STATISTICAL ANALYSIS PLAN

JNIR01

MULTI-CENTER STUDY FOR EVALUATING THE SAFETY AND EFFICACY OF THE RIDAFOROLIMUS ELUTING CORONARY STENT SYSTEM (MEDJ-01) IN CORONARY STENOSIS TRIAL

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final V1.0 (Dated 08Aug2018) for Protocol JNIR01.

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1. List of Abbreviations and Definitions of Terms

ACS	Acute Coronary Syndrome
AE	Adverse Event
ARC	Academic Research Consortium
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
Ccr	Calculated creatinine clearance
CEC	Clinical Events Committee
CI	Confidence Interval
CK	Creatine Kinase
CK-MB	Creatine Kinase Muscle-Brain Isoenzyme
CRF	Cardiovascular Research Foundation
DAPT	Dual Antiplatelet Therapy
DS	Diameter Stenosis
ECG	Electrocardiogram
eCRF	electronic Case Report Form
FFR	Fractional Flow Reserve
FAS	Full Analysis Set
IS	Interpolated Reference Vessel Diameter
LAD	Left Anterior Descending Artery
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Event
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MIN	In Stent Minimum Lumen Diameter
PCI	Percutaneous Coronary Intervention
PPS	Per Protocol Set
PT	Preferred Term
QCA	Quantitative Coronary Angiography
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
STEMI	ST Elevation Myocardial Infarction
TIMI	Thrombolysis In Myocardial Infarction
TLF	Target Lesion Failure
TLR	Target Lesion Revascularization
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization
ULN	Upper Limit of Normal
USADE	Unanticipated Serious Adverse Device Event

WHODD	WHO Drug Dictionary

2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol JNIR01. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 2.0, dated September 18, 2016.

3. STUDY OBJECTIVES

The objective of this clinical trial is to evaluate MedJ-01 safety and efficacy for de novo or restenosis lesion with target vessel diameter of 2.5 mm to 4.25 mm, for patients undergoing coronary artery stent implantation.

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

This is a prospective, multi-center, single-arm, open label clinical trial. Lesions planned to be treated must be declared and recorded at time of enrollment.

The JNIR01 Trial will enroll approximately 100 patients with a wide spectrum of Percutaneous Coronary Intervention (PCI) indications (stable angina as well as Acute Coronary Syndrome (ACS), including subacute STEMI (>72 hours since first hospital presentation).

Clinical follow-up will be performed at 30 days, 6 months, and 1, 2, 3, 4, and 5 years post enrollment.

Adjudication of study endpoints will be determined by an independent clinical events committee (CEC). The CEC will be responsible for the adjudication of the clinical trial endpoint events as well as all deaths that occur throughout the trial and device non-success.

4.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 6.1.4 (Table 3) of the protocol.

4.3. CHANGES TO ANALYSIS FROM PROTOCOL

- The protocol uses the term clinically driven and ischemia driven interchangeably. This SAP defines revascularization events accordingly to the term “clinically driven” as this is consistent with the CEC adjudication form.

- The protocol defines the as-treated (AS) population which contains only those Japanese patients who received the study stent. However, this population is not used in any of the analyses and will not be defined in this SAP.
- The protocol suggests a sensitivity analysis based on modified definitions of peri-procedural myocardial infarction (universal definition and modified SCAI definition). This analysis will not be performed for the purpose of assessing the non-inferiority of JNIR01 to BIONICS in terms of Target Lesion Failure at 12 months.

5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analysis of the primary endpoint and main secondary endpoints after 1 year follow-up
- Final Analysis after 5 years follow-up

Except for analyses involving the use of data from the BIONICS trial and analyses of quantitative coronary angiography and electrocardiogram from Core Laboratories, all final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following sponsor authorization of this SAP and database lock.

The primary analysis, non-inferiority of JNIR01 Target Lesion Failure at 12 months (TLF_{12}) to the BIONICS TLF_{12}, and all analyses involving the use of data from the BIONICS trial will be conducted by Cardiovascular Research Foundation (CRF) following the specifications given in this SAP and using data from the JNIR01 and the BIONICS trials.

Analyses of quantitative coronary angiography and electrocardiogram data from Core Laboratories, Cardiovascular Research Foundation, will also be performed by Cardiovascular Research Foundation.

6. ANALYSIS SETS

Agreement and authorization of patients included/excluded from each analysis set will be obtained from Medinol or representative prior to database lock of the trial.

6.1. ALL PATIENTS SCREENED SET [APSS]

The All Patient Screened Set will include all patients who signed an informed consent.

6.2. FULL ANALYSIS SET [FAS]

The Full Analysis Set (FAS) will contain all enrolled Japanese patients regardless of whether they were given MedJ-01.

Patients are considered enrolled after the guidewire has successfully been passed beyond the target lesion. If the study stent could not be implanted due to reasons that are not related to study device, the patient will be de-registered and will not be considered part of the FAS. Patients not receiving the study stent after it has been advanced beyond the guiding catheter will be analyzed in the FAS. Patients enrolled in the trial with major deviations will also be analyzed in the FAS.

6.3. PER PROTOCOL SET [PPS]

The Per Protocol Set (PPS) will contain all patients who receive the study stent with no major protocol violations. Major protocol violations include enrollment of a patient:

- whose informed consent was not properly obtained
- who did not meet all of the inclusion or exclusion criteria
- who did not receive the study stent due to any reason
- who did not receive at least 12 months of Dual Antiplatelet Therapy (DAPT) post baseline procedure. Details of DAPT to be received post-procedure are given in Section 6.4.9.3 of the protocol.

Major protocol violations leading to exclusion from the PPS will be summarized using the FAS.

6.4. SAFETY ANALYSIS SET [SAF]

The Safety Analysis Set (SAF) will include all patients who signed an informed consent and have had any trial related activities including de-registered patients. Screen failure patients will not be included in the SAF.

7. GENERAL CONSIDERATIONS

7.1. SUMMARY STATISTICS

Descriptive statistics of continuous variables will include number of observations available, mean, standard deviation, median, minimum, maximum, first quartile, and third quartile.

For categorical variables, the number within each category and the percentage out of the total number of observations available will be summarized. For that purpose, all variables with values missing, 'Unknown' or with values associated with 'Not applicable', 'Not Done', 'Not Reported' or 'Not Answered' will be set to missing and will not be included in the denominator for percentage calculation.

7.2. STUDY DAY

Study Day will be calculated from the date of enrollment (Day 1 is the day of enrollment), and will be used

to show start/stop day of assessments and events in the listings.

- If the date of the event is on or after the enrollment date then:
  Study Day = (date of event – enrollment date) + 1.
- If the date of the event is prior to the enrollment date then:
  Study Day = (date of event – enrollment date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear missing in the listings.

7.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but will contribute to the best/worst case value where required (e.g. shift table).

Listings will include scheduled, unscheduled, retest and early discontinuation data.

7.4. WINDOWING CONVENTIONS

Follow up visits (windows) are scheduled at the following time points post procedure: 30 days (±7 days), 6 months (± 30 days), 1 year (-30 days/+14 days), and 2, 3, 4, and 5 years (± 60 days).

7.5. STATISTICAL TESTS

Only non-inferiority of JNIR01 Target Lesion Failure at 12 months (TLF_{12}) to the BIONICS TLF_{12} will be formally tested in this trial. The secondary endpoints will not be formally tested for non-inferiority and testing will be considered descriptive. Details are given in Section 15.

7.6. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

8. STATISTICAL CONSIDERATIONS

8.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

No adjustments for covariates are planned for the statistical analyses.

8.2. MULTICENTER STUDIES

Because a small number of patients are expected at each center, data from all centers will be pooled and no center effect will be investigated.

8.3. MISSING DATA

Missing data will not be imputed (except for the purpose of reporting adverse events and medications by time point, see APPENDIX 2 for partial date imputation conventions).

All available data will be included in the safety analysis. Some efficacy analyses are based on excluding patients who do not have adequate follow-up time.

8.4. MULTIPLE COMPARISONS/ MULTIPLICITY

Only non-inferiority of JNIR01 TLF_{12} to the BIONICS TLF_{12} will be formally tested in this trial and therefore no multiplicity adjustment will be performed. The secondary endpoints will not be formally tested for non-inferiority and testing will be considered descriptive.

8.5. ACTIVE-CONTROL STUDIES INTENDED TO SHOW NON-INFERIORITY OR EQUIVALENCE

JNIR01 is aimed at assessing TLF at one year with the MedJ-01 stent in a Japanese patient population to show non-inferiority of JNIR01 TLF_{12} to the BIONICS TLF_{12}.

The non-inferiority margin will be set to 0.05 (5%). This margin, 1.5 times that of BIONICS, leverages a reasonable clinical threshold with safety concerns over sample size.

If the one-sided 90% confidence interval for the upper bound of the difference (JNIR01 TLF_{12} minus BIONICS TLF_{12}) is less than this pre-specified non-inferiority margin, then the null hypothesis is rejected.

Details of the statistical method used to test non-inferiority are given in Section 15.1.

8.6. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for this study.

9. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP (separate document) describe the presentations for this study and therefore the format and content of the summary tables and listings to be provided by IQVIA Biostatistics and Cardiovascular Research Foundation.

10. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study. A tabulation of patient disposition will be presented for the APSS including number enrolled, number in each patient population, and number of withdrawals, including reasons for withdrawal as documented on the eCRF.

Protocol deviations as reported on the eCRF will be will be presented as part of the listings including the deviation category, description and type.

The number of patients who fail to meet each inclusion criterion or meet any exclusion criterion (including angiographic criterion) will be presented for the FAS.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the FAS.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to the date of enrollment
- Age groups: < 65 years, ≥ 65 years
- Gender (with childbearing potential for females)
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- BMI (kg/m2)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (bpm)

11.1. DERIVATIONS

- BMI (kg/ m2) = weight (kg)/ height (m)2

12. MEDICAL HISTORY

The following medical history information will be presented for the FAS:

- Acute coronary syndrome (Y/N)
- Previous myocardial infarction (Y/N)
- History of angina pectoris (Y/N)
  - CCS class (I, II, III, IV)
- Previous PCI (Y/N)
  - Target vessel
    - Target lesion treated
  - Non-target vessel
  - Method of treatment (PTCA, stenting, other)
- Previous CABG (Y/N)
  - Target vessel
  - Non-target vessel
- LVEF assessed prior to index procedure (Y/N)
  - LVEF (%)
- Family history of premature coronary disease (Y/N)
- Diabetes mellitus (Y/N)
  - Type (I, II)
  - Controlled by (insulin, oral medications, diet/untreated)
- Hypertension (Y/N)
  - Medically treated (Y/N)
- Hyperlipidemia (Y/N)
  - Medically treated (Y/N)
- Previous TIA (Y/N)
- Previous CVA (Y/N)
- Congestive Heart Failure (Y/N)
  - NYHA Class (I, II, III, IV)
- Vascular Disease (Y/N)
- Atrial fibrillation (Y/N)
- History of Bleeding complications (Y/N)
  - BARC Classification (type 0, 1, 2, 3, 4, 5)
- Renal Insufficiency (Y/N)

- History of Smoking/Alcohol (Smoking status, average number of cigarettes per day, number of years smoking, alcohol abuse status)

Other medical/surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 21.0 or a later version. The other medical/surgical history will be summarized by system organ class (SOC) and preferred term (PT) within system organ class for the FAS, with SOC sorted alphabetically and PT within SOC by descending incidence. Investigator verbatim as well as preferred terms and system organ class will be included in the listings.

13. STUDY STENT PROCEDURAL INFORMATION

Site reported procedure characteristics will be summarized on patient level for the FAS and will include the following:

- Any Intervention: pre-dilatation of at least one target lesion performed, any atherectomy, cutting/scoring balloon, any thrombectomy/aspiration, one or more stents implanted in target vessel
- Patients with stents implanted in target vessel (number of stents implanted, number of patients with overlapping stents, total stents length implanted in mm)
- Any post-stent dilatation
- Number of diseased vessels
- Multiple diseased vessels (1, 2, 3, 4)
- Location of diseased vessels (LAD/Diag, LCX/OM/Ramus, RCA/RPDA/RPL, Protected LM, Bypass vein or artery)
- Number of treated lesions
- Multiple lesions treated (1, 2, 3, 4)
- Bailout procedure
- Any procedural complications
- Any staged procedure planned
- Procedure duration in minutes calculated as procedure end date/time – procedure start date/time + 1
- Number of hospital nights calculated as hospital discharge date - procedure start date

14. TARGET LESION CHARACTERISTICS

The following site reported target lesion characteristics will be summarized on lesion level for the FAS:

- Location of lesion
- % Diameter stenosis pre procedure
- Reference Vessel Diameter in mm
- Lesion length in mm
- Pre-Dilatated
    - Balloon Length, mm

  - Nominal Diameter,mm
  - Maximum Balloon Pressure, atm
- FFR performed (Y/N)
  - Hyperemic FFR
- Number of stents per lesion (1, 2, 3, >3, more than one stent implanted)
- Total stent length per lesion, mm
- Maximum stent balloon pressure, atm (For each lesion, the stent with the maximum pressure will be reported)
- Maximum stent diameter, mm (For each lesion, the stent with the maximum stent diameter will be reported)
- Stent post dilated
- % Diameter stenosis (final)

15. EFFICACY OUTCOMES

Per protocol, patients may have multiple target lesions treated. For patient level endpoints, only one lesion per patient is required to meet the criteria for the endpoint. All endpoints are summarized on a patient level, except when noted.

For the binary primary and selected secondary endpoint event rates to be calculated, the denominator will include only patients who have either had the event by the time of interest (end of the visit window), or had follow-up (starting from the beginning of the visit window) for the endpoint. Visit windows are defined in Section 7.5.

For example, at the 1 year analysis (day 365), only patients who have either had the event by day 365 + 14 = 379 or had follow-up up to day 365 - 30 = 335 will be included in the analysis for the endpoint. In this example, if a patient has an event at day 10 post procedure, the patient will be included in the 1 year analysis and counted as an event. However, if a patient drops out of the study at day 10 post procedure without an event (e.g., due to withdrawal of consent) the patient will not be included in the analysis.

All events as reported by the CEC as well as by the sites will be listed.

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy variable is target lesion failure (TLF) at 12 months post-procedure defined as the composite of cardiac death, target vessel related myocardial infarction (MI), or clinically-driven target lesion revascularization (TLR) as adjudicated by the CEC. This endpoint includes spontaneous MIs and peri-procedural MIs adjudicated per the Universal definition [1] and SCAI definition [2], respectively.

15.1.2. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary objective of this study is to measure the non-inferiority of JNIR Target Lesion Failure at 12 months (TLF_{12}) to the BIONICS TLF_{12}.

The trial defines the statistical null hypothesis as

H_{Null}: TLF_{12} (JNIR) > TLF_{12} (BIONICS) + δ

$H_{Alternative}$: TLF_{12} (JNIR) ≤ TLF_{12} (BIONICS) + δ

or in terms of absolute event-rate difference

H_{Null}: TLF_{12} (JNIR) - TLF_{12} (BIONICS) > δ

$H_{Alternative}$: TLF_{12} (JNIR) - TLF_{12} (BIONICS) ≤ δ

where δ=0.05 is the margin of non-inferiority (refer to Section 8.5).

The primary efficacy analysis will be performed for the FAS. Only patients with appropriate follow up (>=335 days post procedure) or who experienced the primary endpoint by the end of the 365 day visit window (day 379) will be included.

A comparison of the proportion of patients with TLF at 12 months will be performed using the Farrington-Manning test of non-inferiority for two binomial proportions with a non-inferiority margin of δ=0.05 at the 0.1 level of significance (one-sided) [3].

The Farrington-Manning test statistic will be calculated as follows:

$$\tau = \frac{\mathrm{TLF}_{12}\,(\mathrm{JNIR}) - \mathrm{TLF}_{12}\,(\mathrm{BIONICS}) - \delta}{\sqrt{\frac{\mathrm{TLF}_{12}\,(\mathrm{JNIR})[1 - \mathrm{TLF}_{12}\,(\mathrm{JNIR})]}{N(\mathrm{JNIR})} + \frac{\mathrm{TLF}_{12}\,(\mathrm{BIONICS})[1 - \mathrm{TLF}_{12}\,(\mathrm{BIONICS})]}{N(\mathrm{BIONICS})}}}$$

where *N*(JNIR) and *N*(BIONICS) are the number of patients from the JNIR trial and BIONICS trial, respectively.

Propensity score matching will identify a covariate-unbiased population of patients between the JNIR and BIONICS patient population. To maximize power and take advantage of the large BIONICS study, 4:1 matching will be done. This covariate-unbiased population will be used to calculate TLF_{12} (BIONICS) and *N*(BIONICS) in the Farrington-Manning test statistic.

The probability a patient (x) belongs to JNIR versus BIONICS, conditional on a set of potential confounding covariates (C), defines the propensity score $\rho(x \mid C)$. Logistic regression will model this probability as

$$\rho(\mathrm{x} \mid \mathrm{C}) = \mathrm{logit}^{-1}\left(\sum_{c \in C} c\right)$$

where $\mathrm{logit}^{-1}(x) = \frac{1}{1+e^{-x}}$.

Matching of patients from JNIR to patients from BIONICS will be done using the following covariates which

are known to confound the relationship between study-stent and outcome:

Covariates considered in propensity-score matching:

Clinical Parameters (as captured in the eCRF):

- Age
- Gender
- Prior MI
- Medically treated diabetes Mellitus
- Prior Revascularization (Either previous PCI or previous CABG captured on the medical history eCRF form)
- Acute Coronary Syndrome

Pre-procedure Angiographic Parameters (as reported in the Quantitative Coronary Angiography (QCA) data):

- Diameter Stenosis
- Reference Vessel Diameter
- Calcification
- TIMI Flow (Pre-procedure)
- Tortuosity
- SYNTAX Score
- Lesion located at LAD

After each patient in both JNIR and BIONICS has received a propensity score, these two groups will be combined and partitioned into propensity score quintiles.

