A randomized controlled trial to compare the safety and efficacy of siroliMUs-eLuTIng biodegradable polymer ulTrA-thin stent (SUPRAFLEXTM Cruz) and everolimus-eLuting biodegradable polymer stent (SYNERGYTM) in treatmENT for three-vessel coronary artery disease

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Primary Objective:To compare the SUPRAFLEX Cruz sirolimus-eluting stent (SES) with the SYNERGY everolimus-eluting stent (EES) with respect to Patient-oriented Composite Endpoint (PoCE: composite of all-cause death, any stroke, any MI, and any…

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

Summary

ID

NL-OMON56460

Source
ToetsingOnline

Brief title
Multivessel TALENT

Condition

- Coronary artery disorders

Synonym
3-vessel coronary artery disease

Research involving
Human

Sponsors and support

Primary sponsor: Clinical Science Institute, National University of Ireland, Galway,
Source(s) of monetary or material Support: Grant giver SMT Ireland Ltd (Sahajanand Medical Technologies Ireland Ltd),Sahajanand Medical Technologies Pvt. Ltd

Intervention

Keyword: Post Market Randomized Controlled Trial, safety and efficacy comparison, sirolimus-eluting biodegradable stent, three-vessel coronary artery disease

Outcome measures

Primary outcome

The Primary Endpoint for this trial is a non-inferiority comparison of

Patient-oriented Composite Endpoint (POCE) of the SUPRAFLEXTM Cruz cohort to

the SYNERGYTM cohort at 12 months post-procedure. POCE4 is a composite clinical

endpoint of

- all cause death

- any stroke, Modified Rankin scale, (MRS >=1);

- any myocardial infarction (MI)*

- any (repeat) revascularization.

*SCAI consensus for peri-procedural MI <=48 hours, and Fourth Universal

Definition (FUD) for spontaneous MI >48 hours after index procedure.

Secondary outcome

The Powered Secondary Endpoint for this trial is a superiority comparison (per

vessel level) of the vessel-oriented composite endpoints (VOCE): a composite of vessel-related cardiovascular death, vessel-related MI, or clinically and physiologically-indicated target vessel revascularisation (CPI-TVR) at 24 months post-procedure.

Other Secondary endpoints:

1. Composite of PoCE at 24 months;

2. All individual components of PoCE and VoCE at all timepoints;

3. TLF / DoCE defined as cardiovascular death, TV MI* and clinically indicated target lesion revascularisation at 12 and 24 months;

4. TVF is defined as cardiovascular death, TV MI* and clinically-indicated target vessel revascularisation at 12 and 24 months;

5. Rates of individual components of TLF at 12 and 24 months;

6. Definite/Probable Stent thrombosis rates according to ARC-II classification at all timepoints;

7. Device success6,

8. Procedure success. (Device success + free from PoCE at discharge).

*SCAI consensus for peri-procedural MI <=48 hours, and Fourth Universal Definition (FUD) for spontaneous MI >48hours after the index procedure.

Study description

Background summary

Stents:
At the Trans-Catheter Cardiovascular Therapeutics (TCT) Conference 2018, results of the TALENT study were presented in a Late-Breaking session, and these results were also published in The Lancet in 2019. The TALENT trial demonstrated non-inferiority of a biodegradable polymer coating and ultra-thin struts sirolimus-eluting SUPRAFLEXTM stent when compared to a durable polymer coating everolimus-eluting XIENCETM stent in terms of occurrence of the device-oriented composite endpoint (cardiac death, target-vessel myocardial infarction, or clinically indicated target lesion revascularisation) (4.9% in SUPRAFLEXTM arm vs 5.3% in XIENCETM arm, absolute difference -0.3% [one-sided 95% upper confidence bound 1.6%], non-inferiority margin of 4.0%, Pnon-inferiority<0.0001).
In the per-protocol analysis of the TALENT study, a 61% relative reduction of ischemia-driven TLR was found in the SUPRAFLEXTM arm compared to the XIENCETM arm (1.2% in SUPRAFLEXTM arm vs 3.1% in XIENCETM arm, absolute difference -1.9%, 95% CI -5.3 to -0.3%, p = 0.021). To amplify that signal, we designed a new randomised controlled trial with the novel SUPRAFLEXTM Cruz stent in patients with three-vessel disease.
The SUPRAFLEXTM Cruz stent is the next generation SUPRAFLEXTM DES ultrathin with a strut thickness of 60µm across all diameters of the device. Instead of a short S-connectors from *peak to peak* between the strut rings, the new design of SUPRAFLEXTM Cruz has unique long dual Z connectors from *valley to valley* between the strut rings which confer to the stent a superior pushability and flexibility without trade-off in radial strength). This device has been extensively used in India over the last 3 years in >250,000 implants.

