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Study name / EAC code:	BIO|Guard-MI / HS058
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In this document, the following content is blackend:
1) Pseudo-code

Table of Content

0. Change history

Version 1.0

- Initial document

Version 2.0

- General document improvement.
- Aim: Inferential analyses of the endpoints are mandatory to be reported in the final CIR.
- Adaptation to the Clinical Investigation Plan Version (CIP) 6.0.
- Date of discharge from index hospitalization is used as effective randomization date in both groups as defined in the CIP.
- Time to death from any cause or heart transplantation added as secondary endpoint as defined in the CIP
- Chapters for the CONSORT diagram and EQ-5D-5L Questionnaire added.
- History of AF deleted as subgroup because such patients are eligible for the study only in exceptional cases and their number is insufficient for a subgroup analysis.
- Confirmatory analysis of the primary endpoint is tested by a log-rank test stratified by NSTEMI vs. STEMI, which is also used for block randomization.
- Precise definition of the EAEC data, which have been implemented in the CDMS after finalizing SAP version 1-0.
- Precise definition of exclusion of data and censoring date for interim analyses
- Precise definition of primary endpoints based on the data from the EAEC evaluation process considering the open study design.[1] This lack of blinding can introduce a bias for several reasons[2], which will be prevented by the following procedure: In its initial adjudication, the EAEC classifies the true cause of the event with all available information including BioMonitor data. Next, for any possible endpoint, the most probably adjudication result without BioMonitor information is documented. The analyses of the primary endpoint will be based on this latter adjudication, which is in better accordance with the objective of the study. These changed procedures have been initiated by Steering Committee and Sponsor and approved by the EAEC members and implemented in the EAEC charter.

[1] The study is conducted in a non-blinded fashion. This is unavoidable due to the fact that the study groups are treated differently with respect to a diagnostic procedure.

[2] In general, more information for the adjudication of endpoints are available in the BioMonitor group. Since the BioMonitor stores information on arrhythmias, it can change the adjudication towards an arrhythmic cause of an event (which would count as primary endpoint), but rarely against it. This asymmetry in available information at the adjudication can change primary endpoints of one type towards another (first example). Then, it would remain without effect on the primary objective of the study, but it would change the distribution of the different kinds of endpoints, with a possible effect on the understanding of the study effect. But as the other two examples show, it can also affect the primary outcome, i.e. it can produce a reduced study effect size:

- Example 1: A patient is hospitalized with decompensated heart failure. Only from the BioMonitor it is recognized that atrial fibrillation preceded the heart failure event. In the control group, this would be assumed a heart failure event, but in the BioMonitor group, this would be correctly recognized as an arrhythmia hospitalization.
- Example 2 : A patient is hospitalized with general malaise. This is attributed to bradycardia episodes and pauses from the BioMonitor memory (both by the treating investigator and the EAEC). In the control group, this would be probably assumed an "other cardiovascular" event, but in the BioMonitor group, it would be adjudicated as an arrhythmia hospitalization.
- Example 3: A patient dies in a car accident after he lost control of the vehicle. A post mortem interrogation of the BM shows that the accident occurred after the patient had an episode of ventricular fibrillation. Thus, it is a cardiovascular, not a non-cardiovascular death, as it would be assumed in the control group.

Version 3.0

- General document improvement, e.g. correction of variable labels and oversights in the previous version
- Information about quality control and unblinding included.
- References to the latest CIP version 7.0, especially the change of the statistical design: According to the original statistical planning, the study was designed as a three-stage adaptive group sequential test procedure according to O'Brian Fleming with survival endpoint, where the inverse normal method is used to combine the separate stage information. This strategy is replaced with a single final analysis of all data after study termination.Information from the latest version of the CDMS considered for the specification of variables derived from raw data.
- Labelling of SAP chapters not relevant for the final analysis.
- Further specification of "major protocol deviations" for the per-protocol analysis.
- More detailed information about the primary endpoint analyses.
- Specification of the variables to be analyzed with respect to the other secondary endpoint "Type of initiated therapies".

1. Introduction

1.1. Aim

The aim of this document is to provide detailed instructions for the confirmatory interim analyses of the primary endpoint and on all descriptive and inferential statistical analyses for the final Clinical Investigation Report (CIR). Inferential analyses of the primary and secondary endpoint(s) as defined in this document are mandatory to be reported in the final CIR.

1.2. General information

The text contains verbatim excerpts from the CIP Version 1.0. Such excerpts are italicized with grey background.

The main aspects and the design of the clinical investigation are presented in chapters 2, 3, and 4.

General statistical procedures are summarized in chapter 5. Those methods are used in case there is no other instruction within this document.

Definitions of the specific dates, e.g. effective randomization and termination are presented in chapter 0.

The analysis sets are defined in chapter 7.

Data for the CONSORT diagram and baseline data are handled in chapters 8 and 9.

The primary endpoint is handled in chapters 10 and 11, and the secondary endpoints are handled in the following chapters. Thereby the following statistical considerations are specified:

- Definition of the analysis set for the following analyzes, e.g. excluding patients without any measured or imputed data for this endpoint.
- Definition of the endpoint(s) to be analyzed including references to the source data, e.g. CRF sheet and item.
- Treatment of missing and spurious data for evaluation of the above endpoint(s).
- Exclusion of particular information from the evaluation of the above endpoint(s) in addition to the exclusion of patients from the analysis set.
- Statistical alternative hypothesis/hypotheses (HA) to analyze the above endpoint(s).
- Statistical tests intended to analyze the above hypothesis/hypotheses.

In case some variables, which are needed to analyze the pre-specified endpoints, are currently not included in the CDMS, they are indicated with yellow background and the Statistical Analysis Plan (SAP) has to be updated before the first interim analysis or the final analysis.

All variables are defined in tables using the following columns:

Data file	Name of a data file exported from the CDMS with one data row per unique identifier (e.g. patient-specific "patient_display_ID_full" or event-specific "record_ID"). A new data file (e.g. "data_SAR") might be generated by merging all relevant data from the original CDMS data files and generating derived variables (e.g. BMI from weight and height or date of first AE episode).
Notes	Information whether data has to be presented with descriptive methods as defined in the following sub-chapter, data for listings, or data needed for generating of derived variables only.
Variable name	Original name of a variable in the CDMS data file or name of a derived variable (indicated with a suffix "_SAR").
Variable label	Original labels from the CDMS data will be used for generating the SAR unless a new label is defined in this document ("NEW"). Labels might be omitted or shortened ("…") if remaining clear.
Variable level	Nominal, ordinal, scale (metric, continuous), or date.
Nominal values	Original values from CDMS data will be used for generating the SAR unless new nominal values are defined in this document ("NEW"). Nominal values might be omitted or shortened ("…") if remaining clear. Nominal values for numeric data this information is not applicable (n.a.).

1.3. Data for which quality control is required

A quality control is needed for analyses of all endpoints(s) as defined in the clinical investigation plan (CIP).

1.4. Unblinding

In the context of the first interim analysis in March 2020, the DSMB discovered inconsistencies in adverse event reporting and consequently recommended unblinding of limited sponsor personnel to perform further investigations on the matter.

For this reason, all persons responsible for SAP 3.0 were unblinded.

2. Objectives

CIP chapter7.1.1 Primary objectives

The primary objective of the BIO|GUARD-MI study is to investigate whether the early diagnosis of cardiac arrhythmias, provided by the BioMonitor in connection with remote monitoring, and the consequent treatment of the patient will decrease the risk to experience a MACE in patients with a history of MI, CHA2DS2-VASc-Score ≥ 4 in men / ≥ 5 in women and LVEF > 35 %.

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CIP chapter7.1.2 Secondary objective: Arrhythmia detection

It will be investigated if the implantation of the ICM leads to a faster detection of an arrhythmia that requires a guideline-recommended therapy than a strategy of conventional follow-up.

CIP chapter7.1.3 Other secondary objectives

In parallel to the primary objective and the definition of MACE, all individual MACE components will be evaluated separately and compared between the study groups.

7.1.3.1 All-cause mortality …

7.1.3.2 Cardiovascular death …

7.1.3.3 Worsening of the patient status due to heart failure …

7.1.3.4 Hospitalization resulting from arrhythmia …

7.1.3.5 Hospitalization resulting from acute coronary syndrome …

7.1.3.6 Hospitalization or death resulting from stroke …

7.1.3.7 Major bleeding requiring hospitalization …

7.1.3.8 Systemic embolism requiring hospitalization …

7.1.3.9 Arrhythmias …

7.1.3.10 Type of initiated therapies …

7.1.3.11 Therapies …

7.1.3.12 Quality of Life (QoL) …

3. Investigational Device

CIP chapter 4.1 Summary description of the investigational device and its intended purpose

Investigational device: BioMonitor or CE-approved successor.

The BioMonitor is an ICM used to automatically detect and record episodes of arrhythmia in patients at risk for bradycardia, tachycardia, asystole and AF. The ICM is not intended to deliver any therapy.

The device reports the recorded episodes and the related statistical data via a physician's programmer and telemetrically via BIOTRONIK Home Monitoring.

4. Design

CIP chapter 8.1 General Considerations

The BIO|GUARD-MI study is a multicenter, prospective, randomized (1:1), controlled, parallel-group, open, international study (including USA) with an event-driven design. The study is operatively divided into 2 phases. In the first phase 640 patients will be enrolled within approximately 2 years after FPI. After 600 patient years of cumulative follow-up have been collected, a blinded analysis will be performed to assess the primary endpoint rate. Based on the assessed rate (see section 11.7), the study will enter the second phase or be discontinued prematurely. This is necessary because it is impossible to obtain solid estimates of the endpoint rates for the included population from the literature. In case of a too low endpoint rate, the study could be expected to fail in its primary objective, even if the BioMonitor group had a much reduced endpoint rate.

In the second phase enrollment will continue in the same way, but in more investigational sites than the first phase, and without interception until up to 2900 patients entered the study. The duration of the second study phase is estimated to last 4 years but ultimately is dependent on when the number of needed endpoints for the final analysis is reached. In the second phase US patients will contribute to the study.

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CIP chapter 11.1.1 Group sequential design

According to the original statistical planning, the study was designed as a three-stage adaptive group sequential test procedure according to O'Brian Fleming with survival endpoint, where the inverse normal method is used to combine the separate stage information. This strategy is replaced with a single final analysis of all data after study termination.

The first interim analysis has been performed. The planned second interim analysis will not be done. Due to the O'Brien Fleming design with a very low alpha_1 = 0.00025 for the first interim analysis, an adjusted significance level for the final analysis alpha_final = 0.02476 will maintain the global 1-sided significance level alpha = 0.025.

