BIOFLOW-VII: **BIO**TRONIK – A Prospective Multicenter Study to Confirm the Sa**F**ety and Effectiveness of the Orsiro Siro**L**imus Eluting Coronary Stent System in the Treatment **O**f Subjects **W**ith up to Three *De Novo* or Restenotic Coronary Artery Lesions – **VII**

Statistical Analysis Plan

Version 1.0

May 18, 2022

BIOTRONIK, Inc.
6024 Jean Road
Lake Oswego, Oregon 97035

Table of Contents

1 Introduction

This statistical analysis plan (SAP) for the BIOFLOW-VII study contains definitions of analysis populations and statistical methods for the analysis of the study data. This SAP specifies the pre-planned analyses to be included in the clinical study reports and is based on the November 6, 2019 protocol version.

1.1 Study Purpose

The objective of this post-approval study is to confirm that the clinical performance of the Orsiro® Sirolimus Eluting Coronary Stent (hereinafter referred to as Orsiro) in a real-world setting is similar to the clinical performance observed for Orsiro in the pivotal BIOFLOW-V study.

1.2 Study Design

BIOFLOW-VII is a prospective, multi-center, single-arm study. The study will enroll 556 subjects to achieve 500 evaluable subjects at up to 50 sites in the United States (US). Clinical outcomes will be collected and reported through 5 years post-index procedure. The design includes comparison against a performance goal based on the BIOFLOW-V trial Orsiro target lesion failure (TLF) rate, taking into consideration TLF rates from other US market-released drug-eluting stents (DES).

1.3 Primary Endpoint

The primary endpoint of the study is Target Lesion Failure (TLF) rate at 1-year post-index procedure. TLF is defined as a composite of cardiac death, protocol-defined target vessel myocardial infarction (MI), or clinically-driven target lesion revascularization (TLR).

The TLF rate will be derived from events adjudicated by the CEC to be a cardiac death, protocol-defined Q-wave or non-Q-wave target vessel myocardial infarction, or a clinically-driven target lesion revascularization according to the CEC Charter definitions.

1.4 Secondary Endpoints

The following secondary endpoints will be evaluated prior to discharge, at 1 month, 1 year, and annually thereafter through 5 years follow-up (unless otherwise specified).

1. All-cause death.
2. Protocol-defined MI.
3. Cardiac death or Protocol-defined MI.
4. Major Adverse Cardiovascular Events (MACE) and individual MACE components (MACE: composite of all-cause death, Q-wave or non–Q-wave MI, and clinically-driven TLR).
5. TLF (evaluated at discharge, 1 month, 2, 3, 4, and 5 years) and individual TLF components (TLF: composite of cardiac death, target vessel Q-wave or non–Q-wave MI, and clinically-driven TLR).
6. Target vessel failure (TVF) and individual TVF components [TVF: composite of cardiac death, target vessel Q-wave or non–Q-wave MI, and clinically-driven target vessel revascularization (TVR)].
7. Stent thrombosis (definite, definite/probable, probable) according to Academic Research Consortium (ARC)-2[1] criteria for acute, subacute, late, very late, and cumulative stent thrombosis.

The secondary endpoints include the following measures assessed at the time of the index procedure:

1. Device success, defined as attainment of < 30% residual stenosis of the target lesion (based on operator visual estimate) using the Orsiro study stent only.

   Note: Post-dilatation is allowed to achieve device success.

2. Lesion success, defined as attainment of < 30% residual stenosis of the target lesion (based on operator visual estimate) using any percutaneous method.

3. Procedure success, defined as attainment of < 30% residual stenosis of the target lesion (based on operator visual estimate) using the Orsiro study stent only without occurrence of in-hospital MACE.

2 Planned Analyses

The planned analyses described below will be performed when the data required to complete the analysis is available. Generally, the results of completed analyses will be provided within the next scheduled clinical progress report, unless BIOTRONIK identifies that a separate communication is required. If the planned analysis time point has not yet been met, progress toward the analysis and current available data will be presented using descriptive statistics within the clinical progress report.

2.1 Analysis Definitions

Descriptive statistics will be used to present and summarize the data collected in the clinical study. Frequency distributions and cross tabulations will be presented for discrete variables. Means, standard errors, and ranges will be presented for continuous variables. Proportions will be calculated using known non-missing values.

Unless otherwise indicated, all statistical tests and/or confidence intervals will be performed at $\alpha = 0.05$ (2-sided).

2.2 Statistical Analysis Sets

2.2.1. Intention to Treat (ITT) Analysis Population

The ITT population is defined as all enrolled subjects who received at least one Orsiro stent and were not considered a screen failure. This is the primary analysis population and data presented within the clinical progress report will be the ITT population unless otherwise specified.

2.2.2. Per-Protocol (PP) Analysis Population

The PP population is defined as all ITT subjects who have no major protocol eligibility violations that could impact the primary endpoint. Subjects that provided written informed consent but did not meet key inclusion/exclusion criteria were exited from the study as screen failures per Table 2 of the protocol. If any key criteria outlined in Table 2 were identified after the subject had been followed through the 1-month follow-up visit, the subject was not exited as a screen failure but will be excluded from the Per Protocol population.

The Per Protocol population will also exclude subjects that did not meet additional protocol eligibility criteria that were deemed to potentially affect the primary endpoint such as 'Presence of an untreated clinically significant stenosis post-procedure whether treatment is planned or not' or 'Subject is receiving chronic anticoagulation (e.g. coumadin, dabigatran, apixaban, rivaroxaban or any other agent)'.

2.3 Primary Endpoint Analysis

The purpose of the primary endpoint is to evaluate the rate of TLF of the Orsiro stent at 1 year compared to a performance goal of 6.9%.

H_o: The TLF rate of the Orsiro stent at 1 year is greater than or equal to a performance goal of 6.9%

Rate ≥ 6.9%

H_a: The TLF rate of the Orsiro stent at 1 year is less than a performance goal of 6.9%

Rate < 6.9%

A rejection of the null hypothesis (H_o) would demonstrate that the primary endpoint is met.

TLF is defined as a composite of cardiac death, target vessel-MI or clinically-driven TLR. Target vessel MI will utilize the SCAI definition[2] for peri-procedural MI and the BIOFLOW-V protocol definition[3] for spontaneous MI.

The primary analysis of the primary endpoint of the TLF rate of the Orsiro stent at 1 year will be in the intent-to-treat (ITT) population. The primary endpoint will be tested against a performance goal of 6.9% using a one-sided, exact test for one proportion with a Type I error level of 0.025. An additional (one-sided) supporting analysis will be performed in the PP population. A Kaplan-Meier survival analysis (time-to-event) for the primary endpoint outcome will be performed for the ITT and PP populations.

For each analysis population, subjects who have sufficient follow-up data (at least 330 days of follow-up), based on all available collected dates, or experienced the primary endpoint will be included in the primary endpoint analysis.

2.4 Sample Size Determination

The estimated sample size for the study is based on TLF results from the BIOFLOW-V study and in consideration of recent published relevant clinical TLF rates of other comparable stents that utilized the SCAI definition[2] of peri-procedural MI. The BIONICS IDE study utilized the Third Universal definition of spontaneous MI[4], which is deemed to be similar to the spontaneous definition of MI used in the BIOFLOW-V study[3].

Comparable stents were evaluated in these two IDE studies involving a total of over 2,000 subjects and had consistent TLF upper 95% confidence bounds in the range of 6.9% - 7.1% (**Table 1**). A performance goal was derived considering this potential TLF rate range and was adjusted to account for the potential differences in the prospectively enrolled BIOFLOW-VII population enrolled under real world post-approval conditions.

Differences in standard of care practices and patient population may impact the final TLF rate. Specifically, cardiac biomarkers are infrequently analyzed post-procedure in asymptomatic patients as standard of care. Analysis of troponins is more frequent in clinical practice, whereas CKMB was measured more frequently as part of the protocol in the BIOFLOW-V study. It is also anticipated that a post-approval real-world population may have different frequencies of factors (e.g. diabetes, prior MI, etc.) and patient and lesion characteristics than those enrolled in IDE trials. These factors could result in a higher observed TLF rate than in BIOFLOW-V or other prior trials.

Table 1: 1-Year TLF Rates for DES Utilizing SCAI Definition of Peri-Procedural MI

Study	TLF Rate at 1 Year	95% Confidence Interval
BIOFLOW-V: Orsiro	2.6% (22/833)	(1.7%, 4.0%)
BIOFLOW-V: Xience	4.5% (19/426)	(2.7%, 6.9%)
BIONICS[5,6,7] EluNIR	5.4% (50/926)	(4.0%, 7.1%)
BIONICS: Resolute	5.4% (50/930)	(4.0%, 7.0%)

The sample size required to evaluate the primary endpoint was estimated using the following design criteria:

- Performance goal: 6.9% (upper 95% CI acceptability for BIOFLOW-VII)
- Target Orsiro TLF rate: 4.0%
- Statistical power: 80%
- Significance level: one-sided 0.025

Table 2: Primary Endpoint Sample Size

	Primary Safety Endpoint 1
Sample Size of Evaluable Subjects	495 subjects
Sample Size Adjusted for Post-Approval Study Requirement	500 subjects
Total Adjusted for Attrition	556 subjects

In order to collect additional data on the performance of the Orsiro stent, the sample size was increased to a target minimum of 500 evaluable subjects at 1-year post-index procedure as recommended by the FDA. Assuming a 10% attrition rate through the first 1 year of subject follow-up, a total enrollment of 556 subjects has been estimated.

2.5 Handling of Missing Data in the Analysis of Primary Endpoint

All reasonable methods will be taken to ensure a minimum of missing data. The impact of missing data on conclusions about the primary study endpoint will be examined in sensitivity analyses, which may include multiple imputation methods, if warranted.

2.6 Analysis of Secondary Endpoints

There are no formal hypotheses for the secondary endpoints. The secondary endpoints in the BIOFLOW-VII study will be analyzed using frequentist methods when the time points defined below have been met. For each endpoint, the proportion and denominator will be calculated and reported. Analyses of secondary endpoints will be carried out on the ITT and PP analysis sets when data is available for all subjects at the time point. However, there will be no direct imputation of missing data.

The following secondary clinical endpoints will be evaluated prior to discharge, at 1 month, 1 year and annually thereafter through 5 years of follow-up (refer to Sec. 1.4 for definitions):

1) All-cause death
2) Protocol-defined MI
3) Cardiac death or protocol-defined MI
4) MACE and individual MACE components
5) TLF and individual TLF components (1-year TLF rate is the primary endpoint)
6) TVF and individual TVF components
7) Stent thrombosis according to ARC-2 criteria[1]

Included in the analysis will be subjects experiencing the event or who have adequate follow-up (e.g., at least 23 days for 1-month time point and at least 330 days for the 1-year time point, 660 days for the 2-year time point, 1020 days for the 3-year time-point, 1380 days for the 4-year time point, and 1740 days for the 5-year time point.)

The following secondary endpoints will also be evaluated (refer to Sec. 1.4 for definitions):

8) Device success
9) Lesion success

10) Procedure success.

Analysis of secondary endpoints 1-7 will be based on CEC adjudicated event data. Analysis of secondary endpoints 8-10 will be based on site-reported data (with CEC adjudicated event data for endpoint 10, as applicable). In evaluating procedure success, MACE will be based on CEC adjudicated event data.

2.7 Analysis of Baseline Demographics and Procedural Characteristics

Demographic and baseline characteristics, procedural characteristics, lesion characteristics will be reported for the BIOFLOW-VII ITT analysis population. Demographic, medical history and other clinically relevant baseline variables will be summarized using descriptive statistics (i.e. number of observations available, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum for continuous variables and counts and percentages for qualitative variables).

2.8 Comparison with BIOFLOW-V

Patient demographics and target lesion characteristics will be compared with those of the BIOFLOW-V (IDE) Orsiro study cohort to ensure that the enrolled patient population is comparable with the BIOFLOW-V Orsiro (IDE) study population. The analyses at 25%, 50%, and 75% of the expected total enrollment were previously completed and the 100% enrolled population comparison will be performed. Analysis of the target lesion characteristics will be based on site-reported data for both studies since Angiographic Core Lab analysis is not systematically performed for all index procedure angiograms in BIOFLOW-VII.

Treatment difference on dichotomous variables are evaluated using Fisher's exact tests. Categorical variables were compared between studies using the Cochran-Mantel-Haenszel (CMH) Modified Ridit Scores, i.e., CMH of general association for nominal variables and CMH of row mean score for ordinal variables. Continuous variables are compared between studies using two-sample t-tests.

Additionally, comparison between summary 1-year Adverse Event rates may be performed.

2.9 Subgroup Analysis

Subgroups for secondary analysis of clinical endpoints include:

- Reference vessel diameter ≤ 2.75 mm / > 2.75 mm.

  Note: Subjects with at least one target lesion ≤ 2.75 mm will be classified with the small vessel subgroup.
- Subjects > 75 years of age/subjects ≤ 75 years of age.
- Women/men.
- Subjects with diabetes/subjects without diabetes.
- Lesion length > 26 mm and ≤ 26 mm in length.
- Single stents versus overlapping stents for lesion lengths > 26 mm.
- Stent diameter ≤ 3.0 mm or > 3.0 mm.
- Subjects with acute coronary syndrome versus non-acute coronary syndrome.

ACS will be defined as: Subjects with unstable angina or any elevated cardiac enzymes at baseline.

There is no formal hypothesis for these subgroup analyses. Subjects with an event and/or with appropriate follow-up will be included in this analysis. The purpose of this analysis is not to formally assess non-inferiority within each subgroup, but simply to assess consistency of results across the various subgroups.

2.10 Poolability Analysis

The poolability of primary study results between clinical sites in the US will be analyzed and reported but there are no pre-specified tests of the statistical significance for site differences. This poolability analysis will be included in the clinical report after the primary endpoint analysis is complete.

2.11 Sex Analysis

Any differences between sexes in the primary study results between clinical sites in the US will be analyzed and reported but there are no pre-specified tests of the statistical significance for sex differences. This sex analysis will be included in the clinical report after the primary endpoint analysis is complete.

2.12 Adverse Event Analysis

Adverse events collected in the BIOFLOW-VII data will be summarized using descriptive statistics that describe the percentage of subjects experiencing an adverse event and rate of adverse event as events per subject-year. The total number of enrolled ITT subjects and cumulative duration of follow-up completed for the enrolled subjects as of the date of the report will be utilized to calculate the descriptive statistics. AE rates will be presented by System Organ Class and Sub-category for the following:

- Site-reported AEs
- Site-reported device/procedure-related AEs
- Site-reported SAEs
- Site-reported device/procedure-related SAEs

2.13 Additional Analyses

The following data collected in BIOFLOW-VII will be summarized using descriptive statistics:

- Antiplatelet medical therapy.
- MI event rates utilizing alternative MI definitions of Third Universal[4], the BIOFLOW-V protocol definition[3], and Academic Research Consortium (ARC)[8] definition as specified in the CEC Charter.
- TLF event rates at 1 year utilizing alternative MI definitions, including Third Universal[4], the BIOFLOW-V protocol definition[3], and Academic Research Consortium (ARC) definition[8].