Best Practice PCI:
On the other hand, the most recent trial in patients with multi-vessel disease applied five treatment principles described as *best practice* in the field of Multivessel PCI. First, patient selection is based on SYNTAX Score II which allows to enrol patients with an anatomic score between 22-32 or >33 provided they have a four years vital prognosis equipoise with the one obtained with surgical revascularisation; secondly, physiological assessment of stenotic lesion and treatment targeting the functionally significant lesion; thirdly, IVUS/OCT for post-stent optimisation since the benefit in outcome has been demonstrated in the ULTIMATE and IVUS-XPL trials; fourthly, PCI of chronic total occlusion (CTO) has to be performed by locally accredited experts in CTO, and lastly, optimal medical treatment before, during and after PCI.
The physiological assessment, iFR for all vessels has however been perceived as time consuming, expensive and cumbersome. Therefore, the investigators have decided to replace a pressure wire derived physiological assessment by QFR (quantitative flow ratio) as a validated angiography derived physiological assessment.
QFR has been validated as an accurate alternative for iFR and FFR in several reports and has obtained Conformité Européenne (CE) mark. In the FAVOR I study, the diagnostic accuracy of QFR has been demonstrated without the need for pharmacologic hyperemia. Thereafter, the FAVOR II China and the FAVOR II

Europe-Japan study demonstrated the diagnostic accuracy of QFR for detection of functional significant lesions in comparison with 2D-QCA using FFR as reference standard In a systematic review and Bayesian meta-analysis, Collet et al confirmed the high sensitivity and specificity of QFR against pressure wire derived physiological assessment. Both FAVOR III China and Europe-Japan are ongoing randomised controlled trials and expected to be completed in 2022. FAVOR III China study aims to demonstrate the superiority of QFR-guided PCI in terms of the clinical outcome and cost-effectiveness compared to angiography-guided PCI. On the other hand, the objective of the FAVOR III Europe-Japan study is to investigate whether a QFR-based diagnostic strategy will result in non-inferior clinical outcome after 12 months compared to a standard pressure-wire guided strategy.
The objective of the Multivessel Talent study is to elucidate the efficacy and safety of the novel SUPRAFLEXTM Cruz stent in comparison with the SYNERGYTM stent applying the five treatment principles of the *best practice* PCI and to use QFR guidance instead of iFR among in these patients with 3-vessel coronary disease.

Optimal medical therapy:
Recently the sub analysis of the Global Leaders trial demonstrated that in 3-vessel disease Ticagrelor monotherapy following one-month DAPT with aspirin reduced the occurrence of all-cause death and new Q-wave MI as well as POCE/NACE without difference in BARC3/5 bleeding, when compared with standard 1-year DAPT followed by aspirin monotherapy. Therefore, one-month DAPT followed by Ticagrelor monotherapy could be encouraged. On the other hand, the ISAR-REACT 5 trial demonstrated that, in patients who presented with acute coronary syndromes, the incidence of death, myocardial infarction, or stroke was significantly lower among those who received Prasugrel than among those who received Ticagrelor, and the incidence of major bleeding was not significantly different between the two groups. Considering altogether, one-month DAPT followed by Prasugrel monotherapy will be encouraged. In addition, the landmark analysis in the Global Leaders trial at 1 year, did not demonstrate any difference between Ticagrelor monotherapy and aspirin monotherapy in clinical outcomes during the second year. Therefore, at one year, Prasugrel monotherapy could be replaced by aspirin monotherapy.

Study objective

Primary Objective:
To compare the SUPRAFLEX Cruz sirolimus-eluting stent (SES) with the SYNERGY everolimus-eluting stent (EES) with respect to Patient-oriented Composite Endpoint (PoCE: composite of all-cause death, any stroke, any MI, and any clinically and physiologically-indicated revascularization) at 12 months in a 3-vessel disease population (non-inferiority);

Secondary objectives:
To compare the SUPRAFLEX Cruz SES with the SYNERGY EES with respect to

Vessel-oriented Composite Endpoint (VoCE, composite of vessel-related cardiovascular death, vessel-related MI, clinically and physiologically-indicated-Target vessel revascularization) per vessel at 24 months in a 3-vessel disease population (superiority);

Study design

This is a prospective, randomized, 1:1, controlled, multi-center, angiographically documented three-vessel disease (3VD) open-label study comparing clinical outcomes between SUPRAFLEX Cruz and SYNERGY in approximately 1550 (2*775 patients). The trial will be sponsored by the National University of Ireland (NUI) Galway and the sponsorship role coordinated by the HRB-Clinical Research facility Galway (CRFG).

There will be approximately 50 sites in Europe. University Hospital Galway, Galway will also be a site. The site activities will also be coordinated by the CRFG.

Patients with de-novo 3VD will be treated according to *state of art PCI* including :
1) SYNTAX Score II recommendation (i.e., PCI only or equipoise CABG/PCI);
2) Heart Team discussion (ESC guidelines: Ia);
3) Functional evaluation for diagnosis in absence of objective evidence of ischemia (ESC guidelines: Ia) (i.e., QFR*); Post-procedure IVUS/OCT optimization (ESC guidelines: IIa);
4) Contemporary CTO techniques
5) Optimal medical therapy (P2Y12 inhibitor, statin, etc).

*QFR on diagnostic angiography will be analysed in a stand-by central academic Core Lab and the results will be disclosed to the site after randomization before treatment.

Intervention

The only study intervention is randomization between the SUPRAFLEX Cruz stent and the SYNERGY stent.

Non-Investigational Medical Therapy:
All patients must receive dual anti-platelet therapy, being aspirin (ASA) and Prasugrel for 1 month, followed by 11 months of Prasugrel only (i.e. monotherapy).
Prasugrel therapy should be used since this regimen showed to have the best safety to efficacy ratio in this 3-vessel disease population3. After that, Prasugrel monotherapy is replaced by aspirin monotherapy at 1 year.
Anticoagulation during the procedure is mandatory, type/dose left to the operator*s discretion

Study burden and risks

Percutaneous coronary intervention (PCI) and intravascular stenting may offer certain advantages as compared to conventional surgical techniques. In addition, coronary stenting with both BMS and DES has been performed successfully for several decades and is considered a standard treatment for coronary artery disease. Furthermore, there is extensive clinical and commercial experience worldwide with cardiac catheterisation and interventional procedures and it is expected that the procedural risks in this study and existing stenting procedure will not be significantly different. Possible benefits may be found for future patients treated with SUPRAFLEXTM Cruz PCI and functional guidance (QFR) and IVUS/OCT stent optimisation based upon results of this study.

The SUPRAFLEXTM Cruz (Sahajanand Medical Technologies, Surat, India) stent platform is made of an L605 cobalt-chromium alloy. SUPRAFLEXTM Cruz has ultrathin strut (60 µm) across all stent diameters, with highly flexible long dual Z connectors from *valley to valley* between the strut rings. Compared with other available stents, SUPRAFLEXTM Cruz has the thinnest strut to date. The stent diameters are from 2.25 mm to 4.0 mm, and the lengths are from 8mm to 48mm (8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48mm). Another feature of SUPRAFLEXTM Cruz is the biodegradable polymeric matrix coating, consists of a poly L-lactide, 50:50 mixed with poly D-L-lactideco-glycolide and polyvinyl pyrrolidone. Sirolimus with a concentration of 1.4 µg/mm² is coated on the conformal surface of the stent together with the polymeric matrix. The polymer will gradually degrade over 9-12 months. The average thickness of the coating ranges from 4 µm to 5 µm. Further, since the drug-polymer coating on the SUPRAFLEXTM Cruz is gone within 9 months, leaving a bare metal stent, this may diminish the potential concerns regarding long-term effect on vessel healing, late and very late thrombosis, and hypersensitivity.
Aside from the potential direct benefits to the participant resulting from this study, there may be benefits to future participants based upon the results of the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Male or female patients* >=18 years.
2. At least 1 stenosis (angiographic, visually determined de novo lesions with >=50% DS) in all 3 major epicardial territories (LAD and/or side branch, LCX and/or side branch, RCA and/or side branch) supplying viable myocardium without left main involvement*;
*patients with ostial LAD or ostial LCX - Medina 0,0,1 or Medina 0,1,0 - may be enrolled; Patients with hypoplastic RCA (or LCX) with absence of descending posterior and presence of a lesion in the LAD and LCX (or RCA) territories may be included in the trial as a 3VD equivalent.
3. The vessel should have a reference vessel diameter ranging from >=2.25 mm to <=4.50 mm (no limitation on the number of treated lesions, vessels, or lesion length).
4. Patients with chronic coronary syndrome1 or stabilized acute coronary syndromes
5. All anatomical SYNTAX Scores are eligible for initial screening with the SYNTAX Score II, provided that the SYNTAX Score II recommends equipoise risk (PCI or CABG) or PCI only;
6. Patient has been informed of the nature of the study and agrees to its provisions and has provided written informed consent as approved by the Ethical Committee and is willing to comply with all protocol-required evaluations;
7. Agree with conditional longer follow up from 2 to 5 years with one phone contact yearly.

Exclusion criteria

1. Under the age of 18.
2. Unable to give informed consent.
3. Patient is a woman who is pregnant or nursing;
4. Known contraindication to medications such as Aspirin, Heparin, Bivalirudin, Prasugrel and Ticagrelor.
5. Prior PCI or prior CABG;
6. Ongoing ST-elevation myocardial infarction (STEMI);
7. Cardiogenic shock
8. Concurrent medical condition with a life expectancy of less than 2 years;
9. Currently participating in another trial and not yet at its primary endpoint;
10. Patient with both ostial LAD and ostial LCX stenosis, or left main stenosis
11. Previous intracranial haemorrhage

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-02-2021
Enrollment:	90
Type:	Actual

Medical products/devices used

Generic name:	SUPRAFLEX Cruz sirolimus-eluting stent
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	19-11-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-12-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-11-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-10-2024
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	NCT04390672
CCMO	NL75233.100.20