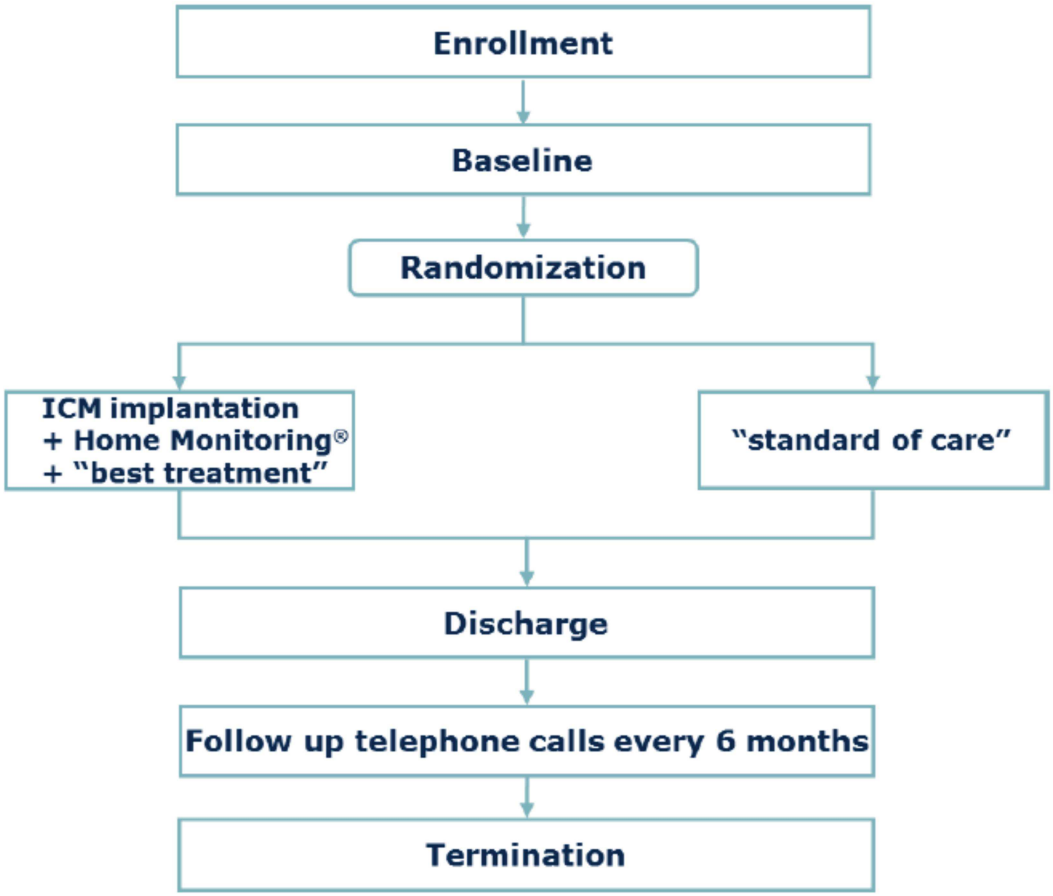
CIP chapter 8.4.1. CRFs and Forms

Table 2: Overview CRFs and Investigations

Investigation	Enrollment	Baseline	Implantation	Discharge	Telephone contacts (every 6 months)	Arrhythmia notification form	General notification form	IHF notification form	Termination
Patient informed consent	x								
Verification of in- and exclusion criteria	x								
Patient demographics		x							
NYHA class		x							
Echo parameters		x							
Specification of MI	x								
Medical history/Co-morbidities		x							
Cardiovascular medication				x					
Lab parameters				x					
Randomization result		x							
BioMonitor implantation			x						
BioMonitor interrogation			x						
BioMonitor programming			x						
Adverse events		x	x	x	x	x	x	x	x
Arrhythmia classification						x			
Evaluation of necessity to contact patient						x	x	x	
Patient interview						x	x	x	
Evaluation of necessity of diagnostic procedure						x	x	x	
Telephone follow-up questionnaire					x				
Quality of life questionnaires					x				
Documentation of: - reason for visit - performed examinations, therapies, modifications						x	x	x	
Documentation of: - regular or premature termination - reason for premature termination									x

CIP chapter 9.1 Overview

Table 3: Study Flowchart



5. General Statistical Procedures

5.1. Descriptive analyses

CIP chapter 11.1.4 Statistical methods

Descriptive analyses: The data are presented using descriptive statistical methods. For metric data sets, the mean values, standard deviation, median, maximum and minimum are stated, if appropriate. Ordinal data are described by the median and interquartile range. For nominal data, absolute numbers and relative frequencies are determined.

For illustration, see the following standard tables with and without subgroup analyses based on dummy data.

Nominal – dichotomous data (example with dummy data)

Variable (N total = 10)	Category	N non-missing	Absolute frequency	Relative frequency [%]
Gender	Female	9	3	33.3
History of atrial fibrillation	Yes	8	4	50.0

Variable (N total = 10)	Category	Group Randomization	N non-missing	Absolute frequency	Relative frequency [%]
Gender	Female	Implant(N group = 4)	4	1	25.0
		Control (N group = 4)	4	2	50.0
		All	9	3	33.3
History of atrial fibrillation	Yes	Implant	4	2	50.0
		Control	4	2	50.0
		All	8	4	50.0

Nominal data – more than two categories (example with dummy data)

Variable (N total = 10)	N non-missing	I N(%)	II N(%)	II N(%)	IV N(%)
NYHA class	8	1 (12.5%)	3 (37.5%)	3 (37.5%)	1 (12.5%)

Variable (N total = 10)	Group Randomization	N non-missing	I N(%)	II N(%)	II N(%)	IV N(%)
NYHA Class	Implant (N group = 4)	3	0 (0.0%)	1 (33.3%)	2 (66.7%)	0 (0.0%)
	Control (N group = 4)	4	1 (25.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)
	All	8	1 (12.5%)	3 (37.5%)	3 (37.5%)	1 (12.5%)

Scale / metric data (example with dummy data)

Variable (N total = 10)	N non-missing	Mean	SD	Min	Lower quartile	Median	Upper quartile	Max
Age [years]	9	56.1	15.9	25.0	50.0	60.0	66.0	77.0
Weight [kg]	8	78.5	13.9	55.0	69.5	78.5	89.0	99.0

Variable (N total = 10)	Group Randomization	N non-missing	Mean	SD	Min	Lower quartile	Median	Upper quartile	Max
Age [years]	Implant (N group = 4)	4	61.8	11.2	50.0	55.0	60.0	68.5	77.0
	Control (N group = 6)	4	50.3	21.5	25.0	32.5	53.0	68.0	70.0
	All	9	56.1	15.9	25.0	50.0	60.0	66.0	77.0
Weight [kg]	Implant	3	85.0	7.0	77.0	77.0	88.0	90.0	90.0
	Control	4	76.0	18.5	55.0	62.5	75.0	89.5	99.0
	All	8	78.5	13.9	55.0	69.5	78.5	89.0	99.0

Ordinal data

Identical tables as for metric data but without mean and SD

5.2. Inferential analyses

CIP chapter 11.1.4 Statistical methods

Inferential analysis of the primary hypothesis: The inverse normal combination test is used to combine the independent increment to a global test statistic. A one-sided logrank test is performed in the context of a confirmatory analysis of the primary hypothesis at every interim and the final analysis.

Explorative multivariable analyses are performed (after the termination of the study, i.e. not after interim analysis) based on the Cox regression model.

Inferential analysis: For the inferential analysis of metric, normal–distributed data, a t-test for interindividual of independent groups or a paired t-test for the intraindividual comparison of paired data is performed. In case the normality assumption of the data is either a priori not justified as specified in the SAP or overtly violated (i.e. by a significant Kolmogorov-Smirnov-Lilliefors or Shapiro-Wilk test result) a non-parametric Wilcoxon-Mann-Whitney rank-sum test or a Wilcoxon-signed-rank test is performed, respectively. For the analysis of relative frequencies, Fisher's exact test is used.

For better comparability of results, a non-parametric Wilcoxon-Mann-Whitney rank-sum test or a Wilcoxon-signed-rank test is performed for all inferential analyses of metric data.

CIP chapter 11.1.1 Statistical design

According to the original statistical planning, the study was designed as a three-stage adaptive group sequential test procedure according to O'Brian Fleming with survival endpoint, where the inverse normal method is used to combine the separate stage information. This strategy is replaced with a single final analysis of all data after study termination.

The first interim analysis has been performed. The planned second interim analysis will not be done. Due to the O'Brien Fleming design with a very low alpha_1 = 0.00025 for the first interim analysis, an adjusted significance level for the final analysis alpha_final = 0.02476 will maintain the global 1-sided significance level alpha = 0.025.

As already specified in SAP 2-0, a stratification for the final analysis of the primary hypothesis is performed for the variable amikind_multi = STEMI/NSTEMI, which is also used for block randomization.

5.3. Significance level

CIP chapter 11.3 Level of significance and the power of the study

The global significance level is of the 1-sided hypothesis is 2.5%.

A statistical power of the final analysis of 80% was used for sample size calculation.

5.4. Missing Data

CIP chapter 11.11 Handling of missing, unused and spurious data

Missing data: With respect to the primary hypothesis, drop-outs are considered as censored data and must not be imputed.

Unused data: Data not needed for pre-specified inferential analyzes are minimized and limited to baseline information which can be obtained without any additional burden for the patient. Such data could be used for descriptive and exploratory analyses.

Spurious data are clarified via the query management, i.e. corrected after approval of an investigator. Outliers are identified during the blind review of the data. In case of a clear evidence of a measurement error, the SAP will be updated before breaking the blind in order to avoid any bias.

5.5. Exclusion of data from confirmatory data analysis

CIP chapter 11.1.2 Full Analysis set based on the ITT principle

... the following patients will be excluded from the analysis set

- *Patients of the BioMonitor group and control group in case of a drop-out before discharge from the index hospitalization*
- *Patients without signed informed consent form*

Details are presented in chapter 7.

1st Interim analyses of the primary endpoint (NOTE: Not relevant for the final analysis)

During the course of the study, data may be entered in the CDMS without instantaneous confirmation of the investigator, monitor, or data manager. In any CDMS data export there are record status information for each electronic CRF.

record_status	record_status_text
1	Completed form
2	New form
3	Open issue(s)
1147	Signed by investigator
1148	Monitor check in progress, form locked
1149	Approved by monitor
1150	Ready for analysis and locked
1151	Open query
1152	Answered query
1195	Adjudication entered

For the final analysis, all CRFs shall have the status "ready for analysis and locked" or "Adjudication entered" but for the interim analysis some other record_status values are sufficient as described in the table below. All other CRFs will be excluded from confirmatory data analysis for the interim analysis.

Close before the 1st the interim analysis all investigational sites will be intensively monitored to check AE reporting, either to identify AEs which might be classified as primary endpoints or to confirm event-free survival. For obvious reasons, this cannot be done on the same day in all investigational sites. To avoid any bias due to non-monitored data, clinical data occurred after the start date 14JAN2020 of this monitoring phase will be excluded from confirmatory data analysis for the interim analysis.

CRFs	Sufficient record_status	Sufficient dates	Reason
enrollment	1149, 1150, 1152	Any date ≤ start of the monitoring window for the interim analysis	Monitor check of patient informed consent needed
study_termination	1149, 1150, 1152	Any date ≤ start of the monitoring window for the interim analysis	Monitor check of correct termination date needed
discharge adverse_events general_notification arrhythmia_notification who_five_well_being_index eq_5d_5l_questionnaire	1147, 1148, 1149, 1150, 1152	Any date ≤ start of the monitoring window for the interim analysis	Monitor check of clinical data is not needed but event-free survival can be confirmed until the start of the monitoring phase only.
baseline	all	Any date ≤ start of the monitoring window for the interim analysis	Randomization result is filled in automatically
eaec_adjudication[3]	all	all	Quality check via 2-of-3 decisions

[3] As the investigators have a 14 days period allowed to report Adverse Events, and in reported Adverse Events the querying process and the securing of required documentation for the EAEC takes time, it is not guaranteed that Monitors will not have to return the sites after this „final" day. However, Adverse Events that had an onset after this day will not be used in the analysis.

5.6. Subgroups

CIP chapter 11.9 Specification of subgroups

Subgroups are predefined for exploratory analyses with respect to

- *the occurrence of the predefined arrhythmias, and to*
- *the primary endpoint and other predefined outcomes.*

All subgroup analyses which are not pre-specified in the chapters 8 or following will be performed as ad-hoc analyses if needed.

CIP chapter 11.9 Specification of subgroups

The following subgroups are predefined according to their presentation at enrollment:

- *All individual components of the CHADS2-score except the age-variable*
- *Age < median vs. ≥ median*
- *"Early enrollment" within 40 days of most recent MI vs. "late enrollment" after more than 40 days*
- *Men vs. women*
- *CHA2DS2-VASc-score ≤ 4 in men / ≤ 5 in women vs. ≥ 5 in men / ≥ 6 in women*
- *LVEF < median vs. ≥ median*
- *BMI: < 30 vs. BMI ≥ 30*
- *History of AF yes vs. no*
- *NSTEMI vs. STEMI*
- *History or presence of kidney failure yes vs. no*

The subgroup "history of AF" defined in the CIP will not be considered for subgroup analyses. This variable is missing in the Baseline CRF because patients with history of atrial fibrillation and a CHADS-VASc score as required by the CIP are indicated to receive oral anticoagulation, which is an exclusion criterion. Thus, patients with history of AF are eligible for the study only in exceptional cases and their number is insufficient for subgroup analyses.

Subgroups CHADS2

Subgroups with respect to all individual components of the CHADS2 score except the age variable, which is grouped according to the median.

