BIOTRONIK - Safety and Clinical Performance of the Sirolimus-Eluting Resorbable Coronary Magnesium Scaffold System (DREAMS 3G) in the Treatment of Subjects with de Novo Lesions in Native Coronary Arteries: BIOMAG-I

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Assessment of safety and clinical performance of the DREAMS 3G in de novo coronary artery lesion in order to achieve and to obtain CE-approval

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

Summary

ID

NL-OMON52481

Source
ToetsingOnline

Brief title
BIOMAG-I

Condition

- Coronary artery disorders

Synonym
coronary stenosis- narrowing of the vessels (arteries) wich supply the hear with blood

Research involving
Human

Sponsors and support

Primary sponsor: BIOTRONIK AG
Source(s) of monetary or material Support: By the study Sponsor: BIOTRONIK AG

Intervention

Keyword: DREAMS 3G, Resorbable Coronary Magnesium Scaffold

Outcome measures

Primary outcome

The primary endpoint will be in-scaffold late lumen loss (LLL) at 6-month

post-procedure.

Secondary outcome

Clinical

* Target Lesion Failure (TLF*) at 1, 6, 12 months and annually thereafter until

60 months post procedure

* Cardiac death at 1, 6, 12 months and annually thereafter until 60 months post

procedure

* Target vessel MI at 1, 6, 12 months and annually thereafter until 36 months

post procedure**

* Clinically driven target lesion revascularization at 1, 6, 12 months and

annually thereafter until 60 months post procedure

* Clinically driven target vessel revascularization at 1, 6, 12 months and

annually thereafter until 60 months post procedure

* Definite and probable scaffold thrombosis rate at 1, 6, 12 months and

annually thereafter until 60 months post procedure (according to ARC-2

definition)

* Procedure success: achievement of a final diameter stenosis of <30% by QCA, using any percutaneous method, without the occurrence of death, Q-wave or non-Q-wave MI, or repeat revascularization of the target lesion during the hospital stay.

* Device Success: final residual diameter stenosis of <30% by QCA, or visual assessment using the assigned device only with:

* Successful delivery of the scaffold to the target lesion, and

* Appropriate scaffold deployment, and

* Successful removal of the delivery system

* defined according to ARC-2 definition and ARC-1 definition

**periprocedural MIs (<48 hours after procedure) will be adjudicated according to SCAI-definitions and ARC-2 definition, non-periprocedural MIs will be adjudicated according to 3rd and 4th universal MI definition and extended historical definition.

Angiographic

* In-segment late lumen loss at 6 months

* In-scaffold and in-segment late lumen loss at 12 months

* Binary in-scaffold and in-segment restenosis rate at 6 and 12 months

* % in-scaffold and in-segment diameter stenosis at 6 and 12 months

OCT and IVUS

Descriptive analysis of vessel morphology, lesion composition and scaffold

strut data

Vasomotion

Descriptive analysis of vessel movement

Study description

Background summary

Standard of care treatment of coronary artery disease with state of the art drug-eluting stents (DES) delivers good clinical outcomes with low target lesion failure (TLF) and stent thrombosis rates. Nevertheless the use of DES presents some limitations, mainly due to the permanent presence of foreign material in the vessel wall. In particular there is a long term risk of stent failure, thrombosis, chronic inflammation due to the metal or polymer components and neoatherosclerosis. Moreover the metal cage can impair the vessel geometry, access and flow into side branches and can inhibit a normal vasomotor function, which may hinder compensatory positive re-modelling and limits use of imaging and future treatment options. Bioresorbable scaffolds (BRS) were developed to overcome these problems, enabling vessel restoration and reducing long term risks. BRS are meant to provide a temporary drug eluting scaffold, which supports the vessel after implantation as long as needed, limiting acute recoil and negative re-modelling, and enable a natural biologic reconstruction of the arterial wall and restoration of the vascular function once the scaffold is resorbed, which may also reduce the need of prolonged dual antiplatelet therapy and the occurrence of related bleeding complications.
The ability of scaffolds to meet these expectations however have been partly questioned by suboptimal results of the Absorb BVS (Abbott Vascular, Santa Clara, CA) showing higher incidence of scaffold thrombosis and target vessel-related myocardial infarction. Notably, while ABSORB BVS Bioresorbable Vascular Scaffold (BVS) consists solely of a poly-L-lactic acid (PLLA) polymer which resorbs over a period of more than 24 months, other scaffolds have different materials and designs. In particular, the Magmaris (here after refered to also as DREAMS 2G) (BIOTRONIK AG, Bülach, Switzerland) consist of a magnesium alloy which resorbs in approximately 12 months. Data from clinical trials thus far have demonstrated the clinical safety and performance of Magmaris and have not shown the same safety concerns as Absorb. DREAMS 2G gained CE-Mark in 2016 and is since then marketed as Magmaris.
Moreover, there are several indicators that Magmaris is less thrombogenic, e.g.

•In 30 patients assessed up to 6 months and 11 up to 12 months, no intraluminal mass was detected by OCT. Furthermore, at 6 months, no malapposed struts were detected because the struts were already embedded in the vessel wall
•DREAMS is laser polished, leading to a very smooth surface
•The strut cross section is rectangular with rounded edges, which might result in better embedding into the vessel wall
•DREAMS does not require stepwise inflation as required for polymeric scaffolds, which may result in better expansion and apposition
•A porcine arterio-venous shunt model compared the acute thrombogenicity of DREAMS 2G, the ultrathin Orsiro DES that uses the same polymer/drug combination as DREAMS 2G, and the ABSORB BVS scaffold. It demonstrated that DREAMS 2G had significantly less (a) platelet adherence, (b) thrombus deposition, and (c) inflammatory cell adhesion than the ABSORB BVS scaffold. Despite a greater strut thickness of DREAMS 2G as compared to Orsiro, the findings were similar in both devices with the exception of significantly less inflammatory cell adhesion in DREAMS 2G.
•Similarly, a study in porcine and rabbit models showed an increased endothelialization and decreased thrombus formation for DREAMS 2G compared to Absorb. Inflammation for DREAMS 2G peaked at 90 days and decreased thereafter; at one and two years, inflammation was lower for DREAMS 2G versus an everolimus-eluting cobalt-chromium stent.
•In-vitro tests showed an improved deliverability of DREAMS 2G as compared to the ABSORB BVS scaffold due to the metallic properties of DREAMS 2G, with less bending stiffness despite higher radial strength, indicating a better vessel conformability and no time dependent recoil of DREAMS 2G in contrast to ABSORB BVS and DESolve, a novolimus-eluting bioresorbable coronary scaffold system.
So far, the clinical trial results have demonstrated very low adverse event rates for Magmaris. While other bioresorbable scaffolds showed relatively high rates of thrombosis, thrombosis rates were low across all Magmaris and precursor studies and consistent with contemporary DES thrombosis rates. Potential factors contributing to this difference in clinical outcomes, include different scaffold design and materials, reduced thrombogenicity, as shown in animal models, shorter resorption time, and the BIOlute* coating as that is also used in the Orsiro Sirolimus Eluting Coronary Stent that has demonstrated consistently low TLF rates in randomized clinical trials.
Despite these positive results, iterative improvement of Magmaris, to enhance performance and usability led to the development of the next generation scaffold, DREAMS 3G. This scaffold is built with a refined magnesium alloy and enhances some scaffold properties, such as radial strength, scaffolding time and marker visibility, broadens the size range and reduces crossing profile and strut thickness. All of these changes are meant to improve the overall clinical outcomes.
BIOTRONIK is proposing to evaluate the safety and performance of next generation DREAMS 3G in a clinical trial program in a first in man study: BIOMAG-I.
NOTE: Please kindly see the introduction section in the study protocol where all Prior BIOTRONIK Bioresorbable Vascular Scaffold (BVS) Investigations and

other Manufacturers* prior investigations are presented.

Study objective

Assessment of safety and clinical performance of the DREAMS 3G in de novo coronary artery lesion in order to achieve and to obtain CE-approval

Study design

A prospective, multi-center, first-in-man trial.
Up to 115 subjects will be enrolled.
Clinical follow-up visits will take place at 1, 6, and 12 months and annually thereafter until 60 months post procedure.
All subjects will undergo an angiographic follow-up at 6- and 12-month follow up.
IVUS, (including IVUS-VH documentation) and OCT will be performed for all subjects at 6-month and 12-month follow-up (if the safety of the subject allows it and as per the investigator*s decision).
Vasomotion will be assessed angiographically with Acetylcholine followed by Nitroglycerine at 12 months follow up in a subgroup of subjects, upon the investigators discretion and if subject consents.

Intervention

Percutaneous transluminal coronary angioplasty (PTCA) including concomitant anticoagulation medication according to protocol and implantation of the DREAMS 3G scaffold

Study burden and risks

Risks
The risk assessment, bench testing and pre-clinical animal testing used to support the safety of the DREAMS 3G are documented in the Investigators Brochure.
As with any subjects undergoing percutaneous coronary intervention, subjects may experience adