BioNIR Ridaforolimus Eluting Coronary Stent System (BioNIR) European Angiography Study

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The BioNIR is non-inferior to the Resolute for the primary angiographic of in-stent late loss at 6 months

Ethical review	Approved WMO
Status	Completed
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON47919

Source
ToetsingOnline

Brief title
NIREUS

Condition

- Coronary artery disorders

Synonym
coronary artery disease, coronary artery stenosis

Research involving
Human

Sponsors and support

Primary sponsor: Medinol Lid.
Source(s) of monetary or material Support: Medinol Ltd.

Intervention

Keyword: BioNIR, Coronary artery stenosis, PCI

Outcome measures

Primary outcome

In-stent late loss at 6 months as measured by the angiographic core laboratory.

Secondary outcome

Angiographic Secondary Endpoints to be evaluated at 6 months:

* In-segment late loss

* Follow-up percent diameter stenosis (in-stent and in-segment)

* Binary restenosis (in-stent and in-segment)

* Length and patterns of angiographic restenosis (Mehran

classification)

Clinical Secondary Endpoints to be evaluated at 30 days, 6 months, and

1, 2, 3, 4 and 5 years except as noted:

* Device, Lesion, and Procedure Success at time of baseline

procedure

* Target lesion failure (TLF; the composite of cardiac death, target

vessel-related MI, or ischemia-driven TLR)

* Major adverse cardiac events (MACE; the composite rate of

cardiac death, any MI or ischemia-driven TLR)

* Target vessel failure (TVF; the composite rate of death, target

vessel-related MI, or ischemia-driven TVR)

* Overall Mortality

* Cardiac Death

* Myocardial Infarction

* Target Vessel Related MI

* Ischemia-driven TLR

* Ischemia-driven TVR

* Stent Thrombosis (ARC definite and probable)

Study description

Background summary

Percutaneous Intervention (PCI) is part of the standard treatment for coronary artery stenoses and has been shown to relieve ischemia and angina in stable coronary disease and improve outcomes in acute coronary syndromes particularly in patients with ST elevation myocardial infarction (STEMI). Stents, originally developed in the 1980s, have almost entirely replaced balloon angioplasty with the advantage of greater procedural success with reduced risk of abrupt closure as well as reduced rates of restenosis. Bare metal stents, however, were still limited by up to 30% restenosis rate due to neointimal proliferation. The advent of drug eluting stents (DES) which released anti-proliferative medications into the stented region markedly reduced the restenosis rate, thereby reducing the rate of repeat revascularization. Concern emerged, however, over late and very late stent thrombosis with the use of DES. Stent thrombosis has been linked to delayed and incomplete endothelialization as well as stent mal-apposition and strut breakage. Additional issues with DES include a local inflammatory reaction, allergic reactions to the stent components, and impairment of endothelial function.
Different DES have been shown to have differing rates of angiographic late loss as well as different rates of clinical events such as target lesion failure (TLF) and stent thrombosis. Different stent design, polymer features, and anti-proliferative drug used may impact these important clinical endpoints. The overall low event rate, however, has necessitated large scale clinical trials to evaluate new stents. Registration studies have also been limited by strict enrollment criteria which have excluded many patient and lesion types which are typically treated in clinical practice including complex lesions and patients with acute coronary syndromes.
The BioNIR is a new DES which uses a closed-cell design and an improved delivery system and therefore may improve outcomes compared to other drug eluting stents. The present trial is aimed at assessing the safety and efficacy

of the BioNIR in comparison to a second generation DES, the zotarolimus-eluting Resolute stent (Medtronic).
The aim of the present trial is therefore to evaluate the BioNIR in comparison to the Resolute in a clinically diverse population representative of contemporary stent use. The trial will enroll a broad population including patients with ACS (unstable angina, NSTEMI, and STEMI). The inclusion of patients with AMI and particularly STEMI is justified given that the majority of PCIs are in patients with ACS with STEMI accounting for up to 30% of ACS cases. In order to reduce the potential for confounding, patients with STEMI will be enrolled only after 24 hours have elapsed from their initial hospital presentation. Typically such patients will have already undergone primary PCI of the culprit lesion. Stent thrombosis is increased in the setting of primary PCI mostly in the first 24 hours. Therefore, confounding is unlikely.

Study objective

The BioNIR is non-inferior to the Resolute for the primary angiographic of in-stent late loss at 6 months

Study design

The NIREUS study is a prospective, multi-centre, single-blind, two-arm, 2:1 randomized clinical study comparing two drug eluting stents, i.e. the non-CE marked investigational device: the BioNIR Ridaforolimus Eluting Coronary Stent System and the comparator CE marked device: the Resolute Zotarolimus Eluting Coronary Stent System.

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

The NIREUS study will take place in Canada and a number of European countries (Belgium, Italy, Netherlands, Poland, Spain) and in Israel. Applications for clinical study approval have begun in Israel and Canada and are expected to be submitted to all other countries by December 2013.

The study will involve 300 patients who will be randomized in a 2:1 ratio to each study arm (200 BioNIR and 100 Resolute, per study arm).

Intervention

All subjects will undergo coronary angiography and PCI with study stent implantation, BioNIR or Resolute. The stent will remain implanted during the follow-up period, in total 5 years

Study burden and risks

Anticipated Clinical Benefits
The potential benefit of the study stent is its effectiveness in inhibition of neointimal growth while enhancing endothelial coverage. The study stent has the potential to reduce rates of restenosis without increasing rates of late and very late stent thrombosis compared to other commercially available DES.

Anticipated Adverse Device Effects
It is expected that the adverse device effects for BioNIR would not differ from the anticipated adverse device effects based on years of clinical experience with rapid exchange DES implantations.

Residual Risks Associated with Investigational Device
Foreseeable adverse events that may result from stent intervention can be found in Section 14.6 as well as the IB section 5.3

Risks Associated with Participation in the Clinical Investigation
There is extensive clinical and commercial experience worldwide with cardiac catheterization and interventional procedures and it is expected that the surgical and procedural risks will not be significantly different in this clinical trial. The risks of non-clinically indicated (i.e., for research purposes) diagnostic angiography are the same or less as clinically indicated angiography.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age * 18 years.
2. Patient with an indication for PCI including angina (stable or unstable), silent ischemia (in absence of symptoms a visually estimated target lesion diameter stenosis of *70%, a positive non- invasive stress test, or FFR *0.80 must be present), NSTEMI, or recent STEMI. For STEMI the time of presentation to the first treating hospital, whether a transfer facility or the study hospital, must be >24 hours prior to randomization and enzyme levels (CK-MB or Troponin) demonstrating that either or both enzyme levels have peaked.
3. Non-target vessel PCI are allowed prior to randomization depending on the time interval and conditions as follows:
a. During Baseline Procedure:
i. PCI of non-target vessels performed during the baseline procedure itself immediately prior to randomization
if successful and uncomplicated defined as: <50% visually estimated residual diameter stenosis, TIMI Grade 3 flow, no dissection * NHLBI type C, no perforation, no persistent ST segment changes, no
*prolonged chest pain, no TIMI major or BARC type 3 bleeding.
b. Less than 24 hours prior to Baseline Procedure:
i. Not allowed (see exclusion criteria #3).
c. 24 hours-30 days prior to Baseline Procedure:
i. PCI of non-target vessels 24 hours to 30 days prior to randomization if successful and uncomplicated as defined above.
ii. In addition, in cases where non-target lesion PCI has occurred 24-72 hours prior to the baseline procedure, at least 2 sets of cardiac biomarkers must be drawn at least 6 and 12 hours after the non-target vessel PCI. If cardiac biomarkers are initially elevated above the local laboratory upper limit of normal, serial measurements must demonstrate that the biomarkers are falling.
iii.
d. Over 30 days prior to Baseline Procedure:
e. PCI of non-target vessels performed greater than 30 days prior to procedure whether or not successful and uncomplicated.
4. Patient or legal guardian is willing and able to provide informed written consent and comply with follow-up visits and testing schedule.;Angiographic inclusion criteria (visual

estimate):
5. Treatment of up to three de novo target lesions, maximum of one de novo target lesion per vessel.
6. Target lesion(s) must be located in a native coronary artery with visually estimated diameter of *2.5 mm to *4.25 mm and diameter stenosis *50% to <100%.
7. Lesion must be *28 mm long and can be covered by a single study stent with maximum length of 33 mm (note: multiple focal stenoses may be considered as a single lesion and be enrolled if they can be completely covered with one stent).
8. TIMI flow 2 or 3.
9. If more than one target lesion will be treated, the RVD and lesion length of each must meet the above criteria.

Exclusion criteria

1. Planned procedures after the baseline procedure in either the target or non-target vessels.
2. STEMI within 24 hours of initial time of presentation to the first treating hospital, whether at a transfer facility or the study hospital or in whom enzyme levels (either CK-MB or Troponin)
*have not peaked.
3. PCI within the 24 hours preceding the baseline procedure and randomization.
4. Non-target lesion PCI in the target vessel within 12 months of the baseline procedure.
5. History of stent thrombosis.
6. Cardiogenic shock (defined as persistent hypotension (systolic blood pressure <90 mm/Hg for more than 30 minutes) or requiring pressors or hemodynamic support, including IABP.
7. Known LVEF <30%.
8. Subject is intubated.
9. Relative or absolute contraindication to DAPT for 12 months (including planned surgeries that cannot be delayed, or subject is indicated for chronic oral anticoagulant treatment).
10. Hemoglobin <10 g/dL.
11. Platelet count <100,000 cells/mm3 or >700,000 cells/mm3.
12. White blood cell (WBC) count <3,000 cells/mm3.
13. Clinically significant liver disease.
14. Renal disease as defined by an estimated creatinine clearance <40 mL/min using Cockcroft-Gault equation.
15. Active peptic ulcer or active bleeding from any site.
16. Bleeding from any site within the prior 8 weeks requiring active medical or surgical attention.
17. History of bleeding diathesis or coagulopathy or likely to refuse blood transfusions.
18. If femoral access is planned, significant peripheral arterial disease which precludes safe insertion of a 6F sheath.
19. Cerebrovascular accident or transient ischemic attack within the past 6 months, or any permanent neurologic defect attributed to CV A.
20. Known allergy to the study stent components, whether in the BioNIR or Resolute, e.g. cobalt, nickel, chromium, molybdenum, Carbosil®, PBMA, Biolinx polymer, or limus drugs (ridaforolimus, zotarolimus, tacrolimus, sirolimus, everolimus, or similar drugs or any other

analogue or derivative or similar compounds).
21. Known allergy to protocol-required concomitant medications such as aspirin, or DAPT (clopidogrel, prasugrel, ticagrelor), or heparin and bivalirudin, or iodinated contrast that cannot be adequately pre-medicated.
22. Any co-morbid condition that may cause non-compliance with the protocol (e.g. dementia, substance abuse, etc.) or reduced life expectancy to <24 months (e.g. cancer, severe heart failure, severe lung disease).
23. Patient is participating in or plans to participate in any other investigational drug or device clinical trial that has not reached its primary endpoint.
24. Women who are pregnant or breastfeeding (women of child- bearing potential must have a negative pregnancy test within one week before treatment).
25. Women who intend to become pregnant within 12 months after the baseline procedure (women of child-bearing potential who are sexually active must agree to use a reliable method of contraception from the time of screening through 12 months after the baseline procedure).
26. Patient has received an organ transplant or is on a waiting list for an organ transplant.
27. Patient is receiving or scheduled to receive chemotherapy within 30 days before or any time after the baseline procedure.
28. Patient is receiving oral or intravenous immunosuppressive therapy or has known life-limiting immunosuppressive or autoimmune disease (e.g., HIV). Corticosteroids are allowed.;Angiographic Exclusion Criteria (visual estimate):
29. Unprotected left main lesions *30%, or planned left main intervention.
30. Stenting of ostial LAD or LCX lesions (stenting of any diseased segment within 5 mm of the unprotected left main coronary artery).
31. Lesions located within an arterial or saphenous vein graft or distal to a diseased arterial or saphenous vein graft.
32. Moderately or heavily calcified lesions.
33. Moderately or heavily tortuous or angulated lesions or vessels.
34. Bifurcation lesions in the presence of a side branch *2.0 mm in diameter.
35. Lesions containing thrombus.
36. Total occlusions.
37. In-stent restenotic lesions or lesions present within 10 mm of a previously implanted stent.
38. Lesions requiring pre-dilatation with any device other than simple balloon angioplasty (e.g. atherectomy or cutting/scoring balloons).
39. Another lesion in the target vessel is present that requires or has a high probability of requiring PCI during the baseline procedure or within 6 months after the baseline procedure.

Study design

Design

Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	15-04-2014
Enrollment:	49
Type:	Actual

Medical products/devices used

Generic name:	Drug Eluting Stent (DES) - BioNIR
Registration:	No

Ethics review

Approved WMO Date:	06-03-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-04-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-11-2019

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT01995500
CCMO	NL46928.101.13