Statistical Analysis Plan

Protocol 1.1

EluNIR Ridaforolimus Eluting Stent System In Coronary Stenosis

BIONICS 38 mm Trial

Statistical Analysis Plan
(SAP)

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Statistical Analysis Plan

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Author:

Mengdan Liu Biostatistician Cardiovascular Research Foundation New York, NY	Signature	Date (DD-MMM-YYYY)

Approvers:

Melek Ozgu Issever Director, Biostatistics and Data Management Cardiovascular Research Foundation New York, NY	Signature	Date (DD-MMM-YYYY)
Ovidiu Dressler, MD *Director of Medical Analytics and Programming* *Cardiovascular Research Foundation* *New York, NY*	Signature	Date (DD-MMM-YYYY)

Sponsor:

Dina Kofler *VP Clinical affairs* *Medinol Ltd.* *PO Box 58165* *Tel Aviv, Kiryat Atidim, Israel*	D.K Signature	28/Feb/2019 Date (DD-MMM-YYYY)

Statistical Analysis Plan

TABLE OF CONTENTS

Contents

1.0 INTRODUCTION

This Statistical Analysis Plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in BIONICS 38 mm trial. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. This plan is based on the trial protocol version 1.1.

The primary endpoint analysis for the BIONICS 38 mm trial will be performed after all patients have completed the 30-day follow-up assessment. The secondary long-term endpoints will be assessed separately after all patients have completed the 1 year follow-up assessment and will not be part of the Clinical Study Report (CSR).

1.1 Study Objectives

The main objective of the BIONICS 38 mm trial is to further assess the safety and efficacy of long (38 mm) Ridaforolimus Eluting Stent - EluNIR on combined endpoint of device success with no 30-day MACE in patients who undergo PCI.

1.2 Study Design

This is a prospective, multi-center, single arm, open label clinical trial.

Approximately 50 subjects will be enrolled with a wide spectrum of PCI indications (stable angina as well as ACS, including subacute STEMI (>24 hours since first hospital presentation) as well as complexity). All target lesions will be treated with EluNIR 38mm stent (Medinol, Tel Aviv, Kiryat Atidim, Israel).

Given the relatively low incidence of PCI to long lesion (8.4% in the ADAPT-DES trial), and the fact that the EluNIR 38 mm stent is approved and marketed in Israel, patients will be consented after PCI. Once a patient has met all general and angiographic eligibility criteria, a 38 mm long EluNIR stent has been passed beyond the guiding catheter, and the patient has signed an informed consent (post-procedure), the patient will be enrolled into the trial.

2.0 ENDPOINTS: DEFINITIONS AND CONVENTIONS

2.1 Primary Endpoint

Combined efficacy and safety endpoint is defined as device success determined by the Angiographic Core Lab (ACL) with no 30-day MACE.

Device success is defined as achievement of a final in-stent residual diameter stenosis of <30% (by QCA), using the EluNIR 38 mm stent only and without a device malfunction.
Final in-stent residual diameter stenosis (%DS) will be derived based on the following parameters from the Angiographic Core Laboratory (ACL) case report form:
%DS = 100*(1 - In-stent MLD / In-stent RVD)

MACE is defined as the composite of cardiac death, any MI, or ischemia-driven TLR.

2.2 Secondary Endpoints

Acute Success evaluated at the time of the baseline procedure by the Angiographic Core Laboratory:

- Device success
  Device success is defined as achievement of a final in-stent residual diameter stenosis of <30% (by QCA), using the assigned device only and without a device malfunction.
- Lesion success
  Lesion success is defined as achievement of a final in-stent residual diameter stenosis of <30% (by QCA) using any percutaneous method.
- Procedure success
  Procedure success is defined as achievement of a final in-stent diameter stenosis of <30% (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.

Secondary Clinical Endpoints evaluated at 30 days, 6 months, and 1 year:

All 30-day, 6-month and 1-year clinical events will be adjudicated and classified by an independent Clinical Events Committee (CEC). Only secondary clinical endpoints evaluated at 30 days will be included in the primary analysis and the CSR.

Myocardial infarction (MI) events will be classified as in Table 1 and adjudicated per the Universal Definition of Myocardial Infarction except for Type 4a (post-PCI) and Type 5 (post-CABG) which will be adjudicated based on the SCAI definitions, as follows:

1) In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level

measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB.

2) In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.

3) In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above, plus new ST-segment elevation or depression, plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

Table 1 Clinical Classification of Different Types of Myocardial Infarction

Type 1 Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2 MI secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension
Type 3 Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4a MI associated with PCI
Type 4b MI associated with stent thrombosis as documented by angiography or at autopsy
Type 5 MI associated with CABG

Secondary clinical endpoints are as follows:

- Target lesion failure (TLF; the composite cardiac death, target vessel related MI, or ischemia-driven TLR)
- Target vessel failure (TVF; the composite rate of death, target vessel related MI or ischemia-driven TVR)
- Major adverse cardiac events (MACE; the composite rate of cardiac death, any MI or ischemia-driven TLR)
- All-cause mortality
- Cardiac death
- Myocardial infarction
- Target vessel related MI
- Ischemia-driven TLR
- Ischemia-driven TVR
- Stent thrombosis (ARC definite and probable)

3.0 ANALYSIS SETS

Full Analysis Set (FAS): All subjects who have been enrolled into the trial, regardless of whether they received the study stent or not will be included in the FAS. Subjects are included in the FAS once the EluNIR 38 mm stent has been advanced beyond the guide catheter. If the study stent is not advanced beyond the guiding catheter, the patient will not be enrolled in the trial.

Per-Protocol (PP) Population: All subjects in the Full Analysis Set (FAS) with no major protocol deviations as identified by the Medical Monitor will be included in the Per-Protocol Analysis Set. Major protocol deviations may include the following categories:

- Informed consent was not properly obtained
- Inclusion or exclusion criteria deviations
- Not receiving DAPT post-baseline procedure according to the standard of care

Major protocol deviations will be identified by the Medical Monitor prior to the database lock for the primary analysis.

Safety Analysis Set: All subjects, including subjects who are consented but do not meet eligibility criteria and not in the FAS will be included in the Safety Analysis Set. Safety Analysis Set will also include all FAS patients.

Table 2 summarizes the analysis sets to be used for each type of analyses.

Table 2 Analyses and analysis sets

Endpoint	FAS	PP Analysis Set	Safety Analysis Set
Primary endpoint	X	X	
Secondary endpoints	X	X	
AEs, Other Safety Data			X
Demographics/baseline characteristics	X		
Angiographic Core Lab Analysis	X		

4.0 GENERAL METHODOLOGY AND CONVENTIONS

4.1 Sample Size and Controlling for Multiplicity

4.1.1 Sample Size

We used the following assumptions for sample size determination:

- Type I error (α) = 0.05 (two-sided)
- Statistical power ($1 - \beta$) = 80%
- Expected Incidence of at least one device-related AE occurs = 3.2%.

Fifty (50) subjects will be enrolled to provides 80% power to observe at least one device-related AE.

4.1.2 Controlling for Multiplicity

There is a single primary endpoint in this trial, thus no adjustment for multiplicity necessary.

4.2 Interim Analyses and Summaries

No formal interim analyses will be performed for this trial.

4.3 General Methods

Data collected in this trial will be presented in summary tables, listings or graphs. For each parameter, the baseline value will be defined as the last non-missing value collected at the time closest to but

before the start of study procedure. Demographic and background characteristics, safety and efficacy data will be summarized.

Descriptive statistics will be used to generate an overall summary of the trial endpoints, baseline and procedural variables, and clinical outcomes. Continuous variables will be summarized as means, medians, standard deviations, minimums, maximums, and 95% confidence intervals for the means. Categorical data will be presented as n/N (%), percentages and exact 95% confidence intervals will be rounded and reported to a single decimal point (xx.x %). Unless otherwise noted, subjects with missing data will be excluded from the denominator.

Survival analysis techniques will be used to analyze the time-to-event variables that occur at or after 30 days of follow-up. Time to event analysis will be performed for each time point separately (i.e. up to 30 days, 6-months (180 days), 1 year (365 days)) and summarized using the Kaplan-Meier estimated event rates and number of events. Only endpoints evaluated at 30-days will be included in the primary analysis and the CSR. Analysis of clinical endpoints evaluated at 6 months and 1-year will be performed separately.

All time-to-event analyses will be performed with time defined from date of procedure to first occurrence of an event. Subjects without events will be censored at their 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 was collected at 1 year and 2 weeks post-procedure, for the 1-year analysis, this subject will be censored at exactly 1 year (365 days)). When analyzing composite endpoints, time is measured from date of procedure to the first event (days).

Per protocol, patients may have multiple target lesions treated. The most conservative lesion level outcome will be used for the calculation of patient level endpoints. All clinical and safety endpoints are summarized on a patient level, except when noted. Angiographic Core Lab endpoints will be summarized on a lesion level.

4.4 Methods to Manage Missing Data

For the primary analysis of the primary endpoint, missing data will be left the same (no imputations). As a sensitivity analysis of the primary endpoint, a tipping point analysis will be performed to test the primary endpoint's robustness to missing data. For all other analyses, no adjustments will be made.

4.5 Definition and Use of Visit Windows in Reporting

Clinical follow-up assessments will be performed at 30 days, 6 months, and 1-year post procedure (the 6-month and 1-year visit may be conducted by telephone). The window for the 30-day follow-up visit

will be ± 7 days. The window for the 6-month follow-up visit will be ± 30 days, and for the 1-year visit, the window will be -30 days/+14 days.

For the primary endpoint component of 30-day MACE, the analysis will include all subjects with evaluable data and sufficient follow-up. This includes subjects who either experience an event or have at least 23 days of follow-up for event-free subjects.

Table 3 Schedule of Data Collection

TYPE OF DATA TO BE COLLECTED	Pre-Procedure[1] (within 30 days)	Pre-Procedure[1] (within 24 hours)	Baseline Procedure	Post-Procedure	30 days (± 7 days)	6 Months (± 30 days) by phone	1 year (-30 days / +14 days) by phone	Unscheduled visits
Patient Informed Consent				✓				
Patient Medical/Clinical History				✓[1]				
Angina Status		✓[1]		✓[1]	✓	✓	✓	✓
General Eligibility Criteria			✓[1]					
Angiographic Eligibility Criteria			✓[1]					
Clinical Laboratory Tests:								
CBC, Creatinine, BUN	✓[1, 2]							
Lipid profile	✓[1, 2]							
CK, CK-MB or Troponin		✓[1–3]		✓[4]				
12-Lead ECG		✓[1]		✓				
Coronary Angiogram & PCI			✓[1]					
Study Stent Information			✓[1]					
Per Protocol DAPT Medications[5]		✓[1]	✓[1]	✓	✓	✓	✓	✓
Concomitant Cardiac Medications[6]		✓[1]		✓	✓	✓	✓	✓
Adverse Events Monitoring			✓[1, 7]	✓	✓	✓	✓	✓

1. Data will be collected only after post-procedural informed consent has been obtained.
2. Should be collected at time of enrollment if not collected at baseline as part of routine SOC.
3. Within 24 hours pre-procedure if collected per site protocol. For subjects with ACS, it is recommended that enzyme levels be within 8 hours of the procedure or have already been shown to be decreasing. For STEMI patients enzyme levels should have peaked for either CK-MB or Troponin (I or T) or both.
4. If Troponin is elevated or CK-MB is elevated ≥ upper limit of normal, serial measurements of CK and CK-MB (preferred) or Troponin (I or T) must be done until a decline is noted
5. Clopidogrel 75 mg daily or prasugrel 5 to 10 mg daily or ticagrelor (90 mg bid) must be given for a minimum of 6 months (12 months in ACS patients) as well as aspirin 75 to 100 mg daily to be taken indefinitely.
6. Concomitant cardiac medications will be recorded by categories (e.g., statin, non-statin lipid lowering, ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, other anti-anginals).
7. All adverse events that occur after EluNIR stent was inserted into the patient's target artery (beyond the guiding catheter) will be recorded.

5.0 ANALYSES AND SUMMARIES

5.1 Baseline and Other Summaries and Analyses

5.1.1 Trial Conduct and Subject Disposition

The frequency and percentage of subjects enrolled by site will be provided as a table.

A tabulation of patient disposition will include the number of subjects screened, enrolled, and discontinued, with reasons for discontinuations (e.g., withdrew consent, was lost to follow-up, investigator withdrawal of subject, administrative reasons, etc.) as documented on the case report form. Adherence to trial inclusion/exclusion criteria, enrollment by site and major protocol deviations as documented on the case report form will be descriptively tabulated. A by-subject listing will include the reference data for these tables.

Compliance to 30-day follow-up visit will be summarized for all subjects in the FAS population and by site.

5.1.2 Baseline and Procedure Summaries

Baseline demographic and clinical variables and procedure characteristics will be summarized overall for the FAS population.

All continuous variables will be summarized as means, medians, standard deviations, ranges and 95% confidence intervals. Categorical variables will be summarized as frequencies, percentages and exact 95% confidence intervals.

5.2 Primary Endpoint

5.2.1 The Primary analysis of the primary endpoint

Combined efficacy and safety endpoint is defined as device success as determined by the Angiographic Core Laboratory (ACL) with no 30-day MACE.

Device success is defined as achievement of a final in-stent residual diameter stenosis of <30% (by QCA), using the EluNIR 38 mm stent only and without a device malfunction.

Final in-stent residual diameter stenosis (%DS) [mm] will be derived based on the following parameters from the Angiographic Core Laboratory (ACL) case report form:

%DS = 100*(1 - In-stent MLD / In-stent RVD)

MACE is defined as the composite of cardiac death, any MI, or ischemia-driven TLR As adjudicated by the CEC).

The primary analysis of the primary endpoint will be summarized as frequencies, percentages and exact 95% confidence intervals. If multiple lesions occur, then lesion to be included in the analysis will be chosen using the worst case scenario.

For the primary analysis of the primary endpoint, missing data will be left the same (no imputations).

5.2.2 Sensitivity/Robustness Analysis

As a sensitivity analysis, the following additional definitions will be used to assess peri-procedural MIs for the primary 30-day MACE endpoint in the FAS population:

- The 3rd universal definition of MI
- A modification of the SCAI definition of periprocedural MI that utilizes a threshold CKMB of ≥5x ULN (rather than ≥10x) in subjects with a normal baseline CK-MB without a requirement for associated clinical signs or symptoms
- A modification of the SCAI definition of periprocedural MI that utilizes a threshold CKMB of ≥3x (rather than ≥10x) in subjects with a normal baseline CK-MB without a requirement for associated clinical signs or symptoms

In addition, a tipping point analysis will test the primary endpoint's robustness to missing data. This involves re-analyzing the primary endpoint, imputing for subjects with missing data on the primary endpoint.

A table will report results of the primary endpoint analysis assuming the best and worst-case scenarios. The best-case scenario assumes all subjects missing the primary endpoint data meet the endpoint. The worst-case scenario assumes all subjects missing the primary endpoint data did not meet the endpoint.

5.3 Secondary Endpoints

Analysis of the secondary endpoints will be performed on the FAS population. Data for all secondary acute success endpoints and in-hospital clinical events will be summarized with patient counts, percentages, and exact 95% confidence intervals. Device and Lesion Success will be analyzed on a lesion level. For Procedure Success, if multiple lesions occur, then lesion to be included in the analysis will be chosen using the worst-case scenario.

Survival analysis techniques will be used to analyze the secondary 30-day, 6-month and 1-year clinical endpoints. Time to event analysis will be performed for each time point separately (i.e. up to 30 days, 6-

months (180 days), 1 year (365 days)) and summarized using the Kaplan-Meier estimated event rates and number of events.

5.4 Subgroup Analyses

No subgroup analysis will be performed for the primary endpoint.

5.5 Multicenter Studies

No adjustment for multiple centers is necessary, as this trial is descriptive in nature.

5.6 Safety Summaries and Analyses

5.6.1 Adverse Events

An AE is any unfavorable and unintended sign or symptom or disease or the deterioration of pre-existing medical condition that is temporally associated with the use of a medicinal product, whether considered related to the medicinal product. Any lab abnormality, physical exam abnormality, or ECG abnormality that is deemed clinically significant by the Investigator will need to be reported as an AE. Stable chronic conditions, such as arthritis, that are present prior to study entry and do not worsen during the trial will not be considered AEs.

AEs and SAEs will be summarized for all subjects in the Safety Analysis Set by tabulating the number of incidents and number of subjects for each event by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0. This will be done throughout the 1-year course of subject follow-up.

Types of AE summaries will be produced as follows:

- Overall summary of AEs, SAEs, including AEs by intensity
- MedDRA coded AEs and SAEs by system organ class and preferred term
- Listings of deaths/SAEs

5.6.2 Device Deficiencies, Malfunctions

Number of subjects with device deficiencies and malfunctions will be summarized as frequencies and percentages.

5.6.3 Laboratory Data

Results of clinical laboratory evaluations will be summarized for FAS population at pre-procedure and post-procedure, when applicable.

The following laboratory parameters are collected at pre-procedure (within 30 days prior to index procedure):

- Serum creatinine
- Creatinine clearance (as calculated by Cockcroft-Gault equation)
- BUN
- Complete Blood Cell Count with differential (to be taken before the administration of Investigational Drug) (White Blood cell count, Hemoglobin, Hematocrit, Platelet count and Monocytes count)
- Lipid profile (fasting)

Cardiac biomarkers:

Cardiac biomarkers Troponin (I or T) or CK-MB will be collected at baseline/pre-procedure (within 24 hours prior to index procedure) and post-procedure/discharge (CK-MB preferred; Troponin T/I acceptable if CK-MB not available).

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

- For pre-procedure, the value closest to the procedure time will be used for analysis.
- For post-procedure, the highest value observed within 48 hours will be used for analysis.

For cardiac biomarkers, the frequency and percentage of subjects falling into each of the following categories will be presented separately for pre-procedure and post-procedure visits:

For CK-MB:

≤ULN, >1 X ULN, ≥ 1-3ULN, ≥ 3 x ULN, ≥ 3-5ULN, ≥ 5 x ULN, ≥5-10ULN, ≥ 10 x ULN

For Troponin (I or T):

≤ULN, >1 X ULN, ≥ 1-3ULN, ≥ 3 x ULN, ≥ 3-5ULN, ≥ 5 x ULN, ≥5-10ULN, ≥ 10 x ULN, ≥ 10-35 ULN, ≥ 35 ULN, ≥35-70XULN, ≥70ULN

Units of all laboratory measurements will be converted into U.S. Conventional units before any descriptive analyses are performed. The collected units for each laboratory parameter and their conversion to Conventional units are presented in the following table:

Table 4 Conversion of Laboratory Parameters

Laboratory Parameter (unit)	Collected unit	Conversion to Conventional
White Blood Cell (10^3/µL)	10^9/L	= 10^3/µL
	10^3/mm^3	= 10^3/µL
	Cells/mm^3	x 0.001 = 10^3/µL
Platelet Count (10^3/µL)	10^9/L	= 10^3/µL
	10^3/mm^3	= 10^3/µL
	Cells/mm^3	x 0.001 = 10^3/µL
Hemoglobin (g/dL)	g/L	x 0.1 = g/dL
	mmol/L	x 1.611 = g/dL
Hematocrit (%)	L/L	x 100 = %
Serum Creatinine (mg/dL)	µmol/L	x 0.01131 = mg/dL
BUN (mg/dL)	mmol/L	x 2.8= mg/dL
Total Cholesterol (mg/dL)	mmol/l	x 38.66 = mg/dL
LDL (mg/dL)	mmol/l	x 38.66 = mg/dL
HDL (mg/dL)	mmol/l	x 38.66 = mg/dL
Triglycerides (mg/dL)	mmol/l	x 88.5 = mg/dL

If instead of BUN, urea is collected by a site, urea will be converted into BUN and the conversion will be performed as follows:

BUN (mg/dL) = Urea (mg/dL) / 2.14

BUN (mg/dL) = Urea (mmol/L) *2.8

5.6.4 Electrocardiogram

Pre-procedure (within 24 hours prior to index procedure) and post procedure ECG findings will be summarized for overall subjects by study visit.

5.6.5 Anginal Status

Anginal status data will be presented using descriptive statistics (frequency and proportions). Anginal status measures will be summarized for each study visit.

5.6.6 Concomitant Medications

Concomitant medication use, including compliance to DAPT, will be summarized by frequency (number and percentage of subjects) at each visit for all subjects based on the FAS analysis population. In addition to concomitant medication use, antiplatelet and anti-coagulant medications administered during baseline procedure will be presented for the procedure visit.

6.0 REFERENCES

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7.0 APPENDICES

Appendix 1. SAS Code for Patient and Lesion Level Data Analysis

Time to Event Data

PROC LIFETEST calculates Kaplan-Meier estimates and performed the log rank test. The TIME statement identifies the variables to be used as the failure time (TIME) and censoring variable (EVENT).

```
PROC LIFETEST;
    TIME EVENTDAYS *EVENT(0);
run;
```

Appendix 2. List of Tables

8.0 VERSION HISTORY

This Statistical Analysis Plan (SAP) for the BIONICS 38 mm Trial is based on protocol version 1.1 dated 23 July, 2018.

Table 4 Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable