Very easy	Rather easy	Neutral	Rather difficult	Very difficult
How easy / difficult was it to install the BIOTRONIK Patient APP?	6 (75.0%)	2 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Was it easy to understand the content presented in the APP?	8 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 18: Patient interview results (part 1)

Patient App interview N = 8 N (%)	No symptoms not used	Very easy	Rather easy	Neutral	Rather difficult	Very difficult
Was it easy to add symptoms in the symptoms diary?	5 (62.5%)	2 (25.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not used	Very useful	Rather useful	Neutral	Not useful	Not useful at all
How useful does the patient rate the symptoms diary?	4 (50.0%)	1 (12.5%)	2 (25.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)
	No symptoms not used	Very useful	Rather useful	Neutral	Not useful	Not useful at all
Was the symptoms diary useful when discussing your symptoms with your doctor?	5 (62.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)

Table 19: Patient interview results (part 2)

Patient App interview N = 8 N (%)	Completely satisfied	Rather satisfied	Neutral	Rather dissatisfied	Very dissatisfied
How satisfied was the patient overall using the patient APP?	4 (50.0%)	3 (37.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)

Table 20: Patient interview results (part 3)

The physician was also asked two questions concerning the clinical usefulness of the symptom diary in the clinical practise. Results are summarized in Table 21.

Physician interview about patient App. N = 8, N (%)	No entries available N (%)	Very helpful N (%)	Rather helpful N (%)	Neutral N (%)	Not helpful N (%)	Not helpful at all N (%)
Patient entries from the symptoms diary (Patient APP) were helpful when discussing symptoms	5 (62.5%)	2 (25.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)
	No entries available N (%)	Very positive N (%)	Rather positive N (%)	Neutral no influence N (%)	Rather negative N (%)	Very negative N (%)
Did patient entries in the symptoms diary (Patient APP) influence the hospital routine due to additional information?	5 (62.5%)	0 (0.0%)	1 (12.5%)	2 (25.0%)	0 (0.0%)	0 (0.0%)

Table 21: Physician interview about the patient APP.

5.5.8 Adverse Events

All in all, 11 adverse events and one device deficiency were reported (Table 22).
Description of the events can be found in section 11.3, page 28.

AE Category	Number of AEs
Non-serious events (total)	**6**
- Thereof non-serious events (unrelated)	2
- Thereof non-serious adverse device effects	4
Serious adverse events (total)	**5**
- Thereof serious adverse events (unrelated)	5
- Thereof serious adverse device effects (incl. procedure related)	0
- Thereof Death (total)	0
- Thereof device related deaths	0
Device Deficiencies (DD)	**1**
- Thereof DD that might have led to a SADE	0
- Thereof DD that could not have led to a SADE	1

Table 22: Numbers of adverse events

5.5.9 Subgroup Analyses

No subgroup analyses were performed.

6 DISCUSSION / CONCLUSION

The study has been conducted as planned in the CIP.

- All insertions have been completed successfully. They took a median of 39 seconds. Including wound closure and cleaning, 5 minutes were needed.
- The investigators rated the insertion tools and most aspects of the procedure as 'good' or 'excellent' in 98% of all cases. The lowest grades were assessed for 'Force needed for tunnelling' with as 'good' or 'excellent' in 91.5% and 'fair' in 8.5% of the cases.
- In two patients from one investigational site, the devices protruded shortly after insertion. These cases were caused by a combination of challenging patient anatomy and possibly suboptimal handling and wound closure. They were concluded without sequelae.
- The 'Remote Assistant III', a manual device to allow the patient to store an ECG in case of symptoms, worked as expected in all 44 cases in which it was tested.
- After insertion, the mean minimum and maximum R-wave amplitudes were 0.8 and 1.0 mV, with a range from 0.2 to 2.0 mV. This is the expected range, based on experience from the predecessor. In the BIO|MASTER BioMonitor 2 study, the range of measured R-waves after insertion was 0.03 to 2.0, with median and mean at 0.63 mV and 0.75 mV, respectively.[5]
- Eighty-nine percent of all heart cycles on ECGs, which showed a regular sinus rhythm, had visible P-waves. These ECGs were recorded by the study device and transmitted by Home Monitoring.
- The wearing comfort at four weeks after insertion was good or excellent in a majority of patients (85%). However, in one patient (2.5%), the device has caused significant pain and discomfort. Further, 7 patients (17.5%) were often or very often aware of the device's presence. This topic will be further investigated in studies with a longer follow-up duration, which are scheduled to start later in 2019.
- Few patients have used the Patient App, so its performance and perceived value is difficult to judge.
- Four adverse device effects were observed, none of which was classified serious.

Overall, the device has shown the expected performance.

[5] BIO MASTER.BioMonitor 2 study, Clinical Investigation Report, 28 Feb 2017

7 ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
AF	Atrial Fibrillation
CABG	Coronary Artery Bypass Grafting
CIP	Clinical Investigation Protocol
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form
DD	Device Deficiency
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
FIT	Fast Insertion Tool
FU	Follow-up
HM	Home Monitoring®
ICD	Implantable Cardioverter-Defibrillator
ICM	Implantable Cardiac Monitor
IQR	Interquartile Range
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PI	Principal investigator
PAC	Premature atrial contraction
PVC	Premature ventricular contraction
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SD	Standard deviation
sECG	Subcutaneous electrocardiogram
TIA	Transient Ischemic Attack

8 ETHICS

8.1 Ethics committees

Table 23 lists all involved ethics committees. All are located in Australia. The study has not been rejected by any ethics committee.

Ethics committee	Date of approval
Metro South Health Service District Human Research Ethics Committee, Woolloongabba, Queensland	14 Jan 2019
Bellberry Human Research Ethics Committees, Eastwood, South Australia	19 Feb 2019
UnitingCare Health Human Research Ethics Committee, Auchenflower, Queensland	19 Feb 2019
The Alfred Research Governance /SSA Authorisation, Melbourne, Victoria	04 Mar 2019
ACT Health Human Research Ethics Committee, Canbarra, ACT	14 Mar 2019
Research Governance Unit St. Vincent Hospital, Melbourne, Victoria	27 Mar 2019
Royal Adelaide Hospital Ethics Committee, Adelaide, South Australia	17 Apr 2019
Adventist HealthCare Limited Ethics Committee, Wahroonga, New South Wales	18 Apr2019

Table 23: Ethics committees and date of approval.

8.2 Competent authority

The study has been reported to the Australian Competent Authority:

Therapeutic Goods Administration
136 Narrabundah Lane
Symonston, ACT 2609
Australia

8.3 Registration

The study has been reported at ClincialTrials.gov under NCT03850327.

9 ADMINISTRATION

Coordinating investigator	A/Prof Justin Mariani	The Alfred Hospital Department of Cardiology 55 Commercial Road Melbourne VIC 3004 Australia
Sponsor	Falko Thiele	BIOTRONIK Australia Pty. Ltd. Level 4, Building 2, 20 Bridge St Pymble NSW 2073 Australia
Project manager	Gabriel Knop	BIOTRONIK SE & Co.KG Woermannkehre 1 12359 Berlin Germany
In-house clinical research associate	Beatrice Richter Emily-Jane Mellor Nadja Strahl	
Data manager	Gabriella Wolf	
Vigilance manager	Stefan Domin	
Statistician	Ulrich Gauger	
CIR author	Jürgen Schrader	

Table 24: Administration

10 CONTACT PERSON

Mathias Freudigmann
Director Clinical Project Management
BIOTRONIK SE & Co. KG
Center for Clinical Research
Woermannkehre 1
12359 Berlin, Germany

11 ANNEXES

11.1 Investigational Sites

Investigational site	PI - *Implanter*	Enrolled	Inserted
Mount Hospital Perth	**Weerasooriya, Rukshen**	8	5
	Rajamani, Kushwin		3
The Alfred Hospital, Melbourne	**van den Brink, Olivier**	7	1
	Mariani, Justin		5
	Lovibond, Sam		1
St. Vincent's Hospital, Melbourne	**Mohamed, Uwais**	7	2
	Matthews, Ian		4
Princess Alexandra Hospital, Woolloongabba	**Gould, Paul**	5	5
The Canbarra Hospital	**Pathak, Rajeev**	5	5
Bundaberg Cardiology, Bundaberg	**Conradi, Andre**	4	1
	DiFiore, David		3
Royal Adelaide Hospital	**Lau, Dennis**	4	4
HeartCare Victoria – Doncaster, Balwyn	**Lin, Tina**	4	4
Sydney Adventist Hospital, Wahroonga	**Illes, Peter**	2	2
HeartCare Partners. Wesley Testing, Auchenflower	**Pavia, Stephen**	2	1
	Arumugam, Deepak		1
Total		48	47

Table 25: Sites, Principal Investigators (PI) and other implanters

All sites were in Australia

11.2 Other Parties

No other third parties were involved.

11.3 Event Listings

11.3.1 Serious Adverse Events (excl. serious adverse device effects)

ID	Dates and Outcome	Relationship	Description
3	**Patient:** AUS042-003 **Procedure / First Use:** 22. Mar. 2019 **Onset:** 23. Mar. 2019 **Resolution:** 30. Mar. 2019 **Outcome:** Resolved	**Device** not related **Procedure** not related	The patient suffered from asystole for 6 seconds and sinus node dysfunction. The investigator assessed this event as possible related to the patient's medical history. **Action taken:** The patient was hospitalized. The BioMonitor [III] was explanted and a pacemaker implanted.
5	**Patient:** AUS052-003 **Procedure / First Use:** 05. Apr. 2019 **Onset:** 23. Apr. 2019 **Resolution:** 25. Apr. 2019 **Outcome:** Resolved	**Device** not related **Procedure** not related	The patient suffered from burning while urinating and was diagnosed with urinary tract infection. **Action taken:** The patient was treated with trimethoprim and Ural sachets.
9	**Patient:** AUS019-007 **Procedure / First Use:** 13. May 2019 **Onset:** 15. May 2019 **Resolution:** 04. Jun. 2019 **Outcome:** Resolved	**Device** not related **Procedure** not related	The patient suffered from bradycardiac (33 episodes of bradycardia with a heart rate of less than 40 bpm) and asystolic episodes (7 asystole events, pauses over 3 seconds) which were recognized by the implantable loop recorder. Sick sinus syndrome was diagnosed. The investigator assessed this event as probable related to patient's medical history. **Action taken:** The loop recorder was explanted and a pacemaker implanted.
10	**Patient:** AUS012-007 **Procedure / First Use:** 10. May 2019 **Onset:** 19. May 2019 **Resolution:** 05. Jun. 2019 **Outcome:** Resolved	**Device** not related **Procedure** not related	The patient suffered from two confirmed asystole episodes, the longest pause was 3.2 sec. and multiple bradycardia episodes. **Action taken:** The BIOMonitor III was reprogrammed, the AF detection was turned off as chronic AF and the sensing filter was improved from 10 Hz-4.5 Hz. The patient was hospitalized. The explantation of the BIOMonitor III and a pacemaker implantation were done.
11	**Patient:** AUS046-005 **Procedure / First Use:** 26. Mar. 2019 **Onset:** 04. Apr. 2019 **Resolution:** 06. Apr. 2019 **Outcome:** Resolved	**Device** not related **Procedure** not related	The patient suffered from sinus pauses (detected by implantable loop recorder) and presyncope. **Action taken:** The patient was hospitalized and a cardiac pacemaker was implanted.

Table 26: Serious Adverse Events. Comments in square brackets added by the CIR writer

11.3.2 Serious Adverse Device Effects

(Table continues next page)

ID	Dates and Outcome	Relationship	Description
1	**Patient:** AUS019-002 **Procedure / First Use:** 18. Mar. 2019 **Onset:** 18. Mar. 2019 **Resolution:** 18. Mar. 2019 **Outcome:** Resolved	**Device** not related **Procedure** causal relationship	Two hours after insertion of the loop recorder the device broke through the wound. There is no documented evidence or witnesses stating that the patient was touching or pushing on the device site prior to the device explanting. When the loop recorder was inserted only five steri-strips (50mmx12 mm) were used to close it. Steri strips were adhered to the skin as per standard practise and the wound was covered. There was no suture. The patient was very anxious during the procedure. **Action taken:** The loop recorder was explanted and steri-strips were applied to the wound. The wound was covered.
2	**Patient:** AUS042-002 **Procedure / First Use:** 20. Mar. 2019 **Onset:** 20. Mar. 2019 **Resolution:** 20. Mar. 2019 **Outcome:** Resolved	**Device** **Sponsor:** causal relationship **Investigator:** probable **Procedure** not related	Patient was scheduled for implantation of loop recorder and AF (already known) ablation. Immediately after insertion of the device, the patient underwent ablation. During ablation, due to the signal problems related to AF, the patient was cardioverted with 200 Joule to improve signal quality and catheter stability as well as facilitate pacing manoeuvres to confirm success of the procedure. The cardioversion patch partially covered the electrode of the loop recorder. After cardioversion no "sensing ECG" and no sensing signal were reported. Communication with the device was possible. A device re-set changed nothing. The investigator assessed this event as probable related to the patch used for cardioversion. **Action taken:** Sensing ECG was done. The loop recorder was replaced with a new one.

ID	Dates and Outcome	Relationship	Description
4	**Patient:** AUS019-003 **Procedure / First Use:** 03. Apr. 2019 **Onset:** 09. Apr. 2019 **Resolution:** 09. Apr. 2019 **Outcome:** Resolved	**Device** **Sponsor:** possible **Investigator:** not related **Procedure** causal relationship	During showering the patient lent over to pick something up and the device fell out of the pocket. According to the investigator the patient felt uncomfortable for a few days. The device began extruding on day 3, and felt out day 5. The insertion wound was still covered with the dressing. The patient did not perform any specific physical activity or exercises since the insertion of the device. The patient acknowledged, however, that while lying on her side trying to sleep, that the breast size may have been problematic. It was stated that the tip might have a spring like effect. Possibly, tip wedges in and then slowly pushes out as there is local tissue swelling, bleeding. **Action taken:** The investigator advised patient to cover the incision area with a band aide. Keep device in plastic bag. Return to site tomorrow for 1 week review and to bring the device.
12	**Patient:** AUS012-006 **Procedure / First Use:** 08. May 2019 **Onset:** 01. Jun. 2019 **Resolution:** NA **Outcome:** Ongoing	**Device** **Sponsor:** possible **Investigator:** not related **Procedure** **Sponsor:** not related **Investigator:** probable	In the last few weeks the patient noticed a dull burning sensation over the top of the device when putting the hand over it. The patient was not bothered by it. **Action taken:** No action has been taken.

Table 27: Serious Adverse Device Effects

11.3.3 Device deficiencies that could not have led to a SADE

ID	Dates and Outcome	Relationship	Description
13	**Patient:** AUS019-007 **Procedure / First Use:** 13. May 2019 **Onset:** 04. Jun. 2019 **Resolution:** NA **Outcome:** NA	**Device** causal relationship **Procedure** not related	According to the investigator it was difficult to remove the loop recorder. The device was deep to the skin in an overweight patient and every time it was tried with the forceps to take it out it slipped further into the tissue. This may reflect the body habitus of the patient combined with the implantation technique. **Action taken:** No further action has been taken.

Table 28: Device Deficiencies

11.4 Premature Study Terminations / Drop-outs

Patient ID	Reason for early study termination		Study duration
AUS006-001	Drop-out according to protocol	Pacemaker indication found	10
AUS009-001	Other	Late study termination - patient's transmission came >1 month after procedure.	95
AUS009-004	Other	Late study termination as 1 month follow up was completed outside of study window.	91
AUS012-001	Patient is lost to follow-up		30
AUS012-003	Other	Pt not enrolled in study as error in initial consent.	0
AUS012-007	Drop-out according to protocol	Pacemaker indication found	26
AUS019-002	Drop-out according to protocol	Device protruded from device pocket	0
AUS019-003	Drop-out according to protocol	Device protruded from device pocket	7
AUS019-007	Drop-out according to protocol	Pacemaker indication found	22
AUS042-002	Drop-out according to protocol	Device damaged by cardioversion	0
AUS042-003	Drop-out according to protocol	Pacemaker indication found	7

Table 29: Reasons for premature terminations.

11.5 CIP deviations

No major CIP deviations occurred.

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