Protocol Modification Notification

Date: April 06, 2021

To: BIOGUARD-MI Clinical Study Sites

From: [redacted]

CC: BIOTRONIK BIOGUARD-MI Study Team

FCSEs and RCRAs

Applicable BIOTRONIK Study Field Personnel

Date of previous protocol: 12 June 2019

The BIOGUARD-MI study aims to investigate whether continuous arrhythmia monitoring and detection, using an ICM (BioMonitor 2 or market released successor, hereafter referred to as BioMonitor) in patients after a myocardial infarction (MI) with LVEF > 35% but with other cardiovascular risk factors, decreases the risk of MACE if patients are appropriately examined and treated for the observed arrhythmias. The population selected for this clinical investigation is expected to have an increased risk of cardiac arrhythmias. It is expected that the BioMonitor will facilitate early diagnosis of cardiac arrhythmias and result in treatment of the arrhythmias or other cardiac conditions that may present, to prevent clinical endpoints and disease progression. This study will enroll up to 2900 subjects at up to 80 clinical study sites worldwide. Up to 360 subjects at up to 20 study sites are planned within the United States.

Date of protocol amendment: April 06, 2021

Description of protocol changes:

Implementation of final study termination visit:

Changes are made to implement an in-office final study termination visit for all active subjects within 2021. After a complete medical record review for adverse events, the study personnel will interview the subject about any adverse events that occurred during study participation. Additionally, the interview may be supported by obtaining additional information about adverse events from family members, primary care providers or other hospitals where care was provided.

At the study termination visit, NYHA classification, recording of current cardiovascular medications, and a subject interview will be performed to analyze the data regarding the change in health status of the subjects in both groups.

Statistical changes:

The statistics section has been updated in accordance with change of the subject visit schedule. By triggering the termination phase with this protocol amendment, the study protocol deviates from the initial planned study concept which defined a specific number of primary endpoints prior to study termination.

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 final analysis of all data after study completion. An interim analysis has been conducted according to the initial strategy, and the influence of this interim analysis on the alpha-error will be considered to maintain the pre-planned global alpha error. The first interim analysis was conducted according to the initial statistical plan. The planned second

interim analysis will not be done. Due to the O'Brien Fleming design with a very low $\alpha_{interim1}$ = 0.00025 for the first interim analysis, an adjusted significance level for the final analysis: α_{final} = 0.02476 will maintain the global 1-sided significance level α= 0.025.

With the implementation of the protocol amendment dated April 06, 2021, the intended number of endpoints may not be reached.

Update of authorship criteria:

The authorship guidelines have been updated. The scoring system for determination of authorship has been changed and will consider four components:

- ➔ Enrollment of patients,
- ➔ Prompt classification of arrhythmias detected by the ICM,
- ➔ Unhesitating contact to the patient, and
- ➔ Conducting an in-office termination visit.

Rationale for changes:

Implementation of final study termination visit:

Based on the results of the first pre-specified interim analysis conducted in March 2020, the DSMB expressed concerns about a potential imbalance in adverse event reporting due to the more frequent investigator contacts of patients with an implantable cardiac monitor which may have a direct impact on the primary study outcome. Consequently, the DSMB requested the Steering Committee and the sponsor identify the root cause of the reporting bias and amend the study protocol accordingly. Based on this unforeseen development the sponsor decided to suspend subject enrollment which was communicated to sites on April 22, 2020.

Since the DSMB recommendation, the sponsor and the Steering Committee have been working to determine reasons for this potential underreporting. During this data analysis, there was some evidence of local differences in the number of reported adverse events between some sites, as well as between countries.

After the events described above, monitoring efforts were intensified at study sites outside of the U.S. which identified a number of unreported events, but failed to reduce the reporting bias substantially. This remaining bias, along with delays between adverse event onset and reporting, led to the conclusion that treatment group subjects may have a stronger tendency (than control group subjects) to visit the study site for cardiac care.

In January 2021, the Steering Committee and DSMB agreed with the approach to implement in-person termination visits for all active study participants. Conducting in-person termination visits at the study site is intended to complement the regular phone calls used to identify all adverse events and has been identified as being a crucial step to support an unbiased assessment of the primary study objective. The termination visit is intended to establish complete adverse event reporting and therefore do not extend the range of collected data, but rather increase data completeness and quality.

Statistical changes:

The original plan 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.

Protocol Modification Notification

As it was decided to enter the termination phase without any further delay, the intended number of endpoints may not be reached, and the study may be underpowered for the primary endpoint.

Steering Committee and sponsor determined that seeing all remaining subjects at a study termination visit takes precedence over a longer study period to capture the required number of endpoint events.

Update of authorship criteria:

The authorship criteria were updated to further define specific reactions to Home Monitoring that will be evaluated as prompt classification of arrhythmias and consecutive contact with subjects is critical for the study concept to be effective. In addition, conducting the in-office termination visit for all active subjects was added as this is important for a complete adverse event reporting.

Impact of changes:

As noted above, the decision to move into the termination phase and complete the analysis after study completion instead of after the required number of endpoint events may result in the study being underpowered for the primary endpoint analysis. However, the scientific intent of the study is not altered. The in-person termination visit does not impact the subject's rights, safety, or welfare, there are no changes to the benefits or risks to the study participants. The noted protocol changes also have no effect on the study devices or study medical procedures. The IDE risk remains unchanged from previously being determined as a significant risk study.

FDA and IRB Review Requirements:

The noted change includes an early study termination, an update of the study design, and change to statistical analysis plan. According to the FDA guidance "Changes or Modifications During the Conduct of a Clinical Investigation; Final Guidance for Industry and CDRH Staff", FDA approval may be required for protocol changes impacting the subject number and study termination as this may impact the scientific soundness of the study. Additionally, as the primary endpoint analysis may be impacted by the early study termination, approval by FDA is required prior to implementation of the protocol change as well as full board IRB approval.

No changes of the ICF are required.

Table 1: Summary of Protocol Changes

BIOGUARD-MI Protocol (Version 12 JUN 2019)	**BIOGUARD-MI Protocol Amendment** (Version 06 APR 2021)
Summary Study duration: The follow-up period of the individual subject is dependent on the time of entry into the study. All study subjects will be followed until the number of needed endpoints for the final analysis is reached or the DSMB determines a premature study termination.	*Summary Study duration:* The follow-up period of the individual subject is dependent on the time of entry into the study. All study subjects will be followed until completion of the final study termination visit or the sponsor determines a premature study termination after consultation with the DSMB and Steering Committee.

Protocol Modification Notification

Summary Follow-up scheme **Termination** • Final subject contact, either via office visit or telephone contact	*Summary Follow-up scheme* **Final Study Termination Visit** • Final subject in-office visit at the site.
Section 4: Study Design The second phase is currently planned to last until approximately 2021. As study stop will be announced once the required number of endpoints is reached, the individual time for subject participation depends on time of enrollment of the subject in the study. As U.S. subjects will start in phase 2 of the study, the estimated individual subject study participation duration is between 0 and 35 months.	*Section 4: Study Design* The second phase is currently planned to last until approximately 2021. Study stop will be announced once all active subjects have completed their final study termination visit or as determined by the sponsor after consultation with the DSMB and Steering Committee.
Section 4: Study Design The follow-up period of the individual subject is dependent on the time of entry into the study. All subjects will be followed until the number of needed endpoints for the final analysis is reached or the DSMB determines a premature study termination.	*Section 4: Study Design* The follow-up period of the individual subject is dependent on the time of entry into the study. All subjects will be followed until a final study termination visit has been completed or the Sponsor determines a premature study termination after consultation with the DSMB and Steering Committee.
No section available	*New section 4.2.4: Final Study Termination Visit* All active subjects will be asked to visit the study site for a final study termination visit. After a complete subject medical record review for adverse events, the study personnel will interview the subject about any adverse events that occurred during study participation. Additionally, the interview may be supported by obtaining additional information about adverse events from family members, primary care providers or other hospitals where care was provided.
Section 6.1.1: Group sequential design The study is designed as a three-stage adaptive group sequential test procedure according to O'Brian Fleming with survival endpoint, where the inverse normal method	*Section 6.1.1: Statistical design* According to original statistical planning, the study was designed as a three-stage adaptive group sequential test procedure according to O'Brian Fleming with survival

is used to combine the separate stage information.	endpoint, where the inverse normal method is used to combine the separate stage information. This strategy is replaced with a final analysis of all data after study completion. An interim analysis has been conducted according to the initial strategy, and the influence of this interim analysis on the alpha-error will be considered to maintain the pre-planned global alpha error.
Section 6.1.4: 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.	*Section 6.1.4: Statistical methods* Inferential analysis of the primary hypothesis: A one-sided log-rank test is performed in the context of a confirmatory analysis of the primary hypothesis at the interim and the final analysis.
Section 6.2: Sample Size It is expected that there will be pC^{1year} = 5% subjects with at least one MACE per year in the control group and $pBioM^{1year}$ = 3.75% subjects with at least one MACE per year in the BioMonitor group, which results in a Hazard Ratio = 0.7452 in favour of the BioMonitor. According to the approximation of Schoenfeld 43 363 events are needed. However, there is a slight increase of the sample size due to the group-sequential design of O'Brien Fleming. The interim analyses and the final analysis should be conducted with 124, 248, and 372 subjects with at least one MACE during the clinical investigation, respectively. In total, up to 2900 subjects may be enrolled. The subject number of up to 2900 is based on an expected endpoint-rate of 5%/3.75% per subject year required to reach the study goal of 372 endpoint events. The subject number will be automatically adjusted in the event the endpoint rate deviates from the expected rate. All subjects will be followed until the end of the clinical investigation. The study	*Section 6.2: Sample Size* The original plan 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. With the implementation of the protocol amendment dated April 06, 2021, the intended number of endpoints may not be reached.

duration will be approximately 3 years, but ultimately study closure is dependent on when the number of needed endpoints for the final analysis is reached. This accounts also for loss of information due to drop-outs which remain in the analysis set. According to the adaptive group-sequential design, the sample size can also be adjusted after the first or second interim analysis based on the recommendations of the DSMB. However, the sponsor must confirm any sample size increase and has the right to refuse it. There is no adjustment of the significance value for stopping for futility.	
Section 6.3: Level of significance and the power of the study The global significance level is of the 1-sided hypothesis is 2.5%. The significance level of the interim analyses and final analysis is given by the O'Brien Fleming method: $\alpha_{interim1}$ = 0.00025, $\alpha_{interim2}$ = 0.007, and α_{final} = 0.0225.	*Section 6.3: Level of significance and the power of the study* The global significance level of the 1-sided hypothesis is 2.5%. 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 $\alpha_{interim1}$ = 0.00025 for the first interim analysis, an adjusted significance level for the final analysis: α_{final} = 0.02476 will maintain the global 1-sided significance level α= 0.025.
Section 6.7: Provision for an interim analysis There are two interim analyses based on 1/3 and 2/3 of the total number of subjects with at least one MACE.	*Section 6.7: Provision for an interim analysis* One interim analysis has been completed. No further interim analysis will be performed.
Section 6.8: Termination criteria The sponsor may decide to discontinue the study due to organizational reasons based on the observed event rates and the general feasibility of the study. Based on the recommendations of the DSMB for the study after the first and second interim analysis, the study will be stopped for futility when there is a low chance for rejection of the Alternative hypothesis at the final analysis or the need for an increase of the sample size, which is refused by the sponsor.	*Section 6.8: Termination criteria* The sponsor may decide to discontinue the study due to organizational reasons based on the observed event rates and the general feasibility of the study. Based on the recommendations of the DSMB for the study after the first interim analysis, the study will be stopped for futility when there is a low chance for rejection of the Alternative hypothesis at the final analysis or the need for an increase of the sample size, which is refused by the sponsor.

Protocol Modification Notification

Stopping for superiority is achieved in case the 1-sided p-value at the interim analyses is below the O'Brien Fleming significance values $\alpha_{interim1}$ = 0.00025 and $\alpha_{interim2}$ = 0.007, respectively.	Stopping for superiority is achieved in case the 1-sided p-value at the interim analyses is below the O'Brien Fleming significance value $\alpha_{interim1}$ = 0.00025.
Section 6.11: Procedure for accounting of all data for analysis Data exports from the Clinical Data Management System and the BIOTRONIK Clinical Data Warehouse with Home Monitoring data will be analyzed with common statistical software packages, e.g. SAS Version 9.3 or IBM SPSS Version 21 for Windows or higher.	*Section 6.11: Procedure for accounting of all data for analysis* Data exports from the Clinical Data Management System and the BIOTRONIK Clinical Data Warehouse with Home Monitoring data will be analyzed with common statistical software packages, e.g. SAS Version 9.4.
Section 7.1: Subject Population Every investigator can enroll as many subjects as desired until the sample size for the entire study has been reached.	*Section 7.1: Subject Population* By decision of the Steering Committee and the sponsor, enrollment was suspended on April 22, 2020.
Section 7.2: Electronic CRFs and Forms	*Section 7.2: Electronic CRFs and Forms* Added eCRF to listing after Discharge eCRF: • Termination visit eCRF
Section 7.2, Table 1: Overview eCRFs and Procedures	*Section 7.2, Table 1: Overview eCRFs and Procedures* Added required data collection in table for Termination: NYHA, Cardiovascular medication, Subject interview
Section 8: Study Procedures Subjects who have successfully been enrolled in the study will be evaluated at discharge, phone calls every 6 months and a termination visit.	*Section 8: Study Procedures* Subjects who have successfully been enrolled and are still active in the study will be evaluated at discharge, phone calls every 6 months, and a final study termination visit.
Section 8.8: Study Termination	*Section 8.8: Study Termination* Added new paragraph after current first paragraph: All active subjects will be asked to visit the study site for a final study termination visit. After a complete subject medical record review for adverse events, the study personnel will interview the subject about any adverse events that occurred during

	study participation. Additionally, the interview may be supported by obtaining additional information about adverse events from other sources, in accordance with local regulations, e.g. from family members, primary care providers or other hospitals where care was provided.
Section 9.2: Point of enrollment and study termination Regular point of termination for all subjects is the date when the formal study termination is announced.	*Section 9.2: Point of enrollment and study termination* Regular point of termination for the individual subject is the respective date of the final study termination visit.
Section 14.2: Reporting Deviations All deviations will be reported in the interim and final clinical investigation reports. BIOTRONIK, Inc. categorizes protocol non-compliance instances as either protocol violations or protocol deviations. Both protocol violations and deviations will be reported in the interim and final clinical progress reports.	*Section 14.2: Reporting Deviations* All deviations will be reported in the annual and final clinical investigation reports. BIOTRONIK, Inc. categorizes protocol non-compliance instances as either protocol violations or protocol deviations. Both protocol violations and deviations will be reported in the annual and final clinical progress reports.
Section 17.2.4: Justification and rules for the assessment of "acquisition of data" A scoring system will consider two components: enrollment of subjects and the complete documentation of the reaction to HM containing the classification of an arrhythmia detected by the ICM, the resulting subject contact and, if a change in therapy is indicated, also the documentation of the therapy changes. **Enrollment**: The importance of subject enrollment for the success of the study is obvious. All subjects are counted if they are randomized and included in the analysis population. **Reaction to HM**: The thoroughly conducted diagnostic work-up and consequent treatment, if required, after ICM detected arrhythmias is the mechanism by which the study attempts to improve the outcome in the treatment arm. Since the study does not enforce therapy, documented cases of arrhythmia and subject contact will be acknowledged	*Section 17.2.4: Justification and rules for the assessment of "acquisition of data"* A scoring system will consider four components: ➔ **Enrollment** of patients, ➔ Prompt **classification of arrhythmias** detected by the ICM ➔ Unhesitating **contact to the patient** ➔ Conducting an **in-office final study termination visit**. **Justification:** The importance of enrollments for the study's success is evident. Without prompt classification of arrhythmias and consecutive contact with patients, the study concept cannot be effective. The conduction of in-office final study termination visits is

independent of the question whether it resulted in a therapy or not. Besides the assumed influence on the primary study outcome, the complete documentation of event chains is an important secondary objective of the study. To be counted, the following requirements must be fulfilled: - An arrhythmia reported by the CEMB was classified by the investigator - The subject was contacted, if applicable - If a diagnostic work-up was considered necessary, the diagnostic results and therapy changes are reported - The overall delay from CEMB report to classification by the investigator did not exceed 7 days - The information was recorded in the corresponding eCRFs and no open queries remain at study termination. To calculate the value of reaction to HM cases, the following rules apply: The time from CEMB notification to subject contact must not exceed 7 days. W*ithin this period, the investigator must have studied the HM content and classified the subject's rhythm, and must have* contacted the subject, if applicable. If this timeline is met, the full value is granted for the case.	important for a complete adverse event reporting. All four elements can be objectively calculated from the study database and together, they provide an objective quantification of the contribution of a study site.
Section 17.2.5: Calculation of total score For all randomized subjects together, 1000 points are granted. For each randomized subject, the number of granted points to the study site is 1000 divided by the number of randomized subjects. For all Reaction to HM cases fulfilling the defined conditions together, 1000 points are granted. For each case, the value granted to the study site is 1000 divided by the total number of cases. These points	*Section 17.2.5: Calculation of total score* For each of the four elements, 1000 points are granted. ➔ For each randomized subject, the number of granted points to the investigational site is 1000 divided by the number of randomized subjects.

may be reduced if the delays occurred, as defined above. The points are added for all study sites. If, for example 3000 subjects will be enrolled and 5000 cases of arrhythmia and contact are documented, all sites will receive 0.33 points per enrolled subject, and 0.2 points per timely documented event chain. The sites will then be ranked by the number of points.	➔ Further 1000 points are distributed evenly over all classified arrhythmias, which have been completed within 5 working days after onset of the arrhythmia. ➔ Equally, further 1000 points are distributed evenly over all contacts to subjects after arrhythmias, which were done within 7 working days of the arrhythmia. ➔ For each subject seen in-office for the final study termination visit, the number of points is 1000 divided by the total number of subjects seen in-office for the final study termination visit. The sites will then be ranked by the sum of points from the four categories. For all publications after the primary publication, investigators who have not been authors of accepted publications will be considered preferentially. The number of authors of a study site on all publications (weighted by the journals' latest impact factors) shall be proportional to the data contribution measured by the score, which is described here.

BIOTRONIK contact information for questions

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