Finally, each JNIR patient in quintile x is matched with 4 random BIONICS patients from the same quintile x. If no remaining BIONICS patients are left to match with JNIR patients in one of the five quintiles, the next closest quintile will be used to choose a BIONICS patient.

The clinical and angiographic covariates used in the propensity-score matching will be summarized for the FAS by treatment group.

The proportion of TLF as well as proportions of cardiac death, target vessel related MI and clinically-driven TLR at 12 months along with the corresponding exact 95% CIs will be presented for the JNIR group and matched BIONICS group. The difference in proportion will be reported. Farrington-Manning one-sided p-value and upper bound of the one-sided 90% CI of the difference in proportion between JNIR and matched BIONICS groups will be presented.

15.1.3. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

The primary analysis will be repeated for the PPS.

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15.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed for the FAS.

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

15.2.1.1. Device, Lesion, and Procedure Success at Time of Baseline Procedure

- Device success is defined as achievement of a final in-stent residual diameter stenosis of <50% by Quantitative Coronary Angiography (QCA) in the target lesion, using the assigned device only and without a device malfunction. Device malfunctions are defined as occurring during the time of use.
  From final procedure QCA, Residual Diameter Stenosis (DS):

  DS = 100*(1-mean (MIN1, MIN2) / mean (IS1, IS2)

  Where 1 refers to projection = Projection 1

  2 refers to projection = Projection 2

  MIN: In stent minimum lumen diameter

  IS: interpolated reference vessel diameter

  If DS <50% and no device malfunction then Device Success = 1

  Else if DS>=50% then Device Success = 0.

- Lesion success is defined as achievement of a final in-stent residual diameter stenosis of <50% (by QCA) in the target lesion using any percutaneous method.
  From final procedure QCA, Residual Diameter Stenosis (DS) is calculated using the formula given above and:

  If DS <50% then Lesion Success = 1

  Else if DS ≥50% then Lesion Success = 0.

- Procedure success is defined as achievement of a final in-stent diameter stenosis of <50% (by QCA) using the assigned device and/or with any adjunctive devices, without the occurrence of cardiac death, Q wave or non-Q wave MI, or repeat revascularization of the target lesion during the hospital stay. Each Event is defined from adjudication, with peri-procedural MIs adjudicated per SCAI [2] definition.

The analysis of device success and lesion success will be performed on lesion level, i.e., the numerator will be the number of target lesions meeting the criteria for device or lesion success, respectively, and the denominator will be the total number of target lesions.

The analysis of procedure success will be performed on patient level, i.e., the numerator will be the number of patients with all target lesions meeting the criteria for procedure success and the denominator will be the total number of patients.

These analyses will be performed by Cardiovascular Research Foundation.

15.2.1.2. Clinical secondary endpoints defined from CEC adjudication data

The following secondary clinical endpoints as adjudicated by the CEC will be evaluated at 30 days, 6 months, and 1, 2, 3, 4, and 5 years, except as noted:

- TLF at 30 days, 6 months, and 2, 3, 4 and 5 years defined as the composite of cardiac death, target vessel related MI, or clinically-driven TLR.
- Major adverse cardiac events (MACE; the composite rate of cardiac death, any MI or clinically-driven TLR)
- Target vessel failure (TVF; the composite rate of all-cause death, target vessel related MI or clinically-driven TVR)
- All-cause mortality
- Cardiac death
- Myocardial infarction
- Target vessel related MI
- Clinically-driven TLR: TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel (i.e. revascularization) performed for clinically driven restenosis or other complication of the target lesion.
- Clinically-driven TVR: TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel (i.e. revascularization) performed for clinical driven restenosis.
- Stent thrombosis: Stent thrombosis is defined according to timing, type, and degree of certainty per ARC definition (Table A:). Stent thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guiding catheter has been removed and the patient left the catheterization lab after the baseline procedure. Stent thrombosis will also be reported by ARC category and, in particular, for ARC categories definite and probable.

Table A: ARC Definition of Stent Thrombosis

Timing	Acute Subacute Late Very late	≤ 24 hours post stent implantation > 24 hours to 30 days post stent implantation > 30 days to 1 year post stent implantation > 1 year post stent implantation
Type	Primary	Occurs in target lesion or margins after baseline procedure
	Secondary	Occurs after revascularization (TLR, TVR, or non-TVR)

Category	Definite	Definite stent thrombosis is confirmed by either angiographic* or pathologic† analysis
	Probable	Probable stent thrombosis is considered to have occurred after intracoronary stenting for either: • any unexplained death within the first 30 days unless that patient had baseline procedure for ST elevation MI • any MI, irrespective of time after baseline procedure, that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause
	Possible	Possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up
* †: Refer to protocol Section 21.1		

15.2.2. ANALYSIS OF SECONDARY EFFICACY VARIABLES

Selected secondary efficacy data will be analyzed as binary variables and summarized with patient counts (or lesion counts as appropriate), percentages, and exact 95% confidence intervals. Treatment group differences will be summarized with 95% confidence intervals. These binary variable summaries will be provided for:

- Device, lesion, and procedure success rates
- Stent thrombosis by category, timing and type
- Site reported bleeding events

The clinical secondary endpoints will be analyzed as time to event variables.

The secondary endpoints will not be formally tested for non-inferiority and testing will be considered descriptive.

Refer to Sections 15.2.2.1 and 15.2.2.2 for details

15.2.2.1. Analysis of Binary Variables

For the summary of secondary endpoints as binary variables by time point, only patient who had the event by the time of interest (end of the visit window for that time point), or had follow-up (starting from the beginning of the visit window) for the endpoint will be included in the analysis. Visit windows are defined in Section 7.5.

Binary secondary endpoints will be compared between treatment groups using a Chi-square test (two-sided) and Wald 95% CI will be provided for the difference. Fisher's exact p-value (two-sided) and corresponding CI for difference will be provided when at least one cell has an expected frequency of less than five.

The difference in proportion (95% CI) will be reported.

15.2.2.2. Analysis of Time to Event Variables

Survival analysis techniques will be used to analyze the time-to-event variables. Time to event analysis will be performed for each time point separately (i.e. up to 30 days, 6 months, and 1, 2, 3, 4, and 5 years). Patients without events will be censored at the patients' early withdrawal date or the last known event-free time point. If this event-free time point occurs after the analysis time point, the days to event variable will be set equal to the analysis time point so that the patient will be included in the analysis (e.g. if the last data point for a patient without an event is at 3 years and 1 week, for the 3 year time to event analysis, this patient will be censored at 3 years). When analyzing composite endpoints, time is measured from enrollment to the first event (days).

Kaplan Meier estimated event rate and number of events will be reported at 30 days, 6 months, and 1, 2, 3, 4, 5 years. The following statistics will be reported at the indicated time: log rank p-value, and hazard ratio (Wald's 95% CI) obtained via Cox proportional hazards regression.

16. QUANTITATIVE CORONARY ANGIOGRAPHY

Analyses of data from the central QCA (Quantitative Coronary Angiography) Core Laboratories will be performed by the Cardiovascular Research Foundation on the FAS. Angiography will be measured once at the patient's baseline visit and will follow this SAP's guidelines for analyzing categorical and continuous variables.

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set unless otherwise specified.

Only data of the JNIR trial will be presented for the safety outcomes. In particular, there will be no statistical comparisons between JNIR and BIONICS trials for the safety outcomes.

17.1. ADVERSE EVENTS

All adverse Events (AEs) collected will be coded using MedDRA, Version 21.0 or a later version.

An overall summary of number of patients within each of the categories described in the sub-section below, will be provided overall and by time point: Prior to hospital discharge, within 30 days (+7 days), 6 months (+30 days), 1 year (+14 days), 2 years (+60 days), 3 years (+60 days), 4 years (+60 days) and 5 years (+60 days). An AE will be included in the summary for a particular time point if the AE started any time prior to the end of the visit window for that time point. See APPENDIX 2 for handling of partial start dates for AEs.

AEs will be summarized using descriptive statistics (i.e., number and percentage of patients) showing the number of events and the number of patients with each event. The summary will include any AE, severity of AEs, investigator assessment of relationship of AEs to study procedure/study device/drug embedded into the study device, serious AEs (SAEs), criteria for SAEs, and unanticipated serious adverse device effect (USADE).

A listing will be provided for serious adverse events/USADE and will include identification of the event by investigator term, date and time started, severity, relationship to study procedure/study device/drug embedded into the study device, action taken, and date and time resolved.

For the analysis at 1 year follow-up, only AEs with onset dates up to 1 Year (+14 days) will be reported as part of the tables.

17.1.1. ALL AEs

Incidence of AEs and SAEs will be presented by System Organ Class (SOC) and Preferred Term (PT).

17.1.1.1. Serious Adverse Events/USADE

Serious adverse events (SAEs) and USADE are identified on the Serious Adverse Event (SAE)/Device Deficiency eCRF page. SAEs are classified according to the following criteria:

- Led to a death
- Led to a serious deterioration in health of the patient, that either resulted in:
  - a life threatening illness or injury
  - a permanent impairment of a body structure or body function
  - in-patient or prolonged hospitalization
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect

The incidence of SAEs, USADE as well as number and percentage of patients by SAE criteria will be reported.

17.1.1.2. Severity

Severity is classified as mild/moderate/severe (increasing severity). AEs with a missing severity will be classified as severe.

17.1.1.3. Relationship to Study Procedure/Study Device/Drug Embedded into the Study Device

Relationship to study procedure/study device/drug embedded into the study device, as indicated by the investigator, is classed as “not related”, “unlikely related”, “possibly related” and “related” (increasing severity of relationship). AEs with a missing relationship will also be regarded as “related”.

17.2. DEVICE DEFICIENCIES, MALFUNCTIONS

Device deficiency is defined as the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

Details of device malfunction/deficiencies and whether any (serious) adverse events were associated with device malfunction/deficiencies (Y/N) will be tabulated.

17.3. DEATHS

A by-patient listing of deaths will be presented.

17.4. LABORATORY EVALUATIONS

The following laboratory parameters are collected at screening only and will be summarized descriptively using standard international units for the FAS:

- Complete Blood Cell Count: Red Blood Cell count (10^6/µL), White Blood Cell count (10^3/µL), Hemoglobin (g/dL), Hematocrit (%), and Platelet count (10^3/µL)
- Serum Creatinine (mg/dL)
- BUN (mg/dL)
- Lipid profile: Total Cholesterol (mg/dL), LDL (mg/dL), HDL (mg/dL), and Triglycerides (mg/dL)

Creatinine clearance (mL/min) will be calculated using Cockcroft-Gault equation as specified in Section 17.4.1 and will be summarized descriptively.

The following cardiac biomarkers will be classified as how many times their value is greater than ULN and will be summarized descriptively at pre-procedure and post-procedure for the Safety Analysis Set:

- CK (times ULN)
- CK-MB (times ULN)
- Troponin T or I (times ULN)

For patients who have multiple cardiac biomarker assessments at any time point, the following rules will be followed:

- For pre-procedure, the latest value before the procedure will be used for analysis.
- For post-procedure, the highest value observed within 48 hours after the procedure will be used for analysis.

17.4.1. LABORATORY SPECIFIC DERIVATIONS

Calculated creatinine clearance (Ccr) will be calculated using Cockcroft-Gault equation as follows:

- Male: Ccr (mL/min) = {(140 – age) x weight (kg)}/{72 x serum creatinine level (mg/dL)}
- Female: Ccr (mL/min) = 0.85 x {(140 – age) x weight (kg)}/{72 x serum creatinine level (mg/dL)}

17.4.2. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

The number and percentage of patients meeting the following abnormal criteria at screening will be presented:

- White Blood Cell count < $3x10^3/\mu L$
- Hemoglobin < 10 g/dL
- Hematocrit < 30%
- Platelet Count < $100 x10^3/\mu L$
- Calculated creatinine clearance < 30 mL/min

For cardiac biomarkers, frequency and percentage of patients falling into each of the following categories will be presented at pre-procedure and post-procedure:

- For CK and CK-MB:
  - ≤ULN, >1 X ULN, > 1-3 ULN, ≥ 3 x ULN, ≥ 3-5 ULN, ≥ 5 x ULN, ≥ 5-10 ULN, ≥ 10 x ULN
- For Troponin T or I:
  - ≤ULN, >1 X ULN, > 1-3 ULN, ≥ 3 x ULN, ≥ 3-5 ULN, ≥ 5 x ULN, ≥ 5-10 ULN, ≥ 10 x ULN, ≥ 10-35 ULN, ≥ 35 ULN, ≥35-70 x ULN, ≥70 ULN

In addition, shift in cardiac biomarkers from pre-procedure to post-procedure values will be presented using the following categories:

- For CK and CK-MB:
  - ≤ULN, > 1-3 ULN, ≥ 3-5 ULN, ≥ 5-10 ULN, ≥ 10
- For Troponin T or I:
  - ≤ULN, > 1-3 ULN, ≥ 3-5 ULN, ≥ 5-10 ULN, ≥ 10-35 ULN, ≥35-70 x ULN, ≥70 ULN

17.5. ECG EVALUATIONS

Analyses of data from the central ECG (Electrocardiogram) Core Laboratories will be performed by Cardiovascular Research Foundation. ECGs will be measured at pre-procedure, post-procedure and 1 year follow-up visit, analysis will follow this SAP's guidelines for analyzing categorical and continuous variables.

12-Lead ECG results as reported in the eCRF will be listed.

17.6. OTHER SAFETY ASSESSMENTS

17.6.1. CONCOMITANT MEDICATIONS

Medication use will be summarized at pre-procedure (within 24 hours of procedure), during procedure and post procedure (separately for: until hospital discharge, 30-day, 6-month, 1, 2, 3, 4 and 5-year), see Section 7.5 for windowing conventions. The following medication types will be summarized: P2Y12 antagonist, aspirin, statin, non-statin lipid lowering, ACE Inhibitors, Angiotensin Receptor Blocker (ARB), beta blockers, calcium channel blockers, other anti anginals, other.

See APPENDIX 2 for handling of partial dates for medications. If there is no termination date indicated and if ongoing is indicated, then the patient is assumed to be on the medication through each time point that the patient has reached.

Medications will be coded to ATC and preferred name using WHO Drug Dictionary (WHODD), 01Mar2017 or later.

A listing of medications, including the medication name, ATC level and preferred name, start and stop date, and discontinuation reason will be presented in the data listings by patient and medication type.

17.6.2. ANGINA STATUS

The number and percentage of patients belonging to the following angina status categories will be summarized by visit:

- Experienced angina
- Status (stable, unstable)
- Highest CCS class (class I, II, III or IV)
- Highest Braunwald I (including I, IA, IB and IC)
- Highest Braunwald II (including II, IIA, IIB and IIC)
- Highest Braunwald III (including III, IIIA, IIIB and IIIC)

17.6.3. COMPLIANCE

Compliance will be summarized overall and by site as the percentage of patients completing study protocol required visit at 30 days, 6 months, and 1,2,3,4, and 5 year. Patients whose visits dates are within the time interval (See Section 7.5) for the visit are summarized in the numerator and the denominator includes patients expected to receive follow-up (based on the FAS), and excludes those who died or withdrew before the study time point.

18. DATA NOT SUMMARIZED OR PRESENTED

All data will be presented in the listings.

19. REFERENCES

[1] Thygesen, K., et al., Third universal definition of myocardial infarction. J Am Coll Cardiol, 2012. 60(16): p. 1581-98.

[2] Moussa, I.D., et al., 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. 62(17): p. 1563-70.

[3] Farrington, C.P. and G. Manning, Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med, 1990. 9(12): p. 1447-54.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to IQVIA Global Biostatistics Standard Output Conventions.

STATISTICS PRESENTATION

- Statistics should be presented in the same order across tables as follows:
- N
- Mean (SD)
- Median (Q1, Q3)
- Min, Max
- If the original data has N decimal places, then the summary statistics should have the following decimal places, unless otherwise specified:
- Minimum and maximum: N
- Mean, median, Q1 and Q3: N + 1
- SD: N + 2
- Percentages will be reported to one decimal place
- Hazard ratio will be reported to two decimal places
- As a rule, confidence intervals (CIs) are output to one place more than the raw data (same number of decimals as the estimate will be used for CIs corresponding to percentages and hazard ratios)
- P-values should be reported to four decimal places, except values >0.9999 which will be presented as '>0.9999' (e.g., 0.99998 is presented as >0.9999); and values <0.0001 will be presented as '<0.0001' (e.g., 0.00009 is presented as <0.0001). Rounding will be applied after the <0.0001 and >0.9999 rule.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Tables	For Listings
MedJ-01/JNIR01	JNIR	JNIR

Treatment Group	For Tables	For Listings
BioNIR/Bionics	Bionics	NA
Screen failure	NA	Screen Failure

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

- Screening
- Pre-Procedure
- Baseline Procedure
- Post-Procedure
- 30 Days
- 6 Months
- 1 Year
- 2 Years
- 3 Years
- 4 Years
- 5 Years

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Center-patient ID,
- Date (where applicable)

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

PARTIAL DATE IMPUTATION ALGORITHM FOR MEDICATIONS:

- Medication partial start date (references to month and year are the month and year of the medication start date):
  1. If year and month are known, and it is the month and year of the enrollment date, impute start date as enrollment date.

2. If year and month are known, and it is not the month and year of the enrollment date, impute start date to the first day of the month.
3. If only year is known, and it is the year of the enrollment date, impute start date as enrollment date.
4. If only year is known, and it is not the year of the enrollment date, impute start date to the first day of the year (1st January).
5. Should any of the previous imputed start dates created be after a complete stop date provided, use the stop date as the start date, instead of the date that would otherwise be created.
6. Otherwise, if start date is unknown leave as missing.

- Medication partial stop date (references to month and year are the month and year of the medication stop date):
  1. If year and month are known, impute stop date to the last day of the month.
  2. If only year is known, impute stop date to the last day of the year (31st December).
  3. Otherwise, if stop date is unknown leave as missing.

PARTIAL DATE IMPUTATION ALGORITHM FOR AES:

AE partial start dates will be imputed in the exact same way as medication partial start dates except that completely missing AE start dates will be imputed to the enrollment date.

AE partial stop dates will not be imputed.