Data file: Identifier patient_display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	descr.	subgroups_chads2_c_SAR[4]	Subgroups Congestive Heart Failure	nominal	0 / 1
data_SAR	descr.	subgroups_chads2_h_SAR[5]	Subgroups hypertension	nominal	0 / 1
data_SAR	descr.	subgroups_chads2_d_SAR[6]	Subgroups diabetes mellitus	nominal	0 / 1
data_SAR	descr.	subgroups_chads2_s_SAR[7]	Subgroups stroke or TIA or systematic thromboembolic event	nominal	0 / 1

[redacted]

Subgroups other

Median cut-offs are based on the ITT analysis set.

Data file: Identifier patient_display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	descr.	subgroups_age_ge_median_SAR[8]	Subgroups age < median (0) vs ≥ median (1)	nominal	0 / 1
data_SAR	descr.	subgroups_mi_enr_ge_41d_SAR[9]	Subgroups enrollment after most recent MI < 41days (0) vs ≥ 41 days (1)	nominal	0 / 1
data_SAR	descr.	subgroups_gender_SAR[10]	Subgroups gender men (0) vs women (1)	nominal	0 / 1
data_SAR	descr.	subgroups_cha2ds2vasc_SAR[11]	subgroups CHA2DS2-VASC low (0) vs high (1)	nominal	0 / 1
data_SAR	descr.	subgroups_lvef_ge_median_SAR[12]	Subgroups LVEF < median (0) vs ≥ median (1)	nominal	0 / 1
baseline	descr.	subgroups_bmi_ge_30_SAR[13]	Subgroups BMI < median (0) vs ≥ median (1)	nominal	0 / 1
data_SAR	descr.	subgroups_stemi_SAR[14]	Subgroups kind of MI NSTEMI (0) vs STEMI (1)	nominal	0 / 1
data_SAR	descr.	subgroups_kidney_failure_SAR[15]	Subgroups kidney failure no (0) vs yes (1)	nominal	0 / 1

5.7. Phase1: Event rate check (NOTE: Not relevant for the final analysis)

CIP chapter 8.1 General considerations

… The study is operatively divided into 2 phases. In the first phase 640 patients will be enrolled within approximately 2 years after FPI. After 600 patient years of cumulative follow-up have been collected, a blinded analysis will be performed to assess the primary endpoint rate. Based on the assessed rate (see section 11.7), the study will enter the second phase or be discontinued prematurely.

…

CIP chapter 11.7 Termination Criteria

There is a blinded evaluation of the MACE rates after the event-check, which is no interim analysis because no therapy effect is investigated. If the total number of patients with at least one MACE in both groups is less than 20 patients per 600 patient-years at the end of the event-check phase, the study will be terminated.

…

Via the Study News report, Issue 15 from June 2018, the investigators were informed that the gateway to study phase 2 has been reached. The EAEC Board evaluated 20 events as primary endpoint-related. Thus, phase 2 for the study was announced.

5.8. Phase2: Interim analyses (NOTE: Not relevant for the final analysis)

CIP chapter 8.1 General considerations

In the second phase enrollment will continue in the same way, but in more investigational sites than the first phase, and without interception until up to 2900 patients entered the study.

…

The first and second interim analysis will be performed after 124 and 248 primary endpoints, respectively[16]. Within the interim analyses the primary hypothesis will be tested based on the ITT analysis set. Additionally, the stratified randomization procedure will be checked whether there are severe deviations between the BioMonitor and the control group which indicate a failure of the randomization procedure.

No Clinical Investigation Report will be generated. Any person involved in this analysis is obliged to keep all information confidential. The Statistical Analysis Report will be delivered to the DSMB only. The DSMB will inform the steering committee and the sponsor whether to continue the study without any amendments, continue the study with an amendment (e.g. change of the sample size based on the adaptive design), or stop the study for proven superiority according to the O'Brien-Fleming design. The DSMB is also responsible to give recommendations for stopping the study for safety reasons or for futility, if applicable[17].

No other analyses will be conducted for the Statistical Analysis Report which is submitted to the DSMB. Only in case the DSMB recommends the discontinuation of the study, and the Sponsor decides to follow this recommendation, the further procedures will be identical to those specified for the final analysis.

5.9. Phase2: Final analysis

CIP chapter 11.2 Sample Size

The original planning assumed that 372 primary events would be required to accept the primary alternative hypothesis with 80% statistical power given an assumed hazard ratio in the population of 0.7452, and the study was to be terminated after this number of endpoints had been collected.

Instead, it was decided to enter the termination phase without any avoidable further delay. Therefore, the intended number of endpoints may not be reached.

After closing the CDMS all analyses specified in this Statistical Analysis Plan have to be performed and a Statistical Analysis Report and a Clinical Investigation Report will be generated.

5.10. Analysis software

All analyses are conducted using SAS Version 9.4 for Windows or higher version (SAS Institute Inc., Cary, NC, USA) statistical software.

6. Randomization & specific Study Dates

6.1. Randomization

Data file: Identifier patient_display_id_full	Variable name	Variable label	Variable level	Nominal values
Baseline	randassign	Randomization result	nominal	Control (no implant) / Implant
data_SAR	rando_SAR[18]	Randomization	nominal	Control / Implant

6.2. Enrollment date

CIP chapter 8.9.5 Point of enrollment and study termination

The point of enrollment is the time at which a patient signs and dates the informed consent form … Study related procedures, documentation and collection/following of adverse events will start from this day on.

Data file: Identifier patient_display_id_full	Variable name	Variable label	Variable level	Nominal values
enrollment	ic_date	Date of informed consent (= date of enrollment)	date	n.a.

6.3. Initial and latest implantation date

Data file:Identifier record_id	Variable name	Variable label	Variable level	Nominal values
implantation	proc_multi	Implantation procedure is	nominal	Initial BioMonitor implantation BioMonitor exchange
implantation	imp_date	Date of implantation	date	n.a.

Data file: Identifier patient_display_id_full	Variable name	Variable label	Variable level	Nominal values
data_SAR	date_initial_implant_SAR[19]	Date initial BM implantation	date	n.a.
data_SAR	date_latest_implant_SAR[20]	Date of latest BM implantation	date	n.a.

6.4. Effective randomization date for the ITT analyses

CIP chapter 8.2.1 Randomization

…

For patients of the BioMonitor group and Control group, the randomization date is defined as the discharge from the index hospitalization.

Time-to-first-event for the ITT analyses start at the effective randomization date[21].

Data file: Identifier patient_display_id_full	Variable name	Variable label	Variable level	Nominal values
discharge	discharge_date	Date of discharge from index hospitalization	date	n.a.
data_SAR	date_effrand_ITT_SAR[22]	Date of effective randomization for ITT analysis (discharge from index hospitalization)	date	n.a.

6.5. Effective randomization date for the PP analyses

CIP chapter 11.1.3 Per-protocol Analysis Set

…

Primary endpoints are not taken into account in the BioMonitor group and in the control group until 1 month after discharge from the index hospitalization.

Time-to-first-event analyzes start at the effective randomization date plus 30 days.

Data file: Identifier patient_display_id_full	Variable name	Variable label	Variable level	Nominal values
discharge	discharge_date	Date of discharge from index hospitalization	date	n.a.
data_SAR	date_effrand_PP_SAR[23]	Date of effective randomization for PP analysis (discharge from index hospitalization) + 30days	date	n.a.

[21] The term "index hospitalisation" refers to one of the following events:

- In patients who are enrolled with an acute myocardial infarction, it is the day on which they are discharged from hospital after conclusion of the treatment for acute myocardial infaction.
- In patients who are not enrolled in the context of an acute myocardial infarction, it is they day they leave the physician who enrolled them, with or without implanted device. It is acknowledged that this is not necessarily an overnight hospitalisation but may be a short visit only.

6.6. Final date for the interim ITT analyses (NOTE: Not relevant for the final analysis)

1st interim analysis

The latest date after index-hospitalization with confirmed information about AEs (see chapter 5.5 is used for censoring for the interim ITT analysis if there is no previous primary endpoint.

Data file: Identifier record_id	Variable name	Variable label	Variable level	Nominal values
general_notification	contact_date	Date of patient contact	date	n.a.
general_notification	visit_date	Date of patient visit in investigational site	date	n.a.
arrhythmia_notification	contact_date	Date of patient visit in investigational site	date	n.a.
arrhythmia_notification	visit_date	Date of patient visit in investigational site	date	n.a.
who_five_well_being_index	interview_date	Date questionnaire performed	date	n.a.
eq_5d_5l_questionnaire	EQ5D5L_interview_date	Date questionnaire performed	date	n.a.
adverse_events	onset_date	Onset date	date	n.a.
adverse_events	sae_date	Date AE became serious	date	n.a.
adverse_events	end_date	End date of AE	date	n.a.
adverse_events	actionhospstart_date	Start date of hospitalization	date	n.a.
adverse_events	actionhospend_date	End date of hospitalization	date	n.a.
Data file: Identifier patient_display_id_full	Variable name	Variable label	Variable level	Nominal values
discharge	discharge_date	Date of discharge from index hospitalization	date	n.a.
study_termination	term_date	Date of study termination	date	n.a.
data_SAR	date_final_1interim_SAR[24]	Final date with confirmed information at or after discharge about AEs for the 1st interim analysis (censoring date if there is no previous primary endpoint)	date	n.a.

6.7. Final date for the final PP analyses

CIP chapter 11.1.3 Per-protocol Analysis Set

…

Time-to-first-event data are censored after occurrence of

- *Cross-overs from the BioMonitor group to the control group or vice versa*
- *Major protocol violations as defined in section 14.1*
- *...*

CIP chapter 14.1 CIP compliance and exceptions

… A deviation is any failure to follow, intentionally or unintentionally, the requirements of the CIP, including laws, guidelines and other regulation as far as required by the CIP, as well as applicable amendments. Deviations that are likely to seriously affect or that actually have seriously affected the rights or safety or wellbeing of subjects or the scientific integrity of the clinical investigation are major deviations (in the U.S. the term "violation" will be used). Otherwise they are minor deviations (in the U.S. simply referred to as "deviations").

The first major protocol violation will used for censoring for the per-protocol analysis when there is no previous primary endpoint:

- Date of initial implantation[25] in patients randomized to the control group.
- Date of "elective replacement indicator" (ERI) reported on an Arrhythmia Notification CRF, in patients randomized to the BioMonitor group if they do not receive a new device.
- First date of other major protocol violations after the effective randomization date. Major protocol deviations are documented in the CDMS file deviation_form_site. None of the events reported here were found to be relevant here except violation of in- an exclusion criteria and cross-overs contrary to randomization. However, these cases will identified by other procedures defined here and this CRF doesn't have to be considered.

[25] Note: A patient with implantation before effective randomization PP is not included in the PP analysis set. Thus, the initial implantation date defined here is implicitly defined as implantation after effective randomization PP.

Data file: Identifier record_id	Variable name	Variable label	Variable level	Nominal values
eri_form	expl_date	Date of explantation	Date	Yes / No
arryhythmia_notification	reason_multi	Reason for assessment	nominal	Arrhythmia/Event notification ERI notification …
arryhythmia_notification	helpvar_dateFormCreated		date	n.a.

Data file: Identifier patient_display_id_full	Variable name	Variable label	Variable level	Nominal values
study_termination	term_date	Date of study termination	date	n.a.
data_SAR	date_final_PP_SAR[26]	Date of first major protocol violation after the effective randomization date of the PP analysis or termination date (censoring date for PP analysis when there is no previous primary endpoint)	date	n.a.

[redacted]

6.8. Termination Date (= censoring date for the final ITT analyses)

CIP chapter 8.9.5 Point of enrollment and study termination

…

Regular point of termination for the individual patient is the respective date of the final study termination visit.

For all non-regular study terminations, the following rules apply:

- *In case of patient death, the date of study termination is the date of death.*
- *In case of HTX, the discharge date from the HTX procedure's hospitalization is the date of study termination.*
- *In case of withdrawal of consent, the date of study termination is the date of withdrawal of consent.*
- *If patient is lost to follow-up, the date of termination is the date of last contact of the investigator or of the CRO that collects AEs. Data from the HMSC will not be used to ascertain the vital status of patients for any primary analysis because this might introduce a bias in favor of the BM arm.*
- *If patient is defined as drop-out patient for any other reason, the date of study termination is the date on which the reason for the drop-out became effective, i.e. the date on which a violation of inclusion criteria was discovered, or on which the investigator excluded the patient for safety reasons.*

The variable term_date compromises the above definition, which is an instruction for the investigator how to report the termination date. The variable term_date will be checked during monitoring and during the blind review of the data before CDMS freeze or closure.

All remaining patients are terminated when the formal study termination is announced. Therefore, no individual study termination can be later than the formal study termination.

Data file: Identifier patient_display_id_full	Variable name	Variable label	Variable level	Nominal values
study_termination	term_date	Date of study termination	date	n.a.
study_termination	regular_yn	regular study termination	nominal	Yes / No

7. Analysis Sets

7.1. ITT Analysis Set

CIP chapter 11.1.2 Full Analysis set based on the ITT principle

The analysis of the primary hypothesis is performed on the full analysis set based on theintention-to treat (ITT) principle; i.e. the set of data from all randomized patients byminimal and justified elimination of subjects. This set is used to estimate the effect of theexperimental intervention with greatest external validity. Subjects allocated to arandomization group are analysed as members of that group irrespective of their compliance to the planned course of treatment, e.g. cross-over to the other group.

The ICH-E9 guideline states that "there are a limited number of circumstances that might lead to excluding randomized subjects from the full analysis set including … the failure to take at least one dose of trial medication and the lack of any data post randomization."

In accordance to this guideline, the following patients will be excluded from the analysis set

- *Patients of the BioMonitor group and control group in case of a drop-out before discharge from the index hospitalization*
- *Patients without signed informed consent form*

Data file: Identifier patient_display_id_full	Variable name	Variable label	Variable level	Nominal values
enrollment	ic_yn	Patient has provided written informed consent	nominal	Yes / No
study_terminatuion	term_date	Date of study termination	date	n.a.
data_SAR	date_effrand_ITT_SAR	Date effective randomization for ITT analysis (discharge from index hospitalization)	date	n.a.
data_SAR	analysis_set_itt_SAR[27]	ITT analysis set	nominal	Yes / No

7.2. PP Analysis Set

CIP. Chapter 11.1.3 Per-protocol Analysis Set

A supportive analysis of the primary hypothesis is performed on the per-protocol set (efficacy sample), which is a subset of the patients from the above full analysis set who complied sufficiently with the protocol. This set is used to ensure that the data would be likely to exhibit the effects of treatment according to the underlying scientific model.

The Per-Protocol Analysis Set is the subgroup of the Full Analysis set after exclusion of

- *Patients with violation of in- or exclusion criteria at enrollment*
- *Patients with major deviations from the CIP in accordance with the definition given in section 14.1*
- *Patients of the BioMonitor group without implanted device or drop-out less than 1 month after implantation*
- *Patients of the control group in case of a drop-out less than 1 month after index hospitalization*

CIP chapter. 14.1 CIP compliance and exceptions

… A deviation is any failure to follow, intentionally or unintentionally, the requirements of the CIP, including laws, guidelines and other regulation as far as required by the CIP, as well as applicable amendments. Deviations that are likely to seriously affect or that actually have seriously affected the rights or safety or wellbeing of subjects or the scientific integrity of the clinical investigation are major deviations (in the U.S. the term "violation" will be used). Otherwise they are minor deviations (in the U.S. simply referred to as "deviations").

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

Intentional, anticipated deviations from the CIP are only allowed if the deviation is required to protect the subject's rights, safety and well-being or the scientific integrity of the study. In such a case, the investigator will contact the sponsor and obtain prior approval for the deviation. If the deviation occurs in an emergency situation or any other unforeseen situation and is required to protect the patient's life or wellbeing, no prior sponsor approval is required. In case of a study deviation, either anticipated or unanticipated, both the investigator as well as the sponsor may request drop-out/premature study termination of the patient, based on the nature and/or consequences of the deviation.

To be more precise, the per-protocol analysis set[28] is given by the ITT analysis set excluding

- patients with violation of in- or exclusion criteria,
- patients with study termination before the effective randomization date for the PP analyses
- patients randomized to the BioMonitor group without implantation
- patients randomized to the the control group with implantation before the effective randomization date for the PP analyses, and
- patients with other major protocol violations before the effective randomization date. Major protocol deviations are documented in the CDMS file deviation_form_site. None of the events reported here were found to be relevant here except violation of in- an exclusion criteria and cross-overs contrary to randomization. However, these cases will identified by other procedures defined here and this CRF doesn't have to be considered.

[28] Note: Patients with major protocol violations later than 30 days after index discharge are included in the per-protocol analysis set. However, data after the occurrence of the protocol violation is not taken into account (see chapter 6.5).

Data file: Identifier patient_display_id_full	Variable name	Variable label	Variable level	Nominal values
enrollment	in01_yn, in02_yn, in03_yn, In04_yn	Inclusion criteria	nominal	Yes /No
enrollment	ex01_yn, ex02_yn, ex03_yn, ex04_yn, ex05_yn, ex06_yn, ex07_yn, ex08_yn, ex09_yn, ex10_yn	Exclusion criteria	nominal	
data_SAR	analysis_set_pp_SAR[29]	Per-protocol analysis set	nominal	Yes / No

[redacted]

8. Data for a CONSORT diagram and "study realization"

This data are analyzed exclusively for the final statistical analysis report. Data are reported for all patients in the complete ITT analysis set as well as separately for the BioMonitor and the control group and for the complete PP analysis set as well as for the BioMonitor and the control group, respectively.

8.1. Enrollment

- Number of patients
- Number of patients per site
- Date of First-Patient-In
- Date of Last-Patient-In

8.2. Termination

- Date of First-Patient-Out
- Date of Last-Patient-Out
-

Data file: Identifier patient_display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
study_ termination	descriptive	regular_ yn	Regular study termination	nominal	Yes No
study_ termination	Descriptive for regular_yn = No	reason_ multi	Please indicate the reason for early study termination	nominal	Patient death Withdrawal of patient consent Investigator initiated drop-out Loss to follow-up Early discovery of a violation of inclusion or exclusion criteria Heart transplantation Other

Data file: Identifier patient_display_id_ full	Notes	Variable name	Variable label	Variable level	Nominal values
enrollment	Case listings for regular_yn = No	ic_date	Date of informed consent	date	n.a.
discharge		discharge_date	Date of discharge from index hospitalization		
study_termination		term_date	Date of study termination		
study_termination		reason_multi	… reason for early study termination	nominal	…

Data file: Identifier patient_display _ id_full	Notes	Variable name	Variable label	Variable level	Nominal values
study_ termination	descriptive data including cumulative duration	days_dis_term_ITT_SAR[30]	Days from effective randomization for ITT analysis to termination	metric	n.a.
study_ termination	descriptive data including cumulative duration	days_dis_term_PP_SAR[31]	Days from effective randomization for PP analysis to termination	metric	n.a.

9. Baseline Data

9.1. Analysis set

These data are analyzed exclusively for the final statistical analysis report. Data are reported for all patients in the complete ITT analysis set[32] as well as separately for the BioMonitor and the control group and for the complete PP analysis set[33] as well as for the BioMonitor and the control group, respectively.

9.2. Variables

Enrollment

Data file: Identifier patient_display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
baseline	descr.	gender_fm	Gender	nominal	Male / Female
baseline					
enrollment	descr.	ami_lma	Left main artery	nominal	True / False
enrollment	descr.	ami_lad	Left anterior descending artery (LAD)	nominal	True / False
enrollment	descr.	ami_cx	Circumflex artery (CX)	nominal	True / False
enrollment	descr.	ami_rca	Right coronary artery (RCA)	nominal	True / False
enrollment	descr.	amitreat_pr	Percutaneous revascularization	nominal	True / False
enrollment	descr.	amitreat_t	Thrombolysis	nominal	True / False
enrollment	descr.	amitreat_0	NEW: Other kind of MI treatment	nominal	True / False
enrollment	descr.	amikind_multi	Kind of MI	nominal	STEMI / NSTEMI
enrollment	descr.	amifirst_yn	First occurrence of MI	nominal	Yes / No
enrollment	descr.	ami_no	Number of previous MI	metric	n.a.

Baseline

Data file: Identifier patient_display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
baseline	descr.				
baseline	desc.	hidden_age	Age at enrollment	Scale	n.a.
baseline	descr.	weight_kg	Weight [kg]	scale	n.a
baseline	descr.	height_cm	Height [cm]	scale	n.a.
baseline	descr.	bmi	BMI [kg/m2]	scale	n.a.
baseline	descr.	bsa	BSA (Mosteller) [m2]	scale	n.a.
baseline	no report	lvef_percent	NEW: LVEF after initial AMI treatment [%]	scale	n.a.
baseline	no report	lvef_percent_ amend1	NEW: LVEF measurement, performed within 6 months before enrollment [%]	scale	n.a.
data_SAR	descr.	lvef_SAR[34]	LVEF (before amendment or -if missing- after amendment) [%]	scale	n.a.
baseline	descr.	lav_ml	Left atrial volume [ml]	scale	n.a.
baseline	descr.	lvdv_ml	Left ventricular diastolic volume [ml]	scale	n.a.
baseline	descr.	lvdvbsa_mlm2	LVDV/BSA [ml/m2]	scale	n.a.
baseline	descr.	lvsv_ml	Left ventricular systolic volume [ml]	scale	n.a.
baseline	descr.	lvsvbsa_mlm2	LVSV/BSA [ml/m2]	scale	n.a.

Data file: Identifier patient_display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
baseline	descriptive	Gender_fm	Gender	nominal	Female / Male
baseline	descriptive	chf_yn	NEW: Congestive Heart Failure	nominal	Yes / No
baseline	descriptive	chfnyha_multi	NYHA class	nominal	I / II / III / IV
baseline	descriptive	nyha_SAR[35]	NYHA class	ordinal	1 / 2 / 3 / 4
baseline	descriptive	str_yn	Stroke	nominal	Yes / No
baseline	descriptive	tia_yn	Transient ischemic attack	nominal	Yes / No
baseline	descriptive	ste_yn	Systemic thromboembolic event	nominal	Yes / No
baseline	descriptive	hyp_yn	Hypertension	nominal	Yes / No
baseline	descriptive	pad_yn	Peripheral artery disease	nominal	Yes / No
baseline	descriptive	dia_yn	Diabetes mellitus	nominal	Yes / No
baseline	descriptive with "Not known " to be analyzed as missing data	vhd_multi	Valvular heart disease	nominal	Yes / No / Not known
baseline		mca_multi	Myocarditis	nominal	Yes / No / Not known
baseline		ren_multi	Renal disease	nominal	Yes / No / Not known
baseline		thy_multi	Thyroid dysfunction	nominal	Yes / No / Not known
baseline		cop_multi	COPD	nominal	Yes / No / Not known
baseline		hep_multi	Hepatic disease	nominal	Yes / No / Not known
baseline		sle_multi	Sleep apnea	nominal	Yes / No / Not known
baseline	descriptive	chads2_SAR[36]	CHADS2 Score	ordinal	0 / 1 / 2 / 3/ 4 / 5 / 6
data_SAR	descriptive	chads2_SAR[37]	CHADS2 Score (SAR)	ordinal	0 / 1 / 2 / 3/ 4 / 5 / 6
baseline	descriptive	cha2ds2vasc[38]	CHA2DS2-VASc-Score	ordinal	0 / 1 / 2 / 3/ 4 / 5 / 6 / 7 / 8 / 9
baseline	descriptive	cha2ds2vasc_SAR[39]	CHA2DS2-VASc-Score (SAR)	ordinal	0 / 1 / 2 / 3/ 4 / 5 / 6 / 7 / 8 / 9

[redacted]

Lab parameter

Data file: Identifier patient_display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
discharge	no report	date_created	Date created	date	n.a.
discharge	descriptive	lab1	Potassium [mmol/l]	scale	n.a.
discharge	descriptive	lab2	Sodium [mmol/l]	scale	n.a.
discharge	no report	lab3	Troponine	scale	n.a.
discharge	no report	lab3_multi	Troponine: Specification	nominal	Troponin C (Tn-C) ng/ml Troponin I (cTnI) ng/ml Troponin T (cTnT) Âµg/l
data_SAR	descriptive	lab3c_SAR[40]	Troponine C [ng/ml]	scale	n.a.
data_SAR	descriptive	lab3i_SAR[41]	Troponine I [ng/ml]	scale	n.a.
data_SAR	descriptive	lab3t_SAR[42]	Troponine T [mue_g/l]	scale	n.a.
discharge	descriptive	lab4	eGFR [ml/min]	scale	n.a.
discharge	no report	lab5	NEW: Haemoglobin	scale	n.a.
discharge	no report	lab5_multi	Please specify		mmol/l g/dl
data_SAR	descriptive	lab5_SAR[43]	Haemoglobin [mmol/l]	scale	mmol/l

Medication

Data file: Identifier patient_display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
discharge	descriptive	concmed01 – concmed11	Cardiovascular medication	nominal	Yes/ No
discharge	descriptive	ncconcmed1-noconcmed4	Non-cardiovascular medication	nominal	Yes/ No
discharge	case listing for concmed09 = True OR concmed11 = True	concmed0911_spec	Please specify (Anticoagulation treatment Other)	text	n.a.

9.3. Treatment of Missing and Spurious Data

Missing data are not imputed.

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

9.4. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

9.5. Descriptive Analyses

Descriptive data are presented via tables as specified in chapter 5.1.

9.6. Hypotheses & Statistical Tests

There are no pre-defined statistical hypotheses / tests for the baseline data in the CIP.

However, a potential imbalance between BioMonitor and control group with respect to the stratification variable amikind_multi = STEMI/NSTEMI will be analyzed based on Fisher's exact test.[44]

[44] Even if the randomization procedure will not sufficient and there will be an imbalance amikind_multi = STEMI / NSTEMI, no bias is expected for the primary endpoint analysis based on the stratified logrank test.

10. Pre-processing EAEC data for the primary and secondary endpoints

Each event from the EAEC-adjudication data file is identified by a parent_record_id variable. There are at least three data lines per event containing the adjudication of the three board members. In case of deviating decisions of the board members for a specific variable, a 2-of-3 decision is used for further analyses. However, a final adjudication of the chair, which is identified by the variable eac_complete_chair = Yes, overrules the evaluations of the other EAEC Members. According to EAEC working procedure, there are at least 2 identical adjudications or a chair decision for each event.

In its initial adjudication, the EAEC classifies the uncorrected[45] cause of the event with all available information including BioMonitor data. Next, for any possible endpoint, the most probably adjudication result without BioMonitor information is documented. The analyses of the endpoints will be based on this variables type_of_event_ae2 and death_prim_cause2, which are in better accordance with the objective of the study. However, for the primary endpoint a safety analysis is also performed for the uncorrected variables type_of_event_ae and death_prim_cause.

CIP Chapter 8.3.1 Primary Endpoint

The primary endpoint is the time from randomization (definition see section 8.2.1) to the first MACE during the clinical investigation. Patients without MACE are censored, i.e. the time from randomization until the earliest date of drop-out, study termination, or date of freezing the Clinical Data Management System database (in case of interim analyses) is considered. Patients who reach the primary endpoint will continue to be followed up until the formal termination of the study is announced (see section 8.1).

A major adverse cardiac event (MACE) comprises the following events:

- *Cardiovascular death*
- *Worsening of the patient status due to heart failure, requiring acute unscheduled hospitalization or urgent visit*

or acute unscheduled hospitalization due to adverse events (AE) of the following list:

- *Arrhythmia*
- *Acute coronary syndrome*
- *Stroke*
- *Major bleeding*
- *Systemic embolism*

Heart transplantation (HTX) is also a component of "worsening of the patient status due to heart failure, requiring acute unscheduled hospitalization or urgent visit".

[45] The „uncorrected" adjudication refers to the assumed true cause of the event after considering of all available information including that coming from the BioMonitor. Because the latter is not available in the control group, this information bias can distort the true treatment effect, and the primary analysis of the treatment effect is based on the adjudication that the EAEC gives und the assumption that no BioMonitor information was available. A detailed justification is given in the EAEC charter.

Data file: Identifier record_id	Notes	Variable name	Variable label	Variable level	Nominal values
eaec_ adjudication	No report	eac_ complete_ chair	Is chair adjudication for this event applied and complete?	nominal	Yes No
eaec_ adjudication	No report	type_of_ event	Please specify type of event	nominal	Death without prior hospitalisation Heart transplantation Acute unscheduled hospitalisation or urgent HF visit Scheduled hospitalisation or Home Monitoring triggered No hospitalisation / no endpoint due to other reason
eaec_ adjudication	No report	type_of_ event_ae[46]	Primary cause of Unscheduled hospitalisation / urgent visit	nominal	Myocardial infarction Heart failure (urgent visit) Heart failure (hospitalisation) Arrhythmia Stroke Major bleeding Transient ischemic attack Systemic embolism other cardio-vascular non-cardiovascular Undetermined hospitalization or undetermined urgent visit
eaec_ adjudication	No report	death_ prim_cause	Primary cause of death	nominal	Myocardial infarction Heart failure Sudden cardiac death Stroke Cardiovascular hemorrhage Systemic embolism other cardio-vascular non-cardiovascular undetermined
eaec_ adjudication	No report	date1_ of_event	Date of event	date	n.a.
eaec_ adjudication	No report	date2_deat h	Date of death	date	n.a.
eaec_ adjudication	No report	death_ occured	Patient death during hospitalization / transplantation	nominal	Yes No

[46] Note new classification "Undetermined hospitalization or undetermined urgent visit"

Data file: Identifier record_id	Notes	Variable name	Variable label	Variable level	Nominal values
eaec_ adjudication	No report	contribution_ significant	The BioMonitor contributed significantly to the adjudication result, so that the result would most probably have been different without the information from the BioMonitor	nominal	Yes No
eaec_ adjudication	No report	type_of_ event_ae2	Primary cause of Unscheduled hospitalisation / urgent visit The most probably adjudication result without BioMonitor information would have been	nominal	Myocardial infarction Heart failure (urgent visit) Heart failure (hospitalisation) Arrhythmia Stroke Major bleeding Transient ischemic attack Systemic embolism other cardio-vascular non-cardiovascular
eaec_ adjudication	No report	death_ prim_cause2	Primary cause of death The most probably adjudication result without BioMonitor information would have been	nominal	Myocardial infarction Heart failure Sudden cardiac death Stroke Cardiovascular hemorrhage Systemic embolism other cardio-vascular non-cardiovascular undetermined
data_eaec_ adjudication_ SAR	No report	type_of_ event_ae_c[47]	Primary cause of Unscheduled hospitalisation / urgent visit (corrected data)	nominal	Myocardial infarction Heart failure (urgent visit) Heart failure (hospitalisation) Arrhythmia Stroke Major bleeding Transient ischemic attack Systemic embolism other cardio-vascular non-cardiovascular
data_eaec_ adjudication_ SAR	No report	death_ prim_cause_c[48]	Primary cause of death (corrected data)	nominal	Myocardial infarction Heart failure Sudden cardiac death Stroke Cardiovascular hemorrhage Systemic embolism other cardio-vascular non-cardiovascular undetermined

Data file: Identifier parent_record_id	Notes	Variable name	Variable label	Variable level	Nominal values
data_ep_SAR	No report	pep_c_2of3chair_SAR[49]	(Corrected) primary EP (based on a 2-of-3 or final chair adjudication of the EAEC)	nominal	Yes No
data_ep_SAR	No report	pep_u_2of3chair_SAR[50]	Uncorrected primary EP (based on a 2-of-3 or final chair adjudication of the EAEC)	nominal	Yes No
data_ep_SAR	No report	date_pep_c_2of3chair_SAR[51]	Date of (corrected) primary EP (based on a 2-of-3 or final chair adjudication of the EAEC)	date	n.a.
data_ep_SAR	No report	date_pep_u_2of3chair_SAR[52]	Date of uncorrected primary EP (based on a 2-of-3 or final chair adjudication of the EAEC)	date	n.a.

For each triplet eaec_adjudication variable, an unique composite variable will be generated based on a 2-of-3 or chairman decision. For better readability, the index (*) is used instead of the index "2of3chair_SAR", which is used for other derived data.

[redacted]

Data file: Identifier parent_record_id	Notes	Variable name	Variable label	Variable level	Nominal values
data_ep_SAR	No report	death_2of3chair_SAR[53]	All cause death (based on a 2-of-3 or final chair adjudication of the EAEC)	nominal	Yes / No
data_ep_SAR	No report	date_death_2of3chair_SAR[54]	Date of death (based on a 2-of-3 or final chair adjudication of the EAEC)	date	n.a.
data_ep_SAR	No report	cvdeath_2of3chair_SAR55	CV death (based on a 2-of-3 or final chair adjudication of the EAEC)	nominal	Yes / No
data_ep_SAR	No report	date_cvdeath_2of3chair_SAR56	Date of HTX (based on a 2-of-3 or final chair adjudication of the EAEC)	date	n.a.
data_ep_SAR	No report	htx_2of3chair_SAR[57]	HTX (based on a 2-of-3 or final chair adjudication of the EAEC)	nominal	Yes / No
data_ep_SAR	No report	date_htx_2of3chair_SAR[58]	Date of HTX (based on a 2-of-3 or final chair adjudication of the EAEC)	date	n.a.

Data file: Identifier parent_record_id	Notes	Variable name	Variable label	Variable level	Nominal values
data_ep_SAR	No report	hf_2of3chair_SAR[59]	Hospitalization or urgent visit for worsening of the patient status due to heart failure, or death due to heart failure (based on a 2-of-3 or final chair adjudication of the EAEC)	nominal	Yes / No
data_ep_SAR	No report	date_hf_2of3chair_SAR[60]	Date of hospitalization or urgent visit for worsening of the patient status due to heart failure, or death due to heart failure (based on a 2-of-3 or final chair adjudication of the EAEC)	date	n.a.
data_ep_SAR	No report	arr_2of3chair_SAR[61]	hospitalization resulting from an arrhythmia or death resulting from arrhythmia (based on a 2-of-3 or final chair adjudication of the EAEC)	nominal	Yes / No
data_ep_SAR	No report	date_arr_2of3chair_SAR[62]	Date of hospitalization resulting from an arrhythmia or death resulting from arrhythmia (based on a 2-of-3 or final chair adjudication of the EAEC)	date	n.a.

[redacted]

Data file: Identifier parent_record_id	Notes	Variable name	Variable label	Variable level	Nominal values
data_ep_SAR	No report	acs_2of3chair_SAR[63]	Hospitalization resulting from acute coronary syndrome or death resulting from acute coronary syndrome. (based on a 2-of-3 or final chair adjudication of the EAEC)	nominal	Yes / No
data_ep_SAR	No report	date_acs_2of3chair_SAR[64]	Date of hospitalization resulting from acute coronary syndrome or death resulting from acute coronary syndrome (based on a 2-of-3 or final chair adjudication of the EAEC)	date	n.a.
data_ep_SAR	No report	stroke_2of3chair_SAR[65]	Hospitalization resulting from stroke (based on a 2-of-3 or final chair adjudication of the EAEC)	nominal	Yes / No
data_ep_SAR	No report	date_stroke_2of3chair_SAR[66]	Date of hospitalization resulting from stroke (based on a 2-of-3 or final chair adjudication of the EAEC)	date	n.a.

[redacted]

Data file: Identifier parent_record_id	Notes	Variable name	Variable label	Variable level	Nominal values
data_ep_SAR	No report	bleed_2of3chair_SAR[67]	hospitalization resulting from major bleeding or death resulting from major bleeding (based on a 2-of-3 or final chair adjudication of the EAEC)	nominal	Yes / No
data_ep_SAR	No report	date_bleed_2of3chair_SAR[68]	Date of hospitalization resulting from major bleeding or death resulting from major bleeding (based on a 2-of-3 or final chair adjudication of the EAEC)	date	n.a.
data_ep_SAR	No report	emb_2of3chair_SAR[69]	hospitalization resulting from systemic embolism or death resulting from systemic embolism (based on a 2-of-3 or final chair adjudication of the EAEC)	nominal	Yes / No
data_ep_SAR	No report	date_emb_2of3chair_SAR[70]	Date of hospitalization resulting from systemic embolism or death resulting from systemic embolism (based on a 2-of-3 or final chair adjudication of the EAEC)	date	n.a.

[redacted]

11. Primary Endpoint

11.1. Analysis set

Any interim analysis is based on the ITT analysis set.

All analyses for the final statistical analysis report are based on the ITT analysis set[71] and the per-protocol analysis set[72]. Thereby, subgroup analyses are performed for the ITT analysis set only.

11.2. Variables

CIP Chapter 8.3.1 Primary Endpoint

The primary endpoint is the time from randomization (definition see section 8.2.1) to the first MACE during the clinical investigation. Patients without MACE are censored, i.e. the time from randomization until the earliest date of drop-out, study termination, or date of freezing the Clinical Data Management System database (in case of interim analyses) is considered. Patients who reach the primary endpoint will continue to be followed up until the formal termination of the study is announced (see section 8.1).

A major adverse cardiac event (MACE) comprises the following events:

- *Cardiovascular death*
- *Worsening of the patient status due to heart failure, requiring acute unscheduled hospitalization or urgent visit*

or acute unscheduled hospitalization due to adverse events (AE) of the following list:

- *Arrhythmia*
- *Acute coronary syndrome*
- *Stroke*
- *Major bleeding*
- *Systemic embolism*

Variables for the ITT analysis set

Data file: Identifier patient_display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	descr.	any_pep_ITT_SAR[73]	Any prim EP occurred at or after effective randomization ITT	nominal	Yes / No
data_SAR	No report	date_1pep_ITT_SAR[74]	Date of 1st prim EP at or after effective randomization ITT	date	n.a.
data_SAR	descr.	days_effrand_to_1pep_ITT_SAR[75]	Days from effective randomization to first prim EP or censoring ITT	scale	n.a.

Variables for the per-protocol analysis set

Data file: Identifier patient_display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	descr.	any_pep_PP_SAR[76]	Any prim EP occurred at or after effective randomization PP	nominal	Yes / No
data_SAR	No report	date_1pep_PP_SAR[77]	Date of 1st prim EP at or after effective randomization PP	date	n.a.
data_SAR	descr.	days_effrand_to_1pep_PP_SAR[78]	Days from effective randomization to first prim EP or censoring PP	scale	n.a.

11.3. Treatment of Missing and Spurious Data

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

11.4. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

11.5. Descriptive Analyses

If applicable, mean and median survival times are presented by using the Kaplan-Meier estimates. Kaplan-Meier survival figures are presented for illustration.

Other descriptive data will be presented via tables as specified in chapter 5.1.

11.6. Hypotheses & Statistical Tests

CIP *Chapter 7.2 Primary hypotheses*

For assessing the primary endpoints, Kaplan-Meier curves will be constructed for the time to first MACE for both study groups according to the intention-to-treat principle. The hazard ratio is defined as the rate of the BioMonitor group divided by the rate of the control group.

The following set of hypotheses (null hypothesis H0 and alternative hypothesis HA) will be tested. More detailed information about the endpoints is provided in section 8.3:

- *H_0: Null hypothesis: H_0 : HR ≥ 1 which means that monitoring patients of the BioMonitor group will not lead to a longer time-to-first-event of MACE compared to the control group.*
- *H_A: Alternative hypothesis: H_A : HR < 1 which means that monitoring patients of the BioMonitor group will lead to a longer time-to-first-event of MACE compared to the control group.*

It is expected that there is a HR < 1 in favour of the BioMonitor group. A rejection of the null hypothesis indicates that the BioMonitor group has a statistically significant longer time to first MACE event compared to the control group.

The confirmatory analysis of the primary hypothesis is performed according to the methods defined in chapter 0. based on the first primary endpoint after the effective randomization date or censoring at the termination date in the ITT analysis set.

The test of the primary hypothesis is repeated according to the methods defined in chapter 0. based on the first endpoint after the effective randomization date for the PP analysis or censoring at the final date for the final PP analyses in the PP analysis set.

In case the primary alternative hypothesis can be accepted, hazard ratios for the BioMonitor versus control group including 95% CI are additionally calculated based on the Cox regression model for the following conditions:

- ITT analysis set, uncorrected adjudication, stratification amikind_multi= STEMI/NSTEMI
- ITT analysis set, corrected adjudication, stratification amikind_multi= STEMI/NSTEMI
- ITT analysis set, corrected adjudication, without stratification
- PP analysis set, corrected adjudication, stratification amikind_multi= STEMI/NSTEMI
- PP analysis set, corrected adjudication, without stratification

The assumption of proportional hazards is checked graphically by log-minus-log survival versus log–time plots.

12. Sec. Endpoint: Time to 1st arrhythmia detection

12.1. Analysis set

This endpoint is analyzed exclusively for the final statistical analysis report based on the ITT analysis set.[79]

12.2. Variables

CIP Chapter 8.3.2 Secondary endpoint: Time to first arrhythmia detection

This secondary endpoint comprises the time from randomization to the detection of an arrhythmia that requires guideline-recommended therapy. Patients without arrhythmia detection are censored, i.e. the time from randomization until the ~~earliest date of drop-out~~, study termination, ~~or date of freezing the Clinical Data Management System database (in case of interim analyses)~~ is considered.

To be more precise, secondary endpoints will not be analyzed during interim analyzes and the earliest date of drop-out is just documented as termination date date_term at the termination CRF.

Data file:Identifier record_id	Notes	Variable name	Variable label	Variable level	Nominal values
advers_events	No report	arr_date	When was the earliest documentation of the arrhythmia?	date	n.a.
adverse_events	No report	arr_yn	Was an arrhythmia documented in the context of this event?	nominal	Yes / No
adverse_events	No report	arrchange_yn	Does the arrhythmia require guideline-recommended change of therapy?	nominal	Yes / No
data_ae_SAR	No report	arrdetect_SAR[80]	Arrhythmia detection with guideline-recommended change of therapy	nominal	Yes / No
data_ae_SAR	No report	date_arrdetect_SAR[81]	Date of a arrhythmia detection with guideline-recommended change of therapy	date	n.a.

Data file: Identifier patient_ display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	descr.	any_arrdetect_ITT_SAR[82]	Any arrhythmia with guideline-recommended change of therapy after effective randomization ITT	nominal	Yes / No
data_SAR	No report	date_1arrdetect_ITT_SAR[83]	Date of 1st arrhythmia with guideline-recommended change of therapy after effective randomization ITT	date	n.a.
data_SAR	descr.	days_effrand_to_1arrdetect_ITT_SAR[84]	Days from effective randomization to 1st arrhythmia detection with guideline recommended therapy or termination ITT	scale	n.a.

12.3. Treatment of Missing and Spurious Data

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

12.4. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

12.5. Descriptive Analyses

If applicable, mean and median survival times are presented by using the Kaplan-Meier estimates. Kaplan-Meier survival figures are presented for illustration.

Other descriptive data will be presented via tables as specified in chapter 5.1.

12.6. Hypotheses & Statistical Tests

CIP Chapter *7.3 Secondary hypotheses*

The objective to show that arrhythmias requiring guideline-recommended therapy will be detected earlier in the BioMonitor group will be formally tested similarly to the primary hypothesis. The HR is defined as the rate of the BioMonitor group divided by the rate of the control group.

H_0: Null hypothesis: $H_0 : HR \leq 1$ which means that monitoring patients of the BioMonitor group will not lead to a shorter time to first arrhythmia that requires guideline-recommended therapy, in the BioMonitor group compared to the control group.

H_A: Alternative hypothesis: $H_A : HR > 1$ which means that monitoring patients of the BioMonitor group will lead to a shorter time to first arrhythmia that requires guideline-recommended therapy compared to the control group.

The hazard ratio for the BioMonitor versus control group including 95%CI is calculated with the Cox regression model. In case of doubt about the validity of the Cox model, the assumption of proportional hazards is checked graphically by log-minus-log survival versus log–time plots.

13. Other sec. EP: Time to all-cause death or heart transpl.

13.1. Analysis set

This endpoint is analyzed exclusively for the final statistical analysis report based on the ITT analysis set.[85]

13.2. Variables

CIP Chapter 8.3.3.1. Time to death from any cause or heart transplantation

Assessment of the time from randomization to death for any reason or heart transplantation during the clinical investigation.

Data file: Identifier patient_ display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	descr.	death_htx_ITT_SAR[86]	Death or heart transplantation ITT	nominal	Yes / No
data_SAR	descr.	days_effrand_to_term_ ITT_SAR[87]	Days from effective randomization to termination ITT	scale	n.a.

13.3. Treatment of Missing and Spurious Data

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

13.1. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

13.2. Descriptive Analyses

If applicable, mean and median survival times are presented by using the Kaplan-Meier estimates. Kaplan-Meier survival figures are presented for illustration.

Other descriptive data will be presented via tables as specified in chapter 5.1.

13.1. Hypotheses & Statistical Tests

The hazard ratio for the BioMonitor versus control group including 95%CI is calculated with the Cox regression model. In case of doubt about the validity of the Cox model, the assumption of proportional hazards is checked graphically by log-minus-log survival versus log–time plots.

14. Other sec. EP: Time to CV death or heart transplantation

14.1. Analysis set

This endpoint is analyzed exclusively for the final statistical analysis report based on the ITT analysis set.[88]

14.2. Variables

CIP Chapter 8.3.3.2 Time to cardiovascular death or heart transplantation

Assessment of the time from randomization to cardiovascular death or heart transplantation during the clinical investigation. A specified endpoint definition will be given by the members of the EAEC ...

Data file: Identifier patient_ display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	descr.	cvdeath_htx_ITT_SAR[89]	CV death or heart transplantation ITT	nominal	Yes / No
data_SAR	descr.	days_effrand_to_term_ITT_SAR[90]	Days from effective randomization to termination ITT	scale	n.a.

14.3. Treatment of Missing and Spurious Data

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

14.4. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

14.5. Descriptive Analyses

If applicable, mean and median survival times are presented by using the Kaplan-Meier estimates. Kaplan-Meier survival figures are presented for illustration.

Other descriptive data will be presented via tables as specified in chapter 5.1.

14.6. Hypotheses & Statistical Tests

Differences of the survival curves BioMonitor versus control group are tested for statistical inference with the log-rank test.

The hazard ratio for the BioMonitor versus control group including 95%CI is calculated with the Cox regression model. In case of doubt about the validity of the Cox model, the assumption of proportional hazards is checked graphically by log-minus-log survival versus log–time plots.

15. Other sec. EP: Time to 1st worsening of the patient status due to heart failure …

15.1. Analysis set

This endpoint is analyzed exclusively for the final statistical analysis report based on the ITT analysis set.[91]

15.2. Variables

CIP Chapter 8.3.3.3 Time to first worsening of the patient status due to heart failure requiring hospitalization or urgent visit

Assessment of the time from randomization to first hospitalization or urgent visit for worsening of the patient status due to heart failure, or death due to heart failure. A specified endpoint definition will be given by the members of the EAEC and documented in the charter agreement

Data file: Identifier patient_ display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	descr.	any_hf_ITT_SAR[92]	Any hospitalization or urgent visit for worsening of the patient status due to heart failure, or death due to heart failure after effective randomization ITT	nominal	Yes / No
data_SAR	No report	date_1hf_ITT_SAR[93]	Date of 1st hospitalization or urgent visit for worsening of the patient status due to heart failure, or death due to heart failure after effective randomization ITT	date	n.a.
data_SAR	descr.	days_effrand_to_1hf_ITT_SAR[94]	Days from effective randomization to 1st[t] hospitalization or urgent visit for worsening of the patient status due to heart failure, or death due to heart failure or termination ITT	scale	n.a.

15.3. Treatment of Missing and Spurious Data

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

15.1. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

15.2. Descriptive Analyses

If applicable, mean and median survival times are presented by using the Kaplan-Meier estimates. Kaplan-Meier survival figures are presented for illustration.

Other descriptive data will be presented via tables as specified in chapter 5.1.

15.3. Hypotheses & Statistical Tests

Differences of the survival curves BioMonitor versus control group are tested for statistical inference with the log-rank test.

The hazard ratio for the BioMonitor versus control group including 95%CI is calculated with the Cox regression model. In case of doubt about the validity of the Cox model, the assumption of proportional hazards is checked graphically by log-minus-log survival versus log–time plots.

16. Other sec. EP: Time to 1st hosp. resulting from an arrhythmia

16.1. Analysis set

This endpoint is analyzed exclusively for the final statistical analysis report based on the ITT analysis set.[95]

16.2. Variables

CIP chapter 8.3.3.4. Time to first hospitalization resulting from an arrhythmia

Assessment of the time from randomization to the first hospitalization resulting from an arrhythmia or death resulting from arrhythmia. A specified endpoint definition will be given by the members of the EAEC and documented in the charter agreement.

Data file: Identifier patient_ display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	descr.	any_arr_ITT_SAR[96]	Any hospitalization resulting from an arrhythmia or death resulting from arrhythmia after effective randomization ITT	nominal	Yes / No
data_SAR	No report	date_1arr_ITT_SAR[97]	Date of 1st hospitalization resulting from an arrhythmia or death resulting from arrhythmia after effective randomization ITT	date	n.a.
data_SAR	descr.	days_effrand_to_1arr_ITT_SAR[98]	Days from effective randomization to 1st hospitalization resulting from an arrhythmia or death resulting from arrhythmia or termination ITT	scale	n.a.

16.3. Treatment of Missing and Spurious Data

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

16.1. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

16.2. Descriptive Analyses

If applicable, mean and median survival times are presented by using the Kaplan-Meier estimates. Kaplan-Meier survival figures are presented for illustration.

Other descriptive data will be presented via tables as specified in chapter 5.1.

16.3. Hypotheses & Statistical Tests

Differences of the survival curves BioMonitor versus control group are tested for statistical inference with the log-rank test.

The hazard ratio for the BioMonitor versus control group including 95%CI is calculated with the Cox regression model. In case of doubt about the validity of the Cox model, the assumption of proportional hazards is checked graphically by log-minus-log survival versus log–time plots.

17. Other sec. EP: Time to 1st hosp. resulting from acute coronary syndrome

17.1. Analysis set

This endpoint is analyzed exclusively for the final statistical analysis report based on the ITT analysis set.[99]

17.2. Variables

CIP cChapter 8.3.3.5. Time to first hospitalization resulting from acute coronary syndrome

Assessment of the time from randomization to the first hospitalization resulting from acute coronary syndrome or death resulting from acute coronary syndrome. A specified endpoint definition will be given by the members of the EAEC and documented in the charter agreement.

Data file: Identifier patient_ display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	descr.	any_acs_ITT_SAR[100]	Any hospitalization resulting from acute coronary syndrome or death resulting from acute coronary syndrome after effective randomization ITT	nominal	Yes / No
data_SAR	No report	date_1acs_ITT_SAR[101]	Date of 1st hospitalization resulting from acute coronary syndrome or death resulting from acute coronary syndrome after effective randomization ITT	date	n.a.
data_SAR	descr.	days_effrand_to_1acs_ITT_SAR[102]	Days from effective randomization to 1st hospitalization resulting from acute coronary syndrome or death resulting from acute coronary syndrome or termination ITT	scale	n.a.

[redacted]

17.3. Treatment of Missing and Spurious Data

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

17.1. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

17.2. Descriptive Analyses

If applicable, mean and median survival times are presented by using the Kaplan-Meier estimates. Kaplan-Meier survival figures are presented for illustration.

Other descriptive data will be presented via tables as specified in chapter 5.1.

17.3. Hypotheses & Statistical Tests

Differences of the survival curves BioMonitor versus control group are tested for statistical inference with the log-rank test.

The hazard ratio for the BioMonitor versus control group including 95%CI is calculated with the Cox regression model. In case of doubt about the validity of the Cox model, the assumption of proportional hazards is checked graphically by log-minus-log survival versus log–time plots.

18. Other sec. EP: Time to 1st hosp. resulting from stroke

18.1. Analysis set

This endpoint is analyzed exclusively for the final statistical analysis report based on the ITT analysis set.[103]

18.2. Variables

CIP Chapter 8.3.3.6 Time to first hospitalization resulting from stroke

Assessment of the time from randomization to the first hospitalization resulting from stroke or death resulting from stroke. A specified endpoint definition will be given by the members of the EAEC and documented in the charter agreement.

Data file: Identifier patient_ display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	descr.	any_stroke_ITT_SAR[104]	Any hospitalization resulting from stroke or death resulting from stroke after effective randomization ITT	nominal	Yes / No
data_SAR	No report	date_1stroke_ITT_SAR[105]	Date of 1st hospitalization resulting from stroke or death resulting from stroke after effective randomization ITT	date	n.a.
data_SAR	descr.	days_effrand_to_1stroke_ITT_SAR[106]	Days from effective randomization to the 1st hospitalization resulting from stroke or death resulting from stroke or termination ITT	scale	n.a.

18.3. Treatment of Missing and Spurious Data

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

18.1. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

18.2. Descriptive Analyses

If applicable, mean and median survival times are presented by using the Kaplan-Meier estimates. Kaplan-Meier survival figures are presented for illustration.

Other descriptive data will be presented via tables as specified in chapter 5.1.

18.3. Hypotheses & Statistical Tests

Differences of the survival curves BioMonitor versus control group are tested for statistical inference with the log-rank test.

The hazard ratio for the BioMonitor versus control group including 95%CI is calculated with the Cox regression model. In case of doubt about the validity of the Cox model, the assumption of proportional hazards is checked graphically by log-minus-log survival versus log–time plots.

19. Other sec. EP: Time to 1st hosp. resulting from major bleeding

19.1. Analysis set

This endpoint is analyzed exclusively for the final statistical analysis report based on the ITT analysis set.[107]

19.2. Variables

CIP Chapter 8.3.3.7 Time to first hospitalization resulting from major bleeding

Assessment of the time from randomization to the first hospitalization resulting from major bleeding or death resulting from major bleeding. A specified endpoint definition will be given by the members of the EAEC and documented in the charter agreement.

Data file: Identifier patient_ display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	descr.	any_bleed_ITT_SAR[108]	Any hospitalization resulting from major bleeding or death resulting from major bleeding after effective randomization ITT	nominal	Yes / No
data_SAR	No report	date_1bleed_ITT_SAR[109]	Date of 1st hospitalization resulting from major bleeding or death resulting from major bleeding after effective randomization ITT	date	n.a.
data_SAR	descr.	days_effrand_to_1bleed_ITT_SAR[110]	Days from effective randomization to 1st hospitalization resulting from major bleeding or death resulting from major bleeding or termination ITT	scale	n.a.

[redacted]

19.3. Treatment of Missing and Spurious Data

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

19.1. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

19.2. Descriptive Analyses

If applicable, mean and median survival times are presented by using the Kaplan-Meier estimates. Kaplan-Meier survival figures are presented for illustration.

Other descriptive data will be presented via tables as specified in chapter 5.1.

19.3. Hypotheses & Statistical Tests

Differences of the survival curves BioMonitor versus control group are tested for statistical inference with the log-rank test.

The hazard ratio for the BioMonitor versus control group including 95%CI is calculated with the Cox regression model. In case of doubt about the validity of the Cox model, the assumption of proportional hazards is checked graphically by log-minus-log survival versus log–time plots.

20. Other sec. EP: Time to 1st hosp. resulting from systemic embolism

20.1. Analysis set

This endpoint is analyzed exclusively for the final statistical analysis report based on the ITT analysis set.[111]

20.2. Variables

CIP Chapter 8.3.3.8 Time to first hospitalization resulting from systemic embolism

Assessment of the time from randomization to the first hospitalization resulting from systemic embolism or death resulting from systemic embolism. A specified endpoint definition will be given by the members of the EAEC and documented in the charter agreement.

Data file: Identifier patient_ display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	descr.	any_emb_ITT_SAR[112]	Any hospitalization resulting from systemic embolism or death resulting from systemic embolism. after effective randomization ITT	nominal	Yes / No
data_SAR	No report	date_1emb_ITT_SAR[113]	Date of 1st hospitalization resulting from systemic embolism or death resulting from systemic embolism. after effective randomization ITT	date	n.a.
data_SAR	descr.	days_effrand_to_1emb_ITT_ SAR[114]	Days from effective randomization to 1st hospitalization resulting from systemic embolism or death resulting from systemic embolism or termination ITT	scale	n.a.

[redacted]

20.3. Treatment of Missing and Spurious Data

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

20.1. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

20.2. Descriptive Analyses

If applicable, mean and median survival times are presented by using the Kaplan-Meier estimates. Kaplan-Meier survival figures are presented for illustration.

Other descriptive data will be presented via tables as specified in chapter 5.1.

20.3. Hypotheses & Statistical Tests

Differences of the survival curves BioMonitor versus control group are tested for statistical inference with the log-rank test.

The hazard ratio for the BioMonitor versus control group including 95%CI is calculated with the Cox regression model. In case of doubt about the validity of the Cox model, the assumption of proportional hazards is checked graphically by log-minus-log survival versus log–time plots.

21. Other sec. EP: Time to 1st arrhythmia

21.1. Analysis set

This endpoint is analyzed exclusively for the final statistical analysis report based on the ITT analysis set.[115]

21.2. Variables

CIP Chapter 8.3.3.9. Time to first arrhythmia

Assessment of the time from randomization to first arrhythmia.

Data file: Identifier record_ID	Notes	Variable name	Variable label	Variable level	Nominal values
adverse_events	No report	arr_yn	NEW: Arrhythmia documented	nominal	Yes / No
advers_events	No report	arr_date	NEW: Earliest documentation of the arrhythmia	date	n.a.
adverse_events	No report	end_date	End date of AE (if applicable: Date of death)	date	n.a.

Data file: Identifier patient_display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	No report	any_arrhythmia_ITT_SAR[116]	Any arrhythmia after effective randomization ITT	nominal	Yes / No
data_SAR	No report	date_1arrhythmia_ITT_SAR[117]	Date of 1st arrhythmia after effective randomization ITT	date	n.a.
data_SAR	descr.	days_effrand_to_1arrhythmia_ ITT_SAR[118]	Days from effective randomization to 1st arrhythmia or termination ITT	scale	n.a.

[redacted]

21.3. Treatment of Missing and Spurious Data

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

21.1. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

21.2. Descriptive Analyses

If applicable, mean and median survival times are presented by using the Kaplan-Meier estimates. Kaplan-Meier survival figures are presented for illustration.

Other descriptive data will be presented via tables as specified in chapter 5.1.

21.3. Hypotheses & Statistical Tests

Differences of the survival curves BioMonitor versus control group are tested for statistical inference with the log-rank test.

The hazard ratio for the BioMonitor versus control group including 95%CI is calculated with the Cox regression model. In case of doubt about the validity of the Cox model, the assumption of proportional hazards is checked graphically by log-minus-log survival versus log–time plots.

22. Other sec. EP: Type of initiated therapies

The main objective of this endpoint is to describe in an exploratorive fashion which therapies are introduced to patients as consequence of BioMonitor detected arrhythmias. Therefore an internal adjudication board classified the information given in text entries of relevant AE reports with respect to cardiac rhythm, initiated or changed drug therapy, and initiated device therapy.

22.1. Analysis set

This endpoint is analyzed exclusively for the final statistical analysis report based on the ITT analysis set.[119]

22.2. Variables

CIP Chapter 8.3.3.10 Type of initiated therapies.

Evaluation of the diagnoses and consequent type of therapies based on ICM-detected arrhythmias.

Data file: Identifier parent_record_id (related to the AE record ID)	Notes	Variable name	Variable label	Variable level	Nominal values
internal_adjudication	descriptive *#	adj_rhythm_multi	Rhythm	nominal	Atrial fibrillation Atrial flutter AV block Bradycardia frequent VPBs non-sustained VT sustained VT polymorphic VT/VF Other SVT Pause None
internal_adjudication	descriptive *	adj_drug	Drug	nominal	Antiarrhythmic BB Diuretic OAC Other None
internal_adjudication	Case listing	adj_drug_txt	Drug text	text	n.a.
internal_adjudication	descriptive #	adj_device	Device	nominal	Ablation Cardioversion ICD Other PM None
internal_adjudication	Case listing	adj_device_txt	Device text	text	n.a.

*2x3 contingency table; # 2x3 contingency table

[119] analysis_set_itt_SAR = Yes

22.3. Treatment of Missing and Spurious Data

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

22.1. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

22.2. Descriptive Analyses

Descriptive data are presented via tables as specified in chapter 5.1.

22.3. Hypotheses & Statistical Tests

A broad range of diagnoses and therapies can be expected for the study population. A reasonable pre-defined scheme to classify the events has not yet been developed. Thus, there are no pre-specified statistical tests for this endpoint.

23. Other sec. EP: Time to 1st therapy.

23.1. Analysis set

This endpoint is analyzed exclusively for the final statistical analysis report based on the ITT analysis set.[120]

23.2. Variables

CIP Chapter 8.3.3.11 Time to 1st therapy

Assessment of the time from randomization to first therapy. In this context therapy is the attempted remediation of the patient's regular heartbeat. To ensure a standardized proceeding, guideline-based therapy recommendations will be provided to the participating investigators within a separate manual.

This endpoint comprises therapies reported in AE report CRF, irrespective of the cause of the patient being in the investigational site. The patient may be called in by an investigator after arrhythmias were detected in the BM or after a physician outside the investigational site assumed it appropriate to send the patient to a highly competent cardiological site. Changes of therapy prescribed by a general practitioner or another physician outside the investigational site are not considered.

Since the investigational sites are highly specialized cardiological units, it is not assumed that they will prescribe a relevant amount of non-cardiovascular therapies. All cardiovascular therapies will be considered for this endpoint, also if they are not directly relevant for the regular heartbeat as stated in the CIP. Especially, this also includes therapies directed at diuresis, blood pressure, coagulation status or ischemia, since all these treatments do also interact with the heart rhythm in some way.

Data file: Identifier record_id	Notes	Variable name	Variable label	Variable level	Nominal values
general_notification	No report	visit_date	Date of patient visit in investigational site	date	n.a.
general_notification_ data_SAR	No report	therapy_general_date	Date of the guideline-recommended change of therapy after an AE	date	n.a.

Data file: Identifier record_id	Notes	Variable name	Variable label	Variable level	Nominal values
arrhythmia_notification	No report	visit_date	Date of patient visit in investigational site	date	n.a.
arrhythmia_notification_ data_SAR	No report	therapy_arr_date	Date of the guideline-recommended change of therapy after an AE	date	n.a.

Data file: Identifier record_id	Notes	Variable name	Variable label	Variable level	Nominal values
adverse_events	No report	parent_record_id	NEW: Record ID of the parent document, i.e. the general notification CRF or arrhythmia notification CRF related to the AE CRF	nominal	…
adverse_events	No report	arrchange_yn	Does the arrhythmia require guideline-recommended change of therapy	nominal	Yes / No

[120] analysis_set_itt_SAR = Yes

Data file: Identifier patient_display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	No report	any_therapy_ITT_SAR[121]	Any therapy after effective randomization (attempted remediation of the patient's regular heartbeat) ITT	nominal	Yes / No
data_SAR	No report	date_1therapy_ITT_SAR [122]	Date of 1st therapy (attempted remediation of the patient's regular heartbeat) ITT	date	n.a.
data_SAR	descr.	days_effrand_to_ 1therapy_ITT_SAR[123]	Days from randomization to 1st therapy (attempted remediation of the patient's regular heartbeat) or termination ITT	scale	n.a.

23.3. Treatment of Missing and Spurious Data

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

23.1. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

23.2. Descriptive Analyses

If applicable, mean and median survival times are presented by using the Kaplan-Meier estimates. Kaplan-Meier survival figures are presented for illustration.

Other descriptive data will be presented via tables as specified in chapter 5.1.

23.3. Hypotheses & Statistical Tests

Differences of the survival curves BioMonitor versus control group are tested for statistical inference with the log-rank test.

The hazard ratio for the BioMonitor versus control group including 95%CI is calculated with the Cox regression model. In case of doubt about the validity of the Cox model, the assumption of proportional hazards is checked graphically by log-minus-log survival versus log–time plots.

24. Other sec. EP: Quality of Life / WHO-5 Well-being Index

24.1. Analysis set

This endpoint is analyzed exclusively for the final statistical analysis report based on the ITT analysis set.[124]

24.2. Variables

CIP Chapter 8.3.3.12 Quality of Life (QoL)

A further secondary endpoint is the assessment of the patient's quality of life. The patient's quality of life will be recorded during the regular telephone contacts using the WHO-5 Well-being Index.

Data file: Identifier record_ID	Notes	Variable name	Variable label	Variable level	Nominal values
who_five_ well_being_index	No report	interview_ interval	Interval (filled in automatically)	nominal	1. Quality of Life (6 M) 2. Quality of Life (12 M) 3. Quality of Life (18 M) 4. Quality of Life (24 M) 5. Quality of Life (30 M) 6. Quality of Life (36 M) 7. Quality of Life (42 M) 8. Quality of Life (48 M) 9. Quality of Life (54 M) 10. Quality of Life (60 M)
		q1_multi	I have felt cheerful and good spirits	ordinal	0,1,2,3,4,5
		q2_multi	I have felt calm and relaxed	ordinal	0,1,2,3,4,5
		q3_multi	I have felt active and vigorous	ordinal	0,1,2,3,4,5
		q4_multi	I woke up feeling fresh and rested	ordinal	0,1,2,3,4,5
		q5_multi	My daily life has been filled with things that interest me	ordinal	0,1,2,3,4,5

Data file: Identifier patient_display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	descr.	wbi_percscore_6m_SAR[125]	WBI percentage score: 6m	scale	0-100
data_SAR	descr.	wbi_percscore_12m_SAR[126]	WBI percentage score: 12m	scale	0-100
data_SAR	descr.	wbi_percscore_18m_SAR[127]	WBI percentage score: 18m	scale	0-100
data_SAR	descr.	wbi_percscore_24m_SAR[128]	WBI percentage score: 24m	scale	0-100
data_SAR	descr.	wbi_percscore_30m_SAR[129]	WBI percentage score: 30m	scale	0-100
data_SAR	descr.	wbi_percscore_36m_SAR[130]	WBI percentage score: 36m	scale	0-100
data_SAR	descr.	wbi_percscore_42m_SAR[131]	WBI percentage score: 42m	scale	0-100
data_SAR	descr.	wbi_percscore_48m_SAR[132]	WBI percentage score: 48m	scale	0-100
data_SAR	descr.	wbi_percscore_54m_SAR[133]	WBI percentage score: 54m	scale	0-100
data_SAR	descr.	wbi_percscore_60m_SAR[134]	WBI percentage score: 60m	scale	0-100
data_SAR	descr.	wbi_percscore_24m_6m_SAR[135]	WBI percentage score: Difference 24m vs. 6m	scale	-100 till 100
data_SAR	descr.	wbi_percscore_48m_6m_SAR[136]	WBI percentage score: Difference 48m vs. 6m	scale	-100 till 100

24.3. Treatment of Missing and Spurious Data

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

Missing data from a specific in hospital follow-up is imputed with the Last-Observation-Carry-Forward method, i.e. data from the nearest previous in-hospital follow-up, if available.

24.1. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

24.2. Descriptive Analyses

Descriptive data are presented via tables as specified in chapter 5.1.

24.3. Hypotheses & Statistical Tests

The percentage Well-Being Index for the 6m in-hospital FU, 24m in-hospital FU, 48m in-hospital FU, differences between 24m and 6m, and differences between 48m and 6m are analyzed BioMonitor versus control group with the Mann-Whitney-U test.

25. Data of Interest: Quality of Life / EQ-5D

25.1. Analysis set

This endpoint is analyzed exclusively for the final statistical analysis report based on the ITT analysis set.[137]

25.2. Variables

CIP Chapter 8.4 Further data of interest

In addition, the EQ-5D-5L questionnaire will be administered during the telephone contacts to estimate utility values at different time points for an economic evaluation.

Data file: Identifier record_id	Notes	Variable name	Variable label	Variable level	Nominal values
eq_5d_5l_ questionnaire	no report	eq5d5l_interview_ interval	Interval (filled in automatically)	nominal	0. Quality of Life (Base) 1. Quality of Life (6 M) 2. Quality of Life (12 M) 3. Quality of Life (18 M) 4. Quality of Life (24 M) 5. Quality of Life (30 M) 6. Quality of Life (36 M) 7. Quality of Life (42 M) 8. Quality of Life (48 M) 9. Quality of Life (54 M) 10. Quality of Life (60 M)
	descr.	EQ5D5L_q1_mobility	health TODAY - MOBILITY	nominal	no problems walking slight problems walking moderate problems walking severe problems walking unable to walk
	descr.	EQ5D5L_q2_selfcare	health TODAY – SELF-CARE	nominal	no problems washing or dressing yourself slight problems washing or dressing yourself moderate problems washing or dressing yourself severe problems washing or dressing yourself unable to wash or dress yourself
	descr.	EQ5D5L_q3_usual_ activities	health TODAY – USUAL ACTIVITIES	nominal	no problems doing your usual activities slight problems doing your usual activities moderate problems doing your usual activities severe problems doing your usual activities unable to do your usual activities
	descr.	EQ5D5L_q4_pain_ discomfort	health TODAY – PAIN/ DISCOMFORT	nominal	no pain or discomfort slight pain or discomfort moderate pain or discomfort severe pain or discomfort extreme pain or discomfort
	descr.	EQ5D5L_q5_anxiety _depression	health TODAY –ANXIETY / DEPRESSION	nominal	not anxious or depressed slightly anxious or depressed moderately anxious or depressed severely anxious or depressed extremely anxious or depressed
	descr.	EQ5D5L_q6_health_ scale	Scale number indicating the respondent's 'health today'	metric	0-100

Data file: Identifier patient_display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
data_SAR	descr.	EQ5D5L_health_scale_bas_SAR[138]	EQ5D5L score: Baseline	scale	0-100
data_SAR	descr.	EQ5D5L_health_scale_6m_SAR[139]	EQ5D5L score: 6m	scale	0-100
data_SAR	descr.	EQ5D5L_health_scale_12m_SAR[140]	EQ5D5L score: 12m	scale	0-100
data_SAR	descr.	EQ5D5L_health_scale_18m_SAR[141]	EQ5D5L score: 18m	scale	0-100
data_SAR	descr.	EQ5D5L_health_scale_24m_SAR[142]	EQ5D5L score: 24m	scale	0-100
data_SAR	descr.	EQ5D5L_health_scale_30m_SAR[143]	EQ5D5L score: 30m	scale	0-100
data_SAR	descr.	EQ5D5L_health_scale_36m_SAR[144]	EQ5D5L score: 36m	scale	0-100
data_SAR	descr.	EQ5D5L_health_scale_42m_SAR[145]	EQ5D5L score: 42m	scale	0-100
data_SAR	descr.	EQ5D5L_health_scale_48m_SAR[146]	EQ5D5L score: 48m	scale	0-100
data_SAR	descr.	EQ5D5L_health_scale_54m_SAR[147]	EQ5D5L score: 54m	scale	0-100
data_SAR	descr.	EQ5D5L_health_scale__60m_SAR[148]	EQ5D5L score: 60m	scale	0-100

25.3. Treatment of Missing and Spurious Data

Spurious data, which were not clarified by the query process before CDMS closure, are indicated. If appropriate, descriptive and inferential analyses are performed both with /without such data.

25.1. Exclusion of Particular Information

No data from the previous defined analysis set are excluded from the analysis except those defined in chapter 5.5, if applicable.

25.2. Descriptive Analyses

Descriptive data are presented via tables as specified in chapter 5.1.

25.3. Hypotheses & Statistical Tests

There are no pre-specified hypotheses.

[redacted]

Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
CDMS	Clinical Data Management System
CI	Confidence Interval
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CRF	Case Report Form
CV	Cardio vascular
DSMB	Data Safety Monitoring Board
EAEC	Endpoint and Adverse Event Board
ECG	Electrocardiogram
FU	Follow-up
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Statistical Analysis Report
SOP	Standard Operating Procedure
SD	Standard Deviation