2.14 COVID-19 Data Collection and Sensitivity Analysis

Per the FDA guidance document "Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency", dated March 2020 and updated on August 20, 2021[9], the following guidance recommendations will be implemented as noted below each point.

1) Contingency measures implemented to manage study conduct during disruption of the study because of COVID-19 control measures.
    - BIOTRONIK will include COVID-19 contingency measures in the clinical report.
2) A listing of all participants affected by the COVID-19 related study disruption by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered.
    - The detailed listings of Protocol Deviations and Protocol Violations included in the clinical report, broken out by subject and protocol noncompliance (PNC) occurrence, will indicate that the PNC was impacted by COVID-19, if reported as such by the site.

3) Analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., trial participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study.

The subject's COVID-19 status is collected for each adverse event for the study. Events occurring prior to the EDC release adding this data collection (July 2, 2020) were retrospectively updated to collect this data.

Additionally, the CEC will adjudicate the COVID status and assessment of event relationship to COVID-19 for all potential endpoint events.

A secondary sensitivity analysis of the primary endpoint according to COVID-19 prevalence will be performed based on CEC adjudicated event data. This sensitivity analysis will be initially performed in the clinical report after the primary endpoint analysis is complete.

1) Sensitivity analysis will be performed to exclude death, protocol-defined MI, and ST events from endpoint analyses that occurred in subjects adjudicated to have a Positive (confirmed positive testing) COVID-19 status.
2) Sensitivity analysis will be performed to exclude death, protocol-defined MI, and ST events that occurred in subjects adjudicated to have a Positive (confirmed positive testing) or Suspected, not confirmed (no testing) COVID-19 status.
3) Sensitivity analysis will be performed to exclude death, protocol-defined MI, and ST events from endpoint analyses that occurred in subjects deemed to have a PNC potentially impacting the safety and efficacy results that was reported as being impacted by COVID-19.

3 Signatures

Signatures and Date

_____

_____

_____

_____

_____

4 References

[1] Garcia-Garcia H, McFadden EP, Farb A, et al. Standardized End Point Definitions for Coronary Intervention Trials The Academic Research Consortium-2 Consensus Document. *Circulation.* 2018;137:2635-2650.

[2] Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol.* 2013 Oct 22;62(17):1563-70.

[3] Adapted from Vranckx P, Cutlip DE, Mehran R, Kint PP, Silber S, Windecker S, Serruys PW. Myocardial infarction adjudication in contemporary all-comer stent trials: Balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. *EuroIntervention.* 2010;5:871–874.

[4] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD: the Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Circulation.* 2012;126:2020-35.

[5] Kandzari DE, Smits PC, Love MP, Ben-Yehuda O, Banai S, Robinson SD, Jonas M, Kornowski R, Bagur R, Iniguez A, Danenberg H, Feldman R, Jauhar R, Chandna H, Parikh M, Perlman GY, Balcells M, Markham P, Ozan MO, Genereux P, Edelman ER, Leon MB, Stone GW. Randomized Comparison of Ridaforolimus- and Zotarolimus-Eluting Coronary Stents in Patients With Coronary Artery Disease. Primary Results from the BIONICS Trial (BioNIR Ridaforolimus-Eluting Coronary Stent System in Coronary Stenosis). *Circulation*. 2017;136:1304-1314.

[6] Medinol LTD. Summary of Safety and Effectiveness Information (SSED). EluNIR™ Ridaforolimus Eluting Coronary Stent System. https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170008B.pdf.

[7] Kandzari DE. EluNIR ridaforolimus eluting coronary stent system. Clinical trials program. BIONICS and NIREUS. TCT. 2017 October. Oral presentation.

[8] Cutlip DE, Windecker S, Mehran R et al. for the Academic Research Consortium. Clinical endpoints in coronary stent trials: A case for standardized definition. *Circulation.* 2007;115:2344–2351.

[9] FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards. Created March 2020, updated August 30,2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency