BIOTRONIK
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BIOFLOW-V

STATISTICAL ANALYSIS PLAN (SAP)

BIOTRONIK – A Prospective Randomized Multicenter Study to Assess the SaFety and Effectiveness of the Orsiro SiroLimus Eluting Coronary Stent System in the Treatment Of Subjects With up to Three *De Novo* or Restenotic Coronary Artery Lesions – V

Protocol #: CIP FINAL V 4.0, 11 Feb 2016

Prepared By: Baim

Project Code: KTI14

Baim Institute for Clinical Research℠

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1 INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis populations, derived variables and statistical methods for the analysis of the BIOFLOW-V trial. This SAP specifies the pre-planned analyses and serves as the base for the clinical study report.

This SAP is based on the final protocol, version 4.0, dated Feb. 11, 2016.

1.1 Trial Objective

The objective of this study is to assess the safety and efficacy of the Orsiro Sirolimus Eluting Coronary Stent System in the treatment of subjects with up to three native de *novo* or restenotic (standard PTCA only) coronary artery lesions compared to the Xience coronary stent system.

1.2 Trial Design

BIOFLOW-V is a prospective, multicenter, randomized, controlled trial combining data on the randomized subjects with data from two historical studies by employing a Bayesian approach.

Subjects with coronary artery disease (CAD) that qualify for percutaneous coronary intervention (PCI) with stenting will be screened per the protocol inclusion and exclusion criteria to achieve a total of at least 1,334 and up to 1,400 randomized subjects. Eligible subjects will be randomized, stratified by study center, in a 2:1 ratio to undergo percutaneous coronary revascularization with either the Orsiro Sirolimus Eluting Stent System (treatment group, at least 889 and up to 933 subjects) or the Xience Everolimus Eluting Stent System (control group, at least 445 and up to 467 subjects). The study will include up to 100 clinical sites in the United States and 50 clinical sites outside of the United States.

BIOFLOW-V randomized subjects will be combined with historical Orsiro, Xience Prime™ and Xience Xpedition™ randomized subjects from the BIOFLOW-II and BIOFLOW-IV trials by employing a Bayesian statistical approach. Only subjects that meet all clinical and angiographic eligibility criteria of the BIOFLOW-V trial will be included in the analysis.

1.3 Primary Endpoint

The primary endpoint of the study is Target Lesion Failure (TLF) rate at 12 months post-index procedure. TLF is defined as all cardiac death, protocol-defined target vessel Q-wave or non-Q-wave 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 manual of operations and definitions.

1.4 Secondary Endpoints

The secondary endpoints include the following measures:

1) Device success, defined as attainment of < 30% residual stenosis of the target lesion using the assigned study stent only. *Note: Post-dilation is allowed to achieve device success.*
2) Lesion success, defined as attainment of < 30% residual stenosis of the target lesion using any percutaneous method.

3) Procedure success, defined as attainment of < 30% residual stenosis of the target lesion using the assigned study stent only without occurrence of in-hospital major adverse cardiac events (MACE; composite of all-cause death, protocol-defined Q-wave or non-Q-wave MI, and any clinically-driven TLR).

The percent residual stenosis, as assessed by the investigator visual estimate or on-line QCA during the procedure, will be used as the primary analysis measure of the final % diameter stenosis for evaluating angiographic success criteria for these endpoints. If investigator assessment of residual stenosis is not available, the final % diameter stenosis as assessed by QCA will be used. In evaluating procedure success, MACE will be based on CEC adjudicated event data.

The following secondary clinical endpoints will be evaluated prior to discharge, at 1, 6 and 12 months and annually thereafter through 5 years follow-up:

4) Death
5) Protocol-defined MI
6) Cardiac death or protocol-defined MI
7) MACE and individual MACE components (all-cause death, protocol-defined Q-wave or non-Q-wave MI, and any clinically-driven TLR)
8) TLF and individual TLF components (cardiac death, protocol-defined target vessel Q-wave or non-Q-wave MI, and any clinically-driven TLR)
9) Target vessel failure (TVF) and individual TVF components (cardiac death, protocol-defined target vessel Q-wave or non-Q-wave MI, and any clinically-driven TVR)
10) Stent thrombosis (all, definite, definite/probable, probable, possible) according to Academic Research Consortium (ARC) criteria for acute, subacute, late, very late and cumulative stent thrombosis

Analysis of secondary endpoints will be based on CEC adjudicated event data

2 PLANNED ANALYSES

2.1 General Analysis Definitions

Bayesian analyses will be performed using the open-source program OpenBUGS version 3.2.3 (Bayesian inference using Gibbs Sampling), Lunn et al.[1]; other analyses, including summaries, will be conducted using SAS (version 9.4), unless otherwise noted. Descriptive statistics for continuous variables will include mean, standard deviation, median, quartiles, minimum, maximum, and sample size for each treatment group. Categorical variables will be summarized using counts and percentages. 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).

[1] Lunn D, Spiegelhalter D, Thomas A, Best N. The BUGS project: Evolution, critique and future directions. Stat Med 2009; 28: 3049–3067

2.2 Prior Data

The Orsiro clinical trial program includes BIOFLOW-II, BIOFLOW-IV and BIOSCIENCE, three randomized controlled trials in which subjects were randomized to the Orsiro stent against the Xience Prime™ or Xience Xpedition™ stents. A brief description of these trials is provided in protocol Section 3.5. The inclusion and exclusion criteria for BIOFLOW-II and BIOFLOW-IV are nearly identical to those proposed for BIOFLOW-V, whereas the inclusion and exclusion criteria in BIOSCIENCE were more liberal to allow enrollment of a broadly inclusive real world population. The primary non-inferiority analysis of the BIOFLOW-V study will use data from the BIOFLOW-II and BIOFLOW-IV trials prospectively using a Bayesian approach. Data from the BIOSCIENCE trial will not be included for analysis due to the more liberal enrollment criteria. A summary of the comparison of the study design of BIOFLOW-II and BIOFLOW-IV trials along with the proposed BIOFLOW-V study was listed below.

	BIOFLOW -II	BIOFLOW-IV	BIOFLOW-V
Eligibility Criteria	All subjects will match BIOFLOW-V clinical and angiographic inclusion/exclusion criteria		
Primary or Secondary Endpoint Definition	**TLF**: cardiac death, target vessel Q-wave or non-Q wave MI, CABG, clinically driven TLR		
Follow-up schedule	1mo, 6mo, 9mo angio, 12mo, 2yr, 3yr, 4yr, 5yr	1mo, 6mo, 12mo, 2yr, 3yr, 4yr, 5yr	1mo, 6mo, 12mo, 2yr, 3yr, 4yr, 5yr
Enzyme measurements	CK, CKMB (optional) and Troponin: • Baseline • Within 6-24 hours after the index procedure or at discharge, whichever comes first	CK, CKMB (optional) or Troponin (if CK and CKMB are not used): • Baseline • Within 6-24 hours after the index procedure or at discharge, whichever comes first	CK, CKMB, Troponin (if CKMB is not available): • Baseline • Within 6-24 hours after the index procedure
Clinical Monitoring	• 100% source verification • Independent core labs for angiography, IVUS & OCT • On-site monitoring • Independent CEC adjudication	• 100% source verification • Independent angiographic core lab • On-site Monitoring • Independent CEC adjudication	• 100% source verification • Independent angiographic core lab • On-site Monitoring • Independent CEC adjudication

To ensure the validity of data from subjects across trials, the following measures will be taken:

- Evaluation of the 12-month TLF rate (a primary endpoint in the BIOFLOW-V and a secondary endpoint in the BIOFLOW-II and IV trials) will be performed in a uniform fashion, using a consistent set of definitions and similar follow-up schedule:
    - The measurement schedule of cardiac enzymes is similar in all trials: cardiac enzymes are collected once within 6-24 hours post index procedure. While all trials mandated collection of CK and CKMB, the BIOFLOW-II also mandated measurement of troponin. The BIOFLOW-IV and BIOFLOW-V trials allow measurement of troponin if CK and CKMB are not used. To address the differences in the collection of

cardiac enzymes between the three trials, a uniform definition of peri-procedural MI that is based on CK and CKMB levels (with troponin levels used only in the absence of CK and CKMB) will be utilized.
  - All trials have similar clinical follow-up schedule at 1 month (telephone contact/clinic visit), 6 months (telephone contact/clinic visit) and 12 months (telephone contact/clinic visit for BIOFLOW-II clinic visit for BIOFLOW-IV and BIOFLOW-V).
  - The BIOFLOW-II and BIOFLOW-IV trials used the same independent angiographic core laboratory. To ensure consistency, angiograms from the BIOFLOW-II, BIOFLOW-IV and BIOFLOW-V trials will be analyzed or validated by the same angiographic core laboratory.
  - All clinical endpoints (potential TLR, MI and death events) will be re-adjudicated by the same independent CEC as will be employed for the BIOFLOW-V data, using uniform definitions.
- Data quality will be confirmed in accordance with the monitoring plan of each trial.
- Only subjects that meet all BIOFLOW-V clinical and angiographic eligibility criteria will be included. The criteria include the following:

Clinical Inclusion Criteria

Subjects must meet all of the following criteria to participate in the trial:

1) Subject is ≥18 years or the minimum age required for legal adult consent in the country of enrollment.
2) Subject is an acceptable candidate for PCI.
3) Subject is an acceptable candidate for CABG.
4) Subject has clinical evidence of ischemic heart disease, stable or unstable angina pectoris or documented silent ischemia.
5) Subject is eligible for dual anti-platelet therapy treatment with aspirin plus either clopidogrel, prasugrel, ticagrelor or ticlopidine.
6) Subject has provided written informed consent.
7) Subject is willing to comply with study follow-up requirements.

Angiographic Inclusion Criteria

Each target lesion/vessel must meet all of the following angiographic criteria for the subject to be eligible for the trial:

1) Subject has up to three target lesions in up to two separate target vessels (two target lesions in one vessel and one target lesion in a separate vessel).
2) Target lesion must be de novo or restenotic lesion in native coronary artery; restenotic lesion must have been treated with a standard PTCA only.
3) Target lesion must be in major coronary artery or branch (target vessel).
4) Target lesion must have angiographic evidence of ≥ 50% and < 100% stenosis (by operator visual estimate). If the target lesion is < 70% stenosed, there should be clinical evidence of ischemia such as a positive functional study (e.g. exercise treadmill test, thallium stress test, SPECT, or stress echo), cardiac computed tomography (CT), electrocardiography, fractional flow reserve, or post infarct angina.
5) Target vessel must have a Thrombolysis In Myocardial Infarction (TIMI) flow > 1.
6) Target lesion must be ≤ 36 mm in length by operator visual estimate.
7) Target vessel must have a reference vessel diameter of 2.25–4.0 mm by operator visual estimate.
8) Target lesion must be amenable to treatment with a maximum of two overlapping stents.

Clinical Exclusion Criteria

Subjects will be excluded from the trial if any of the following criteria are met:

1) Subject has clinical symptoms and/or ECG changes consistent with acute ST elevation MI (STEMI) within 72 hours prior to the index procedure.
   - Note: Hemodynamically stable non-STEMI (NSTEMI) subjects are eligible for study enrollment
2) Subject is hemodynamically unstable.
3) Subject is pregnant and/or breastfeeding or intends to become pregnant during the duration of the study.
4) Subject has a known allergy to contrast medium that cannot be adequately pre-medicated, or any known allergy to thienopyridine, aspirin, both heparin and bivalirudin, L-605 cobalt-chromium (Co-Cr) alloy or one of its major elements (cobalt, chromium, tungsten and nickel), acrylic, fluoropolymers, silicon carbide, PLLA, sirolimus or everolimus.
5) Revascularization of any target vessel within 9 months prior to the index procedure or previous PCI of any non-target vessel within 30 days prior to the index procedure.
6) Planned treatment of a lesion not meeting angiographic inclusion and exclusion criteria during the index procedure or after the index procedure.
7) Planned surgery within 6 months of index procedure unless dual antiplatelet therapy can be maintained throughout the peri-surgical period.
8) History of a stroke or transient ischemic attack (TIA) within 6 months prior to the index procedure.
9) Subjects with active bleeding disorders, active coagulopathy, or any other reason, who are ineligible for DAPT.
10) Subject will refuse blood transfusions.
11) Subject has documented left ventricular ejection fraction (LVEF) < 30% as evaluated by angiography, echocardiogram, radionuclide ventriculography or any non-invasive imaging method within 90 days prior to the index procedure.
12) Subject is dialysis-dependent.
13) Subject has impaired renal function (i.e., blood creatinine > 2.5 mg/dL or 221 µmol/L determined within 7 days prior to the index procedure).
14) Subject has leukopenia (i.e. < 3,000 white blood cells/mm3), thrombocytopenia (i.e. < 100,000 platelets/mm3) or thrombocytosis (i.e. > 700,000 platelet/mm3).
15) Subject is receiving oral or intravenous immunosuppressive therapy (inhaled steroids are permitted), or has known life-limiting immunosuppressive or autoimmune disease (e.g., human immunodeficiency virus, systemic lupus erythematosus; diabetes mellitus is permitted).
16) Subject is receiving chronic anticoagulation (e.g. coumadin, dabigatran, apixaban, rivaroxaban or any other agent).
17) Subject has life expectancy of < 1 year.
18) Subject is participating in another investigational (medical device or drug) clinical study. Subjects may be concurrently enrolled in a post-market study, as long as the post-market study device, drug or protocol does not interfere with the investigational treatment or protocol of this study.
19) In the investigator's opinion, subject will not be able to comply with the follow-up requirements.

Angiographic Exclusion Criteria

Subjects will be excluded from the trial if any of the target lesions/vessels meets any of the following angiographic criteria:

1) Target lesion is located within a saphenous vein graft or arterial graft.

2) Target lesion is a restenotic lesion that was previously treated with a bare metal or drug eluting stent (in-stent restenosis).
3) Target lesion has any of the following characteristics:
    a. Lesion location is within the left main coronary artery, or within 3 mm of the origin of the left anterior descending (LAD) or left circumflex (LCX).
    b. Involves a side branch of > 2.0 mm in diameter.
    - Note: Lesions within 3 mm of the origin of the right coronary artery may be treated.
4) Target vessel/lesion is excessively tortuous/angulated or is severely calcified, that would prevent complete inflation of an angioplasty balloon. This assessment should be based on visual estimation.
5) Target vessel has angiographic evidence of thrombus.
6) Target lesion is totally occluded (100% stenosis).
7) Target vessel was treated with brachytherapy any time prior to the index procedure.

2.3 Bayesian Analysis

To assess the non-inferiority of the Orsiro stent compared to the Xience stent in the BIOFLOW-V study, a Bayesian approach using hierarchical models to formally incorporate data from the BIOFLOW-II and BIOFLOW-IV trials will be employed. The approach proposes using Binomial analysis for the presence of a TLF event and a Bayesian model that allows for a bias between the TLF event rates of the BIOFLOW-II and BIOFLOW-IV trials and the TLF event rates of the BIOFLOW-V trial in both the Orsiro and Xience groups. The parameters defining the bias are selected so that the proposed method is robust to misspecifications of the initial assumptions.

Whenever not specified, priors in Bayesian analyses will be non-informative or weakly informative priors. The following priors will be employed unless otherwise specified: normal priors with mean 0 and large variance for slope parameters, inverse gamma priors with parameter 0.001 and 0.001 and Beta (1,1) for probability parameters.

2.4 Criteria for Success

The criterion for success is based on the posterior probability of the alternative hypothesis (i.e., of non-inferiority being met). The Orsiro group will be declared non-inferior to the Xience group if the posterior probability of the alternative hypothesis H_A is large, that is

$$P(H_A|Data) = P\left(\pi_X^V - \pi_O^V > -\delta \middle| Data\right) > \pi^*$$

where π_X^V and π_O^V are the 1-year TLF for the Xience and Orsiro groups of the BIOFLOW-V study, respectively, δ is the non-inferiority margin and $H_A: \pi_X^V - \pi_O^V > -\delta$ is the alternative hypothesis indicating that non-inferiority is met and $\pi^* = 0.975$ is the level of evidence we require to declare the alternative hypothesis true.

2.5 Sample Size Determination

The BIOFLOW-V trial will assess non-inferiority of the 12-month TLF rate for the Orsiro stent vs. TLF rate in subjects treated with the Xience stent. The null hypothesis H_0 is that the Orsiro stent will have a primary endpoint (TLF) rate equal to or exceeding that of the Xience group by the non-inferiority margin or more. The alternative hypothesis H_A is that the Orsiro stent will have TLF rate less than the Xience group rate plus the non-inferiority margin. Specifically:

$$H_0: \pi_X^V - \pi_O^V \leq -\delta$$
$$H_A: \pi_X^V - \pi_O^V > -\delta$$

Where π_O^V is the true 12-month TLF rate for the Orsiro stent, π_X^V is the true 12-month TLF rate for the Xience arm, and δ is the non-inferiority margin.

The assumptions for this analysis are:

- True 12-month TLF rate is 7.0% in both treatment groups ($\pi_X^V = \pi_O^V$).
- Power is 89%.
- 3.85% is the absolute non-inferiority margin (55% relative non-inferiority margin).
- Discount the results of the BIOFLOW-IV data by 20% and BIOFLOW-II data by 30%.
- Standard deviation of the bias terms between the odds of BIOFLOW-II TLF 12-month rates and odds of BIOFLOW-V 12-month rates is 0.3.
- Standard deviation of the bias terms between the odds of BIOFLOW-IV TLF 12-month rates and odds of BIOFLOW-V 12-month rates is 0.3.
- Non-inferiority assessment will be assessed using the posterior probability of the alternative hypothesis as specified above, where $\pi^* = 0.975$

Rejection of the null hypothesis signifies that the Orsiro stent is not inferior to the Xience stent with regards to 12-month TLF. A total of 1,200 subjects (800 in the Orsiro group and 400 in the Xience group) will have 89.6% power to reject the above null hypothesis in favor of the alternative under the stated assumptions. To account for loss to follow-up (expected to be approximately 10%), a total of 1,334 subjects will need to be randomized. The one-sided type I error estimates are 4.0%, 3.3%, and 4.2% if the actual odds for the 12-month TLF rate of event in the Xience group of the BIOFLOW-IV study are the same, 10% lower and 10% higher when compared with the odds for the 12-month TLF rate of event in the Xience group of the BIOFLOW-V study.

2.5.1 True Rate

The current assumption of the 12-month TLF rate of 7.0% is based on expected inclusion criteria for BIOFLOW studies and results from recent everolimus eluting stent trials.

2.5.2 Non-Inferiority Margin

The non-inferiority margin was calculated based on a meta-analysis rate of the difference in treatment effect between DES and BMS. Randomized clinical trials comparing treatment with DES and treatment with BMS with 9 months or longer clinical follow-up data were included in the meta-analysis. Nine-month rates were used whenever 12-month rates were not available. Depending on study definitions, TVF or MACE rates were used to match as closely as possible the TLF definition in this study.

The meta-analytic rate of the difference in treatment effect between DES and BMS was 10.0% with a lower bound of the 2-sided 95% CI of 8.2%. A common practice is to take 50% of this lower bound of the DES-BMS difference as the non-inferiority margin, therefore an absolute non-inferiority margin of 3.85%, which is approximately 46% of the lower bound, is supported.

2.6 Statistical Analysis Sets

2.6.1 Intention to Treat (ITT) Analysis Population

The Intent-to-Treat (ITT) population is defined as all randomized subjects. Subjects are analyzed according to the stent to which they were randomized (regardless of the actual stent that they received). This is the primary analysis population.

2.6.2 Per-Protocol (PP) Analysis Population

The Per-Protocol (PP) population is defined as all randomized subjects who received at least one assigned study stent, have sufficient follow-up data (at least 330 days of follow-up or experienced the primary endpoint) and no major protocol eligibility violations (i.e. inclusion/exclusion criteria violations that could impact the primary endpoint).

2.6.3 Modified Intent-to-Treat Analysis Population

The Modified ITT population is defined as all randomized subjects who received at least one study stent according to their treatment assignment.

2.6.4 Analysis Sets for BIOFLOW-II and BIOFLOW-IV (Bayesian Analysis Population)

Only BIOFLOW-II and BIOFLOW-IV randomized subjects who satisfy BIOFLOW-V clinical and angiographic inclusion/exclusion criteria and who have sufficient follow-up data (at least 330 days of follow-up or experience the primary endpoint) will be included in the BIOFLOW V Bayesian analysis.

The subjects in BIOFLOW-II and BIOFLOW-IV who meet the inclusion/exclusion criteria of BIOFLOW-V will be determined before the BIOFLOW V database is locked and will be done by an independent statistician without the knowledge of any of the outcome data.

A sensitivity analysis of the ITT primary endpoint analysis will be performed by including all BIOFLOW-II and BIOFLOW-IV randomized subjects who have sufficient follow-up data (at least 330 days of follow-up or experience the primary endpoint) whether or not the subjects satisfy the BIOFLOW-V inclusion/exclusion criteria.

2.7 Analysis of Primary Endpoint

This study will assess non-inferiority of the 12-month TLF rate for the Orsiro stent vs. the Xience stent. The analysis will be carried out on the ITT set (primary), modified ITT and PP analysis sets. The null hypothesis H_0 is that the Orsiro stent will have a primary endpoint (12-month TLF) rate equal to or exceeding that of the Xience group by the non-inferiority margin or more. The alternative hypothesis H_A is that the Orsiro stent will have a 12-month TLF rate less than the Xience group rate plus the non-inferiority margin. The hypothesis is defined as follows:

$$H_0: \pi_X^V - \pi_O^V \leq -\delta$$
$$H_A: \pi_X^V - \pi_O^V > -\delta$$

where π_O^V is the true 12-month TLF rate for the Orsiro stent, π_X^V is the true 12-month TLF rate for the Xience arm, and δ is the non-inferiority margin chosen to be 0.0385 (or 3.85%) as noted in section 2.5.2, Non-Inferiority Margin.

The proposed model is a Bayesian hierarchical model that assumes a bias between the 12-month TLF rates in BIOFLOW-II and BIOFLOW-V as well as BIOFLOW-IV and BIOFLOW-V studies.

Estimation of the parameters and hypotheses testing of the primary hypotheses is based on the posterior distribution of the parameters. The posterior distribution for parameters which do not have closed form posterior inferences will be carried out by sampling from the posterior distribution of the parameters. The freely available program OpenBUGS (Bayesian inference using Gibbs Sampling) will be used to obtain samples from the posterior distribution of the parameters. Using OpenBUGS, 100,000 samples will be obtained from the posterior distribution of 12-month TLF rates after the initial 5,000 will be discarded. To decrease autocorrelation, only every tenth sample will be used in calculations.

We will check convergence of the MCMC sampler using the Brooks-Gelman-Rubin method[2]. Convergence of the sampler will be established if the ratio of within-chain and between-chain variability for multiple chains starting at different initial values will be close to 1.

The percent of posterior samples that satisfy $\pi_X^V - \pi_O^V > -\delta$ will be used to estimate the posterior probability of the alternative hypothesis will be calculated and reported in the table below.

Table reporting the posterior probability of the Alternative Hypothesis:

Alternative Hypothesis	Posterior Probability
Orsiro is non-inferior to Xience ($\pi_X^V - \pi_O^V > -\delta$)	XX.X%

This probability will be contrasted against $\pi^* = 0.975$ as outlined in Section 2.4.

In addition the posterior means and standard deviations of the parameters will be reported along with 95% Credible Intervals as outlined in the table below.

Table reporting the posterior summaries of the 1-year TLF rates in BIOFLOW-V:

	Mean	SD	Lower Bound 95% Credible Interval	Upper Bound 95% Credible Interval
π_X^V	X.XX	X.XX	X.XX	X.XX
π_O^V	X.XX	X.XX	X.XX	X.XX

[2] Brooks SP, Gelman A. Alternative methods for monitoring convergence of iterative simulations. Journal of Computational and Graphical Statistics. 1998;7:434-455

In addition, an adjusted Bayesian analysis based on multivariable hierarchical logistic regression adjusted for age, diabetes, history of PCI, ischemic status and LVEF will be performed. Treatment effect with logistic regression is expressed on the log ODDS ratio scale. The value of non-inferiority margin used for the non-inferiority test on the log ODDS scale in the adjusted analyses is obtained by transforming the probability-scale non-inferiority margin of 0.0385 to the log-odds scale. The transforming is achieved using the formula:

$$\log\{(0.07 + 0.0385) / (1- 0.07 - 0.0385)\}- \log\{0.07 / (1- 0.07)\}=0.481$$

Thus, for the adjusted analyses, the non-inferiority will be met if

$$P\left(\text{logit}(\pi_X^V) - logit(\pi_O^V) > -0.481 \middle| Data\right) > 0.975$$

2.7.1 Center Heterogeneity

Consistency of treatment effect across centers will be tested within each of the three studies (BIOFLOW-II, BIOFLOW-IV and BIOFLOW-V). To assess consistency of treatment effect size across study centers, Bayesian models will be employed for the subject level data. Any study center with less than 5 subjects per treatment group will be pooled with other study centers by geographic region prior to carrying out this assessment.

Individual data for treatment i (i=1 for Xience and i=2 for Orsiro), study j ($j = 1$ for BIOFLOW-V, $j = 2$ for BIOFLOW-II and $j = 3$ for BIOFLOW-IV) and individual k will be assumed to follow a Bernoulli distribution:

$$Y[i, j, k] \sim dbern(p[i, j, center[k]])$$

where center is an index variable that indicates the center that the individual k was recruited in.

The assumptions are based on a similar model to the model proposed in Legrand et al.[3]. The event rate is assumed to have an additive effect for center that varies within study:

$$logit\left(p\left[i, j, center[k]\right]\right) = \delta[j, center[k]] + \gamma\left[j, center[k]\right] * (i = 2)$$

The two random effects can be interpreted as the influence of the center on the overall TLF rate in study j and on the overall treatment effect, respectively. The center effects $\delta[j, center[k]]$ and $\gamma\left[j, center[k]\right]$ in study j, are assumed to be exchangeable and a priory to follow a normal distribution with mean *mu_delta[j]* and *mu_gamma[j]* and standard deviation *sigma_delta[j]* and *sigma_gamma[j]*, respectively. A uniform prior on (0.1, 10) will be assumed on the random effect variances in study j (*sigma_delta[j]* and *sigma_gamma2[j]*) Geltman et al.[4] Independent weakly informative N(0, 100) priors will be assumed for mu_delta's and mu_gamma's. The standard deviation of the random effects can be viewed as a measure of heterogeneity across centers and treatment effect. A value of 1 for standard deviation of random effects '...corresponds to substantial heterogeneity.' Spiegelhalter et al.[5]; therefore, if in BIOFLOW-V the

[3] Legrand C, Ducrocq V, Janssen P, Sylvester R, Duchateau L. A Bayesian approach to jointly estimate centre and treatment by centre heterogeneity in a proportional hazards model. *Stat Med* 2005; 24(24):3789-804.

[4] Gelman A, Carlin JB, Stern HS, Rubin DB. Bayesian Data Analysis, 1995 Chapman & Hall

[5] Spiegelhalter, D.J., Abrams, K.R. and Myles, J.P. Bayesian Approaches to Clinical Trials and Health-Care Evaluation, John Wiley and Sons, 2004, page 169

posterior probability that *sigma_gamma[1]>1* exceeds 0.85 *and* the credible intervals discussed above indicate the interaction is qualitative in nature, then this may preclude all sites from being pooled for the primary analysis, in which case the primary analysis may be re-run excluding study centers causing the interaction. A similar determination will be made for BIOFLOW-II and BIOFLOW-IV selected subjects that are included in the Bayesian ITT analysis.

2.7.2 Region (US/OUS) Heterogeneity

To assess consistency of treatment effect size across regions (United States [US] vs. Outside United States [OUS]), region and an interaction of region and treatment will be included in the Bayesian model for the BIOFLOW-V study. For the interaction coefficient, we will calculate

$$p_{int} = 2 * min\{P(\beta_{int} > 0|\text{Data}), p(\beta_{int} < 0|\text{Data})\}$$

as the 2-sided posterior probability of observing an interaction value that is more extreme than 0. This value is similar to a traditional p-value. If $p_{int} < 0.15$ we will conclude that heterogeneity across region is significant and the treatment effect will be calculated and tested within region.

2.7.3 Sensitivity Analysis

A sensitivity analysis will be performed on the primary endpoint on the ITT population. TLF will be re-defined as all cardiac death, ARC-defined myocardial infarction (MI), or clinically driven target lesion revascularization (TLR). A Bayesian analysis will be performed on the composite event rate, and a frequentist analysis will be performed on TLF rates and its components.

2.8 Handling of Missing Data in the Analysis of Primary Endpoint

Every effort will be undertaken to limit premature discontinuations and ascertain completeness of data collection. The following analysis strategies will be adopted to handle missing data with results compared for consistency prior to carrying out the above analysis:

1) Only subjects who experienced the primary endpoint (TLF at 12 months) or who had appropriate follow-up (at least 330 days post baseline, given the 30-day visit window allowed around the 12-month visit) will be included in the analysis.

2) All subjects will be included in the analysis set including data for subjects missing primary endpoint status due to not experiencing the event and not reaching at least 330 days of follow-up. Data for these subjects will be included as 'NA'. Bayesian method will be used for the imputation. A model will be used for the event probabilities:

   $$Y[i,j,k] \sim dbern(p[i,j,k]$$

   with

   $$logit(p[i,j,k]) = beta * X[k] + logit(p[i,j])$$

where $X[k]$ are predictors values for subject k. A noninformative prior will be assumed on the slope parameters $beta$ and similarly to the analysis of the primary endpoint, bias will be assumed between TLF rates in different studies.

The following variables will be included in the model as covariates:

- Age (>75, <=75)
- Gender
- Diabetes
- Lesion length (>26 mm, <=26mm)
- RVD (>2.75mm, <=2.75mm)

3) Time to event analysis using a Bayesian time to event exponential regression analysis. The protocol specifies that time to event analysis using a Bayesian Cox regression analysis will be performed as a sensitivity analysis but subsequently we determined that an exponential regression is better for allowing incorporating a bias term between the log hazard rates in BIOFLOW-V and BIOFLOW II and BIOFLOW-IV. For each study, a separate hazard ratio comparing Xience to Orsiro stent will be included. Similar to the method proposed as a primary method, a bias will be assumed between the log hazard of BIOFLOW-II or BIOFLOW-IV and the log hazard of the BIOFLOW-V.

Model

For ease of presentation we assume that no censoring occurs. The below model will accommodate censoring.

For a subject i in the BIOFLOW-V study, if $Y_{X,i}^{V}$ is the time to event, let

$$Y_{X,i}^{V} \sim exponential(\lambda_X^V) \text{ and } Y_{o,i}^{V} \sim exponential(\lambda_O^V)$$

be the distributions of the time (years) to event in the Xience and Orsiro groups, respectively. The values λ_X^V and λ_O^V are the hazards in the Xience and Orsiro groups.

Evidence from BIOFLOW-IV study: It is first discounted using the discount factor a^{IV}. The discounted data are then assumed to follow exponential distributions with hazard rates λ_X^{IV} and λ_O^{IV} in the Xience and Orsiro groups, respectively. For a subject i in the BIOFLOW-IV study, if $Y_{X,i}^{IV}$ is the time to event, let

$$Y_{X,i}^{IV} \sim exponential(\lambda_X^{IV}) \text{ and } Y_{O,i}^{IV} \sim exponential(\lambda_O^{IV})$$

A bias term is assumed to link the TLF hazard rates in BIOFLOW-V and BIOFLOW-IV in each treatment group

- $log(\lambda_X^V) = log(\lambda_X^{IV}) + \delta_X^{IV}$ and $log(\lambda_O^V) = \log(\lambda_O^{IV}) + \delta_O^{IV}$

Evidence from BIOFLOW- II study: It is first discounted using the discount factor a^{II}. The discounted data are then assumed to follow Exponential distributions with hazard rates λ_X^{II} and λ_O^{II} in the Xience and Orsiro groups, respectively,

$$Y_{X,i}^{II} \sim exponential(\lambda_X^{II}) \text{ and } Y_{O,i}^{II} \sim exponential(\lambda_O^{II})$$

A bias term is assumed to link the TLF rates in BIOFLOW-II and BIOFLOW-V in each treatment group.

$$log(\lambda_X^V) = log(\lambda_X^{II}) + \delta_X^{II} \text{ and } log(\lambda_O^V) = log(\lambda_O^{II}) + \delta_O^{II}$$

Prior distribution

The bias terms are assumed to follow a normal distribution with mean 0 and standard deviation τ_1 and τ_2.

$$\delta_X^{II} \sim Normal(0, \tau_1) \text{ and } \delta_O^{II} \sim Normal(0, \tau_1)$$

$$\delta_X^{IV} \sim Normal(0, \tau_2) \text{ and } \delta_O^{IV} \sim Normal(0, \tau_2)$$

As with primary endpoint analysis, a value of 0.3 will be assumed for both τ_1 and τ_2. Non-informative prior distributions are assumed for TLF rates in the BIOFLOW-V study

$$\lambda_X^V \sim gamma(0.1,0.1) \text{ and } \lambda_O^V \sim gamma(0.1,0.1)$$

The non-inferiority condition will be expressed in terms of 1-year TLF rates in the BIOFLOW-V study as with the primary hypothesis

$$P(H_A|Data) = P\left(\pi_X^V - \pi_O^V > -\delta \middle| Data\right) > \pi^*$$

where the 12-month TLF rates will be calculated as

$$\pi_X^V = 1 - \exp(-\lambda_X^V) \text{ and } \pi_O^V = 1 - \exp(-\lambda_O^V)$$

4) A tipping point analysis will be carried out. Here, it is assumed that for all Xience patients with missing primary endpoint (12-month TLF) status, TLF did not occur. For Orsiro patients with missing data, it will be first assumed that the primary endpoint of TLF occurred for exactly one such patient; then the primary analyses will be re-run to assess if non-inferiority is met under this assumption. Then it will be assumed the primary endpoint occurred for exactly two Orsiro patients with missing data, and the primary non-inferiority analysis will be rerun. The process will continue sequentially in this manner until all Orsiro patients with missing data are considered to have met the primary endpoint of TLF. Of interest is the "tipping point", or i.e., the number of imputed Orsiro TLFs where non-inferiority is not met in this analysis.

2.9 Analysis of Secondary Endpoints

The secondary endpoints in the BIOFLOW-V study will be analyzed using frequentist methods. For each endpoint, the proportion and sample size will be calculated and reported for the Xience group and for the Orsiro group. Fisher's exact test will be used to test the difference between the groups. Analyses of secondary endpoints will be carried out on the ITT, Modified ITT and PP analysis sets for BIOFLOW-V. However, there will be no direct imputation of missing data. Secondary Endpoints include the following measures:

1) Device success
2) Lesion success
3) Procedure success

BIOFLOW-V will utilize the percent residual stenosis, as assessed by the investigator for the primary analysis measure of the % residual stenosis for evaluating angiographic success for the aforementioned secondary endpoints. If investigator assessment of residual stenosis is not available, the in stent final % diameter stenosis as assessed by QCA will be used. MACE included in the procedure success will use the primary analysis definitions.

Treatment group difference (Orsiro minus Xience) in the success rates and the two-sided 95% confidence intervals of the difference will be presented.

The following secondary clinical endpoints will be evaluated prior to discharge, at 1-, 6- and 12-months and annually:

4) Death
5) Protocol-defined MI
6) Cardiac death or protocol-defined MI
7) MACE and individual MACE components
8) TLF and individual TLF components
9) TVF and individual TVF components
10) Stent thrombosis according to ARC criteria

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, at least 166 days for the 6-month time point, and at least 330 days for the 12-month time point).

All the re-adjudicated clinical endpoints in BIOFLOW-II and BIOFLOW-IV will be summarized by study and treatment group.

2.10 Analysis of Baseline Demographics and Procedural Characteristics

Demographic and baseline characteristics, procedural characteristics, lesion characteristics will be compared between the two treatment groups in each BIOFLOW-V analysis population (ITT, modified ITT and PP) and the BIOFLOW- II and -IV Bayesian analysis population by treatment. Demographic, medical history and other clinically relevant baseline variables will be summarized by treatment using descriptive statistics (i.e. number of observations available, mean, standard deviation, minimum, and maximum for continuous variables and counts and percentages for qualitative variables). Treatment difference on dichotomous variables will be evaluated using Fisher's exact tests. Categorical variables will be compared between treatments using the Cochran-Mantel-Haenszel (CMH) Modified Ridit Scores[6], i.e. CMH of general association for nominal variables and CMH of row mean score for ordinal variables.

Continuous variables will be compared between treatments using two-sample t-tests.

2.11 Subgroup Analysis

Subgroups for primary endpoint (TLF at 12-Month) using Bayesian analysis for the BIOFLOW-V study include:

[6] van Elteren, P.H. (1960), "On the Combination of Independent Two-Sample Tests of Wilcoxon," Bulletin of the International Statistical Institute, 37, 351-361.

1) Reference vessel diameter ≤ 2.75 mm/ > 2.75 mm. Subjects with at least one target lesion ≤ 2.75 mm will be classified with the small vessel subgroup.
2) Subjects > 75 years of age/subjects ≤ 75 years of age.
3) Women/men.
4) Subjects with diabetes/subjects without diabetes.
5) Lesion length > 26 mm and ≤ 26 mm in length
6) Single stents versus overlapping stents for lesion lengths > 26 mm
7) Subjects with baseline ACS versus without ACS.

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

Treatment group difference (Orsiro minus Xience) in the primary endpoint rate and the two-sided 95% credible interval of the difference will be presented within each subgroup. Only BIOFLOW-V data will be included in these analyses. A test of interaction on the primary endpoint will be performed to formally assess heterogeneity of treatment effect on the primary endpoint across subgroups in the same manner that will be used the assessment of region heterogeneity discussed above. 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. Subjects with an event or with appropriate follow-up will be included in this analysis.

2.12 Adverse Event Analysis

Adverse events collected in the BIOFLOW-V data will be summarized using descriptive statistics

- Site-reported U(S)ADE presented by system organ class and preferred term
- Site-reported AE presented by system organ class and preferred term
- Site-reported SAE presented by system organ class and preferred term
- Site-reported device-related AEs presented by system organ class and preferred term

Posterior probability calculations comparing the treatment groups will only be presented for AEs and SAEs whose frequency exceeds 10. If p_O and p_X are the probability of the AE with the Orsiro and Xience stents, we will report the posterior distribution that $p_O > p_X$, that is, the posterior probability that the probability of the AE is larger with the Orsiro stent than with Xience stent. Non-informative independent priors Beta (0.1, 0.1) will be assumed on p_O and p_X, respectively.

2.13 Additional Analyses

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

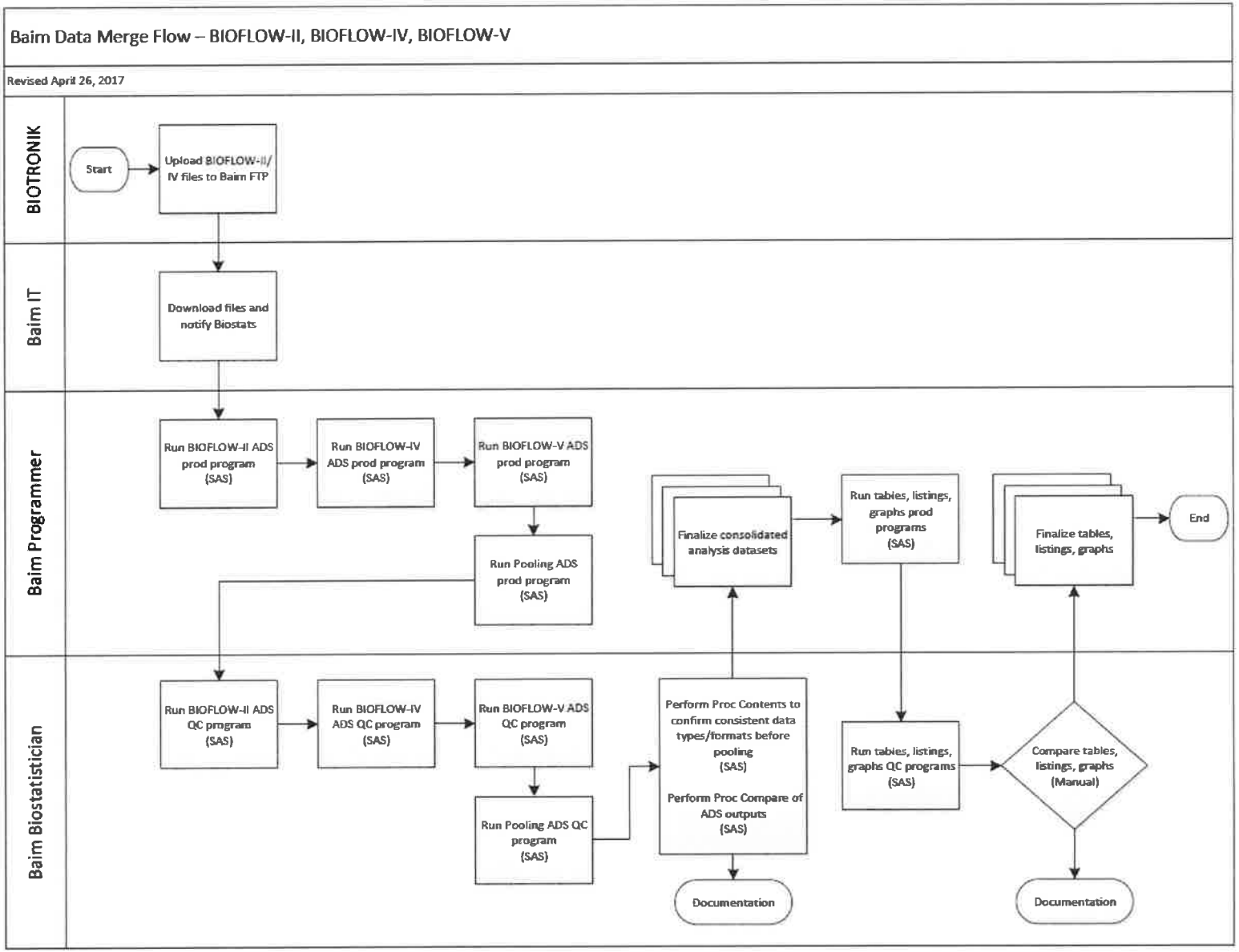
- Subject enrollment by site and compliance by follow-up visits
- Baseline cardiovascular and antidiabetic medication
- Dual Antiplatelet Therapy Compliance (DAPT) at Visit Intervals
- Subjects with missing adequate post-procedure cardiac enzymes will be presented by discharge time.

- Analysis on subjects with missing cardiac enzymes, including the baseline characteristics for subjects with missing adequate pre-procedure and missing post-procedure cardiac enzymes, respectively. This analysis will also be performed in BIOFLOW-II and -IV.
- Primary endpoint analyzed removing the peri-procedural MIs.

3 BIOFLOW-II and BIOFLOW-IV DATA for ANALYSIS

Data from BIOFLOW-II and BIOFLOW-IV studies will be uploaded by Biotronik as zip files on a Baim internal FTP. Baim's IT Department will copy the zip files to standard network folders, one for each protocol, where Baim's clinical data is stored, per guideline GIT.011. Zip files will be opened using WinZip software and their contents will be extracted to the same subfolders. Baim's Project Management representative will be notified once the download and extract of both protocols' zip files. In creating the analysis data, data for the BIOFLOW-II and BIOFLOW-IV studies will be processed using the same scripts used for data processing for BIOFLOW-V to assure a uniform definition of the analysis data across the 3 studies. The resulting data for the 3 studies will be merged into a single dataset (analysis data set, ADS), which will follow a separate document (ADS specification) containing all the specific data mappings across BIOFLOW-II, BIOFLOW-IV and BIOFLOW-V. The detailed schematic of the steps, qualify control (QC) associated with the data merge process are outlined in the data merge flow diagram below.

Combined analysis (of II, IV and V using Bayesian statistics) will be performed for the TLF (primary endpoint) and its components; combined analysis will not be performed for other secondary endpoints.


Baim Data Merge Flow – BIOFLOW-II, BIOFLOW-IV, BIOFLOW-V
Revised April 26, 2017
BIOTRONIK
Start
Upload BIOFLOW-II/IV files to Baim FTP
Baim IT
Download files and notify Biostats
Baim Programmer
Run BIOFLOW-II ADS prod program (SAS)
Run BIOFLOW-IV ADS prod program (SAS)
Run BIOFLOW-V ADS prod program (SAS)
Run Pooling ADS prod program (SAS)
Finalize consolidated analysis datasets
Run tables, listings, graphs prod programs (SAS)
Finalize tables, listings, graphs
End
Baim Biostatistician
Run BIOFLOW-II ADS QC program (SAS)
Run BIOFLOW-IV ADS QC program (SAS)
Run BIOFLOW-V ADS QC program (SAS)
Run Pooling ADS QC program (SAS)
Perform Proc Contents to confirm consistent data types/formats before pooling (SAS)
Perform Proc Compare of ADS outputs (SAS)
Documentation
Run tables, listings, graphs QC programs (SAS)
Compare tables, listings, graphs (Manual)
Documentation

4. Addendum

Bayesian superiority analysis is performed if the primary hypothesis of non-inferiority is met. The superiority hypothesis is evaluated by computing the posterior probability of the superiority alternative hypothesis. This posterior probability is compared against the same threshold pre-specified for the non-inferiority test (97.5%).