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1. Introduction

1.1. Aim

The aim of this document is to provide detailed instructions on all descriptive and inferential statistical analyses for the 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 CIR.

1.2. General information

The text contains verbatim excerpts from the CIP. Such excerpts are italicized with grey background; e.g.

CIP chapter 7.1 Objectives
This study is designed as a post-market clinical follow-up study to identify and evaluate residual risks associated with the use of the BIOMONITOR III system that are discovered or remain even after risk analysis, risk mitigation and successful conformity assessment. The results will be used to update the clinical evaluation. Furthermore, the study will also provide additional data as required by regulatory authorities outside of the CE-region.

The main aspects and the design of the clinical investigation are presented in chapters 0-4.

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 6.

Specific analysis sets are defined in chapter 0.

Descriptive and inferential statistical analyses are handled in following chapters.

Thereby the following statistical considerations are specified:

- Definition of the analysis set for the following analyses, 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.
- Descriptive analyses including tables and figures
- Statistical alternative hypothesis/hypotheses (HA) to analyze the above endpoint(s) if available.
- Statistical tests intended to analyze the above hypothesis/hypotheses if available.

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") additionally, a new data file ("data_SAR") is 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)
- Descriptive — Information whether data has to be presented with descriptive methods as defined in the following sub-chapter ("Yes") or data needed for generating of derived variables only ("No")
- Variable name — Original name of a variable in the CDMS data file or name of a derived variables (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"); values might be omitted or shortened ("…") if remaining clear; for numeric data this information is not applicable (n.a.)

Data file, identifier patient_display_id_full	Descriptive	Variable name	Variable label	Variable level	Nominal values

2. Objectives

CIP chapter 7.1 Objectives

This study is designed as a post-market clinical follow-up study to identify and evaluate residual risks associated with the use of the BIOMONITOR III system that are discovered or remain even after risk analysis, risk mitigation and successful conformity assessment. The results will be used to update the clinical evaluation. Furthermore, the study will also provide additional data as required by regulatory authorities outside of the CE-region.

3. Investigational Device

CIP chapter 4 Investigational device

The devices used in this clinical investigation are the following BIOTRONIK devices:

- *BIOMONITOR III incl. Incision Tool and Insertion Tool (FIT OneStep)*
- Programmer devices ICS 3000 or Renamic
- Programmer Software PSW 1901.A/S
- CardioMessenger (different models)
- Remote Assistant III

4. Study Design & Time Course

CIP chapter 8.1 General considerations

The BIO|MASTER.BIOMONITOR III is designed as an open, prospective, single arm, non-randomized international study.

CIP chapter 8.1.4 Methods

During the course of the study, all clinical procedures are performed according to clinical routine. All parameters and measurements that are recorded within the study are described in this section and are documented on the following electronic Case Report Forms (eCRFs). The corresponding time schedule is described in section 9.1:

- *Enrollment*
- *Baseline*
- *Medical History*
- *Insertion*
- *1st follow-up*
- *3-month follow-up*
- *12-month follow-up*
- *Adverse Event*
- *Device Deficiency*

- *Device Log*
- *Explantation/Deactivation*
- *Concomitant Medication Log*
- *Deviation Log (site)*
- *Device Accountability Details (for Australia only)*
- *Termination*

5. General Statistical Procedures

5.1. Descriptive analyses

CIP chapter ...

...

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

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

Nominal – dichotomous data

Variable (N total = 10)	Category	N non-missing	Absolute frequency	Relative frequency [%]
Sex	Female	9	5	55.6
History of AF	Yes	8	4	50.0

Variable (N total = 10)	Category	Group Randomization group	N non-missing	Absolute frequency	Relative frequency [%]
Sex	Female	Control (N group = 3)	3	2	66.7
		Therapy 1 (N group = 4)	4	3	75.0
		All	9	5	55.6
History of AF	Yes	Control	2	0	0.0
		Therapy 1	4	3	75.0
		All	8	4	50.0

Nominal data – more than two categories

Variable (N total = 10)	N non-missing	Very good N(%)	Good N(%)	Medium N(%)	Poor N(%)
Patient self assessment at enrollment	7	2 (28.6%)	2 (28.6%)	1 (14.3%)	2 (28.6%)
Patient self assessment at 12m FU	8	1 (12.5%)	3 (37.5%)	3 (37.5%)	1 (12.5%)

Variable (N total = 10)	Group Randomization group	N non-missing	Very good N(%)	Good N(%)	Medium N(%)	Poor N(%)
Patient self assessment at enrollment	Control (N group = 3)	2	1 (50.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
	Therapy 1 (N group = 4)	3	0 (0.0%)	1 (33.3%)	1 (33.3%)	1 (33.3%)
	All	7	2 (28.6%)	2 (28.6%)	1 (14.3%)	2 (28.6%)
Patient self assessment at 12m FU	Control	2	0 (0.0%)	1 (50.0%)	1 (50.0%)	0 (0.0%)
	Therapy 1	4	0 (0.0%)	2 (50.0%)	1 (25.0%)	1 (25.0%)
	All	8	1 (12.5%)	3 (37.5%)	3 (37.5%)	1 (12.5%)

Scale / metric data

Variable (N total = 10)	N non-missing	Mean	SD	Min	Lower quartile	Median	Upper quartile	Max
Age [years]	7	51.7	15.0	25.0	40.0	57.0	60.0	70.0
Height [cm] as measured at enrollment	8	177.3	14.4	150.0	170.0	179.0	187.5	195.0

Variable (N total = 10)	Group Randomization group	N non-missing	Mean	SD	Min	Lower quartile	Median	Upper quartile	Max
Age [years]	Control (N group = 3)	2	55.0	7.1	50.0	50.0	55.0	60.0	60.0
	Therapy 1 (N group = 4)	3	56.7	15.3	40.0	40.0	60.0	70.0	70.0
	All	7	51.7	15.0	25.0	40.0	57.0	60.0	70.0
Height [cm] as measured at enrollment	Control	3	183.3	10.4	175.0	175.0	180.0	195.0	195.0
	Therapy 1	3	175.0	21.8	150.0	150.0	185.0	190.0	190.0
	All	8	177.3	14.4	150.0	170.0	179.0	187.5	195.0

Ordinal data

Variable (N total = 10)	N missing	Min	Lower quartile	Median	Upper quartile	Max
NYHA class enrollment	2	1.0	1.0	1.0	2.5	4.0
NYHA class 24m	3	1.0	1.0	1.0	3.0	4.0

Variable (N total = 10)	Group Randomization group	N non-missing	Min	Lower quartile	Median	Upper quartile	Max
NYHA class enrollment	Control (N group = 3)	3	1.0	1.0	1.0	3.0	3.0
	Therapy 1 (N group = 4)	4	1.0	1.0	1.5	3.0	4.0
	All	8	1.0	1.0	1.0	2.5	4.0
NYHA class 24m	Control	2	1.0	1.0	2.0	3.0	3.0
	Therapy 1	3	1.0	1.0	2.0	4.0	4.0
	All	7	1.0	1.0	1.0	3.0	4.0

5.2. Inferential analyses

For the primary endpoint, a one-sample one-tailed binomial test will be carried out. Furthermore, a 95% confidence interval (Wilson-score method) for the SADE-free rate will be calculated. Hence, a Kaplan-Meier curve will be plotted.

Since all secondary endpoints are hypothesis-free, no inferential statistics will be carried out. Nonetheless, 95% confidence intervals for the respective parameters will be calculated.

5.3. Significance level

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

The significance level alpha is 0.025, the power is set to 90%.

A one-sided p-value < 0.025 is considered to indicate statistical significance. No adjustment for multiple testing is foreseen, i.e. all analyses except those related to the primary endpoint are considered to be exploratory.

5.4. Missing Data

CIP chapter 11.11 Handling of missing, unused and spurious data

Missing or spurious data will not be imputed and not be used for analysis. More details will be specified in the SAP.

Missing data will not be imputed. Free text will be used to clarify other data.
Spurious data will be clarified via the query management, i.e. corrected after approval of an investigator. Remaining outliers will be identified during the review of the data before data base closure and will be reported in the Blind Review Report. In case of a clear evidence of a measurement error, the Statistical Analysis Plan will be updated in order to avoid any bias. Spurious data, which were not clarified by the query process before database closure, will be indicated. If appropriate, analyses will be performed both with /without such data.

5.5. Exclusion of data from confirmatory data analysis

CIP chapter 11.12 Exclusion of data from the confirmatory data analysis

In the following cases, data are to be excluded from analysis of the primary endpoint:
•No data are allowed to be collected and included in the absence of a documented consent.
•Data of patients will be excluded from analysis in case a patient terminates the study prior to any insertion attempt.

•Patients without primary endpoint but premature study termination earlier than 77 days after insertion (91 days = 3 month minus 14 days tolerance) are not included in the analysis set to avoid an over-estimation of the SADE-free rate.

•Any event that occurred later than the pre-specified time window for the 3-month follow-up in patients who did not have a 3-month follow-up (91 days plus 14 days tolerance = 105 days) does not contribute to the primary endpoint.

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

The analysis will use all data that are stored in the study database. It is in the responsibility of the persons entering data and of those checking data before the final data export that the data comply with the approval of the patient.

5.6. Subgroups

CIP chapter 11.9 Specification of subgroups

No subgroups are defined.

5.7. Interim analyses

CIP chapter 11.6: Provisions for an interim analysis

The main differences between BioMonitor 2 and BIOMONITOR III are limited to a reduced device size and a novel simplified injection-like insertion procedure. The focus of this study is primarily on the safety of the BIOMONITOR III system including the insertion procedure.

Therefore the primary endpoint is to evaluate the SADE-free rate related to the BIOMONITOR III and the incision and insertion tool set from insertion until the 3-month follow-up. When all enrolled patients have either completed the 3-month follow-up or their study participation has been terminated, the data for the primary endpoint are completed. At this point in time, an interim Clinical Investigation Report will be written. The content of this report will be pre-defined in a Statistical Analysis Plan.

Individual data collected in this study, which do not concern the primary endpoint, may be analysed before the study is completed. If they shall be published, the stipulations of section 21 apply. Safety reasons, the support of regulatory submissions and publication opportunities may trigger unscheduled interim analyses.

Such unplanned interim analyses and reports, if any, will contain at least descriptive statistics of baseline and insertion data and descriptive statistics of the defined endpoints. Inferential statistics of endpoints may be included to support publication activities. The precise scope of each interim analysis will be defined in the SAP before the individual interim analyses.

In case of a suspension of the clinical investigation, an interim analysis will be performed to generate a clinical investigation report according to the MDR requirements. No multiplicity adjustment is foreseen.

5.8. Software

All analyses will be carried out using validated software, e.g. SAS version 9.4 or upgrades.

6. Specific Study Dates

6.1. Enrollment date

Data file, identifier patient_display_id_full	Variable name	Variable label	Variable level	Nominal values
enrollment	DMICDT	Patient: Date of IC signature	date	n.a.

6.2. Insertion date

Data file, identifier patient_display_id_full	Variable name	Variable label	Variable level	Nominal values
insertion	PRIMSTDT	Date of insertion procedure	date	n.a.

6.3. Termination date

Data file, identifier patient_display_id_full	Variable name	Variable label	Variable level	Nominal values
termination	DSTRDT	Date of study termination	date	n.a.

7. Analysis Sets

7.1. Full Analysis Set

[redacted]

Data file, identifier patient_ display_id_full	Variable name	Variable label	Variable Level	Nominal values	Notes
enrollment	DMSUBSPS	Patient signed the informed consent personally	Nominal	Yes No	
enrollment	DMRPRSPS	An independent witness signed the informed consent since the patient is unable to write	Nominal	Yes No	
dataSAR	full_set_sar	All patients	Nominal	Yes No	

[redacted]

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

The following data shall be reported:

- Number of patients with enrollment data
- Number of enrollments per site
- Date of FPI, LPI, LPO per site and total
- Cumulative and mean/median FU duration from insertion to last available CRF information
- Cumulative and mean/median FU duration from enrollment to termination date on termination CRF

The following variables will be calculated:

Data file, identifier patient_ display_id_full	Variable name	Variable label	Variable Level	Nominal values
insertion	PRIMSTDT	Date of insertion	date	n.a.

enrollment	dmicdt	Date of informed consent	date	n.a.
Follow-up_1st	svstdt -> svstdt_fu1	Date of visit 1. FU	date	n.a.
Follow-up_3months	svstdt -> svstdt_fu3m	Date of visit 3 months FU	date	n.a.
Follow-up_12months	svstdt -> svstdt_fu12m	Date of visit 12 months FU	date	n.a.
hospitalization_log	hostdt	Hospitalization Start date	date	n.a.
data_sar	sar_hospstdt_first[1]	onset date of first hosp.	date	n.a.
data_sar	sar_hospendt_last[2]	date of resolution/death of last AE	date	n.a.
adverse_event	aestdt	Onset Date of AE	date	n.a.
data_sar	sar_aestdt_first[3]	onset date of first AE	date	n.a.
data_sar	sar_aeendt_last[4]	date of resolution/death of last AE	date	n.a.
termination	dstrdt	Date of study termination	date	n.a.
data_SAR	sar_last_crf[5]	Date of last CRF information	date	n.a.
data_SAR	sar_time_crf[6]	time [days] from insertion to last CRF	scale	
data_SAR	sar_time_term[7]	time [days] from insertion to termination	scale	
data_SAR	sar_time_max[8]	time [days] from insertion to termination or last CRF	scale	

For all patients with premature study duration or missing insertion or any violation of in-/exclusion criteria the following variables shall be listed:

- All in-/exclusion criteria
- Date of enrollment
- Date and reason of premature study termination
- Date and type of all other available CRFs (except for AE-CRFs)

[redacted]

9. General data

9.1. Analysis set

All analyses are performed for the full analysis set[9].

9.2. Variables

[redacted]

[redacted]

9.3. Treatment of Missing and Spurious Data

See general definitions in chapter 5.4

9.4. Exclusion of Particular Information

See general definitions in chapter 5.5

No data are excluded from the analysis from the above analysis set and variables.

9.5. Descriptive Analyses

See general definitions in chapter 5.1 and exceptions for reporting numbers and text below the variable tables, if appropriate.

9.6. Hypotheses & Statistical Tests

There are no pre-defined statistical hypotheses.

10. Primary Endpoint1

CIP chapter 7.2.1 - Primary endpoint and hypothesis

SADE-free rate until the 3-month follow-up

A primary endpoint is an SADE (see definition in section 18) that is possibly, probably or causally related to the BIOMONITOR III, the Incision Tool or the Insertion Tool, or the insertion procedure, which occurs before the 3-month follow-up.

SADEs will be adjudicated by an internal adjudication board, whereby the seriousness and device relatedness will be re-examined. If any amply documented external physical influence (e.g. accident, sport) or medical AE caused the SADE, it does not contribute to this endpoint. SADEs that occur later than the 3-month follow-up, and SADEs with onset date later than 105 days after insertion procedure (3 months defined as 91 days after implantation + 14 days would still be in accordance to the CIP) in case the 3-month follow-up was not conducted or conducted outside the specified time interval, do not contribute to this endpoint.

The parameter of interest is the SADE free rate, which will be calculated by

$$\frac{\text{Number of patients with one or more primary endpoint until the 3 months FU}}{\text{Number of patients at the 3 months FU or with primary endpoint}}$$

in percent. The period of observation starts with the insertion of the BIOMONITOR III and takes until the 3-month follow-up.

10.1. Analysis set

The number of patients with at least one primary endpoint until the 3 months FU (the numerator) will be determined by assessing the variable "AERELPET" in the "AE evaluation" form. This form is filled by the AE evaluation board and the variable "AERELPET" is set to "Yes" if and only if all conditions defined in 7.2.1 in the CIP are met.

The denominator will be calculated as follows:

1. The number of patients with 3 months FU will be counted by the number of non-missing entries in SVSTDT in the "3 month FU" form.
2. The number of patients with primary endpoint will be calculated as defined above.
3. In case of patients lying in the intersection of both sets, these patients will be counted once.
4. Patients without SADE and termination date less than 77 days after insertion will be disregarded.

Patients who do not attend the 3 months FU, but who have not terminated study participation earlier than 77 days after insertion will be included in the analysis.

For the calculation of the Kaplan-Meier analysis, the following time variables will be used:

1. For patients with at least one primary endpoint: time from insertion to time of first primary endpoint [redacted]
2. For patients without primary endpoint: time from insertion to last information available [redacted]

For the KM analysis data of all patients is used.

10.2. Variables

Data file, identifier patient_ display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
AE evaluation	sorted by patient_ display_id_ full and AESTDT and removed duplicates	AERELPET	Adverse event is relevant for primary endpoint	nominal	Yes No
3-month FU		SVSTDT	Date of visit	date	
3-month FU		sar_3mFU_available [10]	3m FU available?	nominal	Yes No
Termination		sar_term_77[11]	Termination less than 77 days after insertion?	nominal	Yes No

10.1. Treatment of Missing and Spurious Data

See general definitions in chapter 5.4

10.2. Exclusion of Particular Information

See general definitions in chapter 5.5

No data are excluded from the analysis from the above analysis set and variables.

10.3. Descriptive Analyses

See general definitions in chapter 5.1 and exceptions for reporting numbers and text below the variable tables, if appropriate.

Furthermore a Kaplan-Meier analysis (including Kaplan-Meier plot) will be calculated and the estimation of the SADE-free rate (including two-sided 95% confidence interval) at 3 months (= 90 days) will be given.

10.4. Hypotheses & Statistical Tests

Null hypothesis: $H_0: \quad p_{SADE} \leq 90\%$

Alternative hypothesis: $H_A: \quad p_{SADE} > 90\%$

The hypothesis will be tested by using an exact binomial test against the value of 0.9. An exact two-sided confidence interval for the SADE-free rate.

[redacted]

11. Secondary Endpoint1

CIP chapter 7.2.2: Secondary endpoints

R-wave amplitude
The secondary endpoint 1 evaluates the R-wave amplitude at the 1st follow-up and at 3-month follow-up by measuring both, the lowest and the highest amplitude value via the programmer.

The secondary endpoint "R-wave amplitude" will be calculated as the mean value from the lowest and the highest amplitude.

11.1. Analysis set

All analyses are performed for the full analysis set[12].

11.2. Variables

Data file, identifier patient_ display_id_full	Notes	Variable name	Variable label	Variable level
insertion		DUHLRWA -> DUHLRWA_ins	Highest amplitude value [mV]	Scale
insertion		DULLRWA -> DULLRWA_ins	lowest amplitude value [mV]	Scale
insertion		DULRWA_ins_m[13]	mean of highest and lowest value [mV]	Scale
follow_up_1st		DUHLRWA -> DUHLRWA_fu1	Highest amplitude value [mV]	Scale
follow_up_1st		DULLRWA -> DULLRWA_fu1	lowest amplitude value [mV]	Scale
follow_up_1st		DULRWA_fu1_m[14]	mean of highest and lowest value [mV]	Scale
follow_up_3months		DUHLRWA -> DUHLRWA_fu3	Highest amplitude value [mV]	Scale
follow_up_3months		DUHLRWA -> DULLRWA_fu3	lowest amplitude value [mV]	Scale
follow_up_3months		DULRWA_fu3_m[15]	mean of highest and lowest value [mV]	Scale
follow_up_12months		DUHLRWA -> DUHLRWA_fu12	Highest amplitude value [mV]	Scale
follow_up_12months		DUHLRWA -> DULLRWA_fu12	lowest amplitude value [mV]	Scale
follow_up_12months		DULRWA_fu12_m[16]	mean of highest and lowest value [mV]	Scale

[redacted]

11.1. Treatment of Missing and Spurious Data

See general definitions in chapter 5.4

[redacted]

11.2. Exclusion of Particular Information

No data are excluded from the analysis from the above analysis set and variables.

11.3. Descriptive Analyses

See general definitions in chapter 5.1 and exceptions for reporting numbers and text below the variable tables, if appropriate.

In addition, boxplots will be generated.

11.4. Hypotheses & Statistical Tests

There are no pre-defined statistical hypotheses.

12. Secondary Endpoint2

CIP chapter 7.2.2: Secondary endpoints

Noise burden

The secondary endpoint 2 evaluates the noise burden at the 1st follow-up and at 3-month follow-up by retrieving the percentage of noise via the programmer.

12.1. Analysis set

All analyses are performed for the full analysis set[17].

12.2. Variables

Data file, identifier patient_ display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
follow_up_1st		DUNSE	Noise [%]	Scale	
follow_up_3months		DUNSE	Noise [%]	Scale	
follow_up_12months		DUNSE	Noise [%]	Scale	

Moreover, the proportions of patients with "Noise smaller 5% vs. at least 5%" will be reported for the 1 month FU, 3 months FU and 12 months FU separately and in total (all FU together). Therefore the variable "DUNSE" will be recoded accordingly.

12.1. Treatment of Missing and Spurious Data

See general definitions in chapter 5.4

12.2. Exclusion of Particular Information

No data are excluded from the analysis from the above analysis set and variables.

12.3. Descriptive Analyses

See general definitions in chapter 5.1 and exceptions for reporting numbers and text below the variable tables, if appropriate.

In addition, boxplots will be generated.

12.4. Hypotheses & Statistical Tests

There are no pre-defined statistical hypotheses.

[redacted]

13. Secondary Endpoint3

CIP chapter 7.2.2: Secondary endpoints

Assessment of P-wave visibility

The secondary endpoint 3 evaluates the P-wave visibility at 1st, 3- and 12-month follow-up. The investigator will evaluate whether P-waves can be recognized in the stored sECGs showing sinus rhythm. The number of heart cycles and observed P-waves which can undoubtly be identified in ECGs will be assessed by the investigator.

13.1. Analysis set

All analyses are performed for the full analysis set[18].

[redacted]

13.2. Variables

Data file, identifier patient_ display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
follow_up_1st		EGCCCNUM01	Exact number of cardiac cycles	Scale	
follow_up_1st		EGPWNUM01	Exact number of clearly identifiable P-waves	Scale	
sar_data		sar_pwavevis_fu1_1[19]	P-wave visibility FU1 1st [%]		
follow_up_1st		EGCCCNUM02	Exact number of cardiac cycles	Scale	
follow_up_1st		EGPWNUM02	Exact number of clearly identifiable P-waves	Scale	
sar_data		sar_pwavevis_fu1_2[20]	P-wave visibility FU1 2nd [%]		
sar_data		sar_pwavevis_fu1_tot[21]	P-wave visibility pooled [%]		

[redacted]

follow_up_3months		EGCCCNUM -> EGCCCNUM_3m	Exact number of cardiac cycles	Scale	
follow_up_3months		EGPWNUM -> EGPWNUM_3m	Exact number of clearly identifiable P-waves	Scale	
sar_data		sar_pwavevis_fu3[22]	P-wave visibility 3m [%]		
follow_up_12months		EGCCCNUM -> EGCCCNUM_12m	Exact number of cardiac cycles	Scale	
follow_up_12months		EGPWNUM -> EGPWNUM_12m	Exact number of clearly identifiable P-waves	Scale	
sar_data		sar_pwavevis_fu12[23]	P-wave visibility 12m [%]		
sar_data		sar_pwavevis_tot[24]	P-wave visibility total [%]		

13.3. Treatment of Missing and Spurious Data

See general definitions in chapter 5.4

[redacted]

13.4. Exclusion of Particular Information

No data are excluded from the analysis of the above analysis set and variables.

Also data from the 3 months and 12 months FU which are outside the defined time range will be considered her.

13.5. Descriptive Analyses

See general definitions in chapter 5.1 and exceptions for reporting numbers and text below the variable tables, if appropriate.

In addition, boxplots will be generated.

Moreover, the rate of patients with a P-wave visibility of at least 5% shall be reported for each follow-up separately and the number of patients with a P-wave visibility of at least 5% at all available follow-ups shall be reported.

13.6. Hypotheses & Statistical Tests

There are no pre-defined statistical hypotheses.

14. Secondary Endpoint4

CIP chapter 7.2.2: Secondary endpoints

SADE-free rate until the 12-month follow-up

The secondary endpoint 4 is the SADE-free rate related to the BIOMONITOR III 12 months after insertion.

[redacted]

14.1. Analysis set

All analyses are performed for the full analysis set[25].

For the calculation of the Kaplan-Meier analysis, the following time variables will be used:

1. For patients with at least one primary endpoint: time from insertion to time of first primary endpoint (sar_aestdt_first).
2. For patients without primary endpoint: time from insertion to last information available (sar_time_max).

For the KM analysis data of all patients is used.

14.2. Variables

Data file, identifier patient_ display_id_full	Notes	Variable name	Variable label	Variable level	Nominal values
AE evaluation	sorted by patient_ display_id_ full and AESTDT and removed duplicates	AERELPET	Adverse event is relevant for primary endpoint	nominal	Yes No

14.3. Treatment of Missing and Spurious Data

See general definitions in chapter 5.4

14.4. Exclusion of Particular Information

No data are excluded from the analysis from the above analysis set and variables.

[redacted]

14.5. Descriptive Analyses

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A Kaplan-Meier analysis (including Kaplan-Meier plot) will be calculated and the estimation oft he SADE-free rate (including two-sided 95% confidence interval) at 12 months (= 365 days) will be given.

14.6. Hypotheses & Statistical Tests

There are no pre-defined statistical hypotheses.

15. Data of Interest

CIP chapter .7.5 Further data of interest

Beyond the objectives defined in section 7.1, the study is designed to collect further data of interest. The data on the following topics will be considered `data of interest´ and may be analyzed, as appropriate:

- Demographics
- Medical history
- Indication for ICM
- Usage of incision tool and assessment of incision tool handling
- Assessment of insertion procedure: performance of insertion tool and ease of use (e.g. insertion time, handling and positioning)
- Insertion site
- Insertion success rate
- Wound closure
- Positioning of BIOMONITOR III
- Comfort after wound healing
- Explantation data of BIOMONITOR III
- Additional implantation of BIOMONITOR III
- Serial number of used study devices
- Performance of arrhythmia detection (will be assessed by comparing the BIOMONITOR III detected arrhythmia episodes recorded against a 48-hour Holter ECG, if applicable)
- Syncope and AF: detailed analysis of sensing performance in device-triggered ECG-episodes
- AF burden
- Assessment of device programming: individualized programming and re-programming of the device
- Assessment of programmer and programmer software performance
- Remote Assistant III trigger success rate after insertion procedure
- Home Monitoring Data (e.g. transmission success)
- HM workflow efficiency

Assessment of BIOMONITOR III repositioning (if applicable)

- Assessment of BIOMONITOR III migration (if applicable)
- Usability of Patient App (if applicable)
- Information on application of imaging techniques, if applicable (e.g. MRI, mammography)
- Diagnosis and further treatment
- Adverse events and device deficiencies

The topics "demographics", "medical history", and "indication for ICM" are already included in chapter 9.

[redacted]

"Adverse events and device deficiencies" will be reported as provided by the safety report from the vigilance department.

The topics "arrhythmia detection performance", "sensing performance in device triggered ECG episodes" and all analyses based on Home Monitoring data are beyond the scope of this document.

15.1. Analysis set

All analyses are performed for the full analysis set[26].

15.2. Variables

15.2.1 Data of interests derived from the insertion CRF only:

This includes the following data of interest:

- Usage of incision tool and assessment of incision tool handling
- Assessment of insertion procedure: performance of insertion tool and ease of use (e.g. insertion time, handling and positioning)
- Insertion site
- Insertion success rate
- Wound closure
- Positioning of BIOMONITOR III
- Remote Assistant III trigger success rate after insertion procedure (for all patients and split by BMI with a cut-off of 30)
- Assessment of BIOMONITOR III repositioning (if applicable)

[redacted]

15.2.2 Data of interests derived from the insertion CRF and the FU CRFs:

This includes the following data of interest:

- Assessment of device programming: individualized programming and re-programming of the device
- Assessment of programmer and programmer software performance

15.2.3 Data of interests derived from the FU-CRFs:

This includes the following data of interest:

- Comfort after wound healing
- Usability of Patient App (if applicable)
- Information on application of imaging techniques, if applicable (e.g. MRI, mammography)

15.2.4 Data of interests derived from the FU-CRFs and the CRF "Deactivation/Explantation" and FU

This includes the following data of interest:

- Assessment of BIOMONITOR III migration (if applicable)I

[redacted]

15.2.5 Data of interests derived from the CRFs "Deactivation/Explantation" only

This includes the following data of interest:

- Explantation data of BIOMONITOR III
- Diagnosis and further treatment
- Additional implantation of BIOMONITOR III

In addition to the descriptive reporting of the parameters related to diagnosis and further treatment, a case-by-case listing shall be provided for all patients with a deactivation or explantation. This listing shall contain the following variables:

Baseline CRF:

CEINDICM	Primary type of ICM indication
COINDICM	Specification of other primary type of ICM indication

Deactivation/Explantation CRF:

DXEXREA	Reason for explantation/deactivation
PRDGNDT	Date of diagnosis
DUBMDGN	Did the BIOMONITOR III contribute to this diagnosis?
DUBMDGNA	How did the BIOMONITOR III contribute to the diagnosis?
CVARTYP	Specify arrythmia type detected
QSFTRT01	Ablation procedure
QSABPR	Specify the ablation procedure
QSFTRT02	Medication
QSCM01	Anticoagulation
QSCM02	Antiarrhythmics
QSCMOTH	Other
QSFTRT03	ICD implantation
QSFTRT04	Pacemaker implantation
QSFTRTOT	Other
QSBMU	Further use of the BIOMONITOR III

15.1. Treatment of Missing and Spurious Data

See general definitions in chapter 5.4

15.2. Exclusion of Particular Information

See general definitions in chapter 5.5

No data are excluded from the analysis from the above analysis set and variables.

15.3. Descriptive Analyses

See general definitions in chapter 5.1 and exceptions for reporting numbers and text below the variable tables, if appropriate.

15.4. Hypotheses & Statistical Tests

There are no pre-defined statistical hypotheses.

References

References for specific statistical procedures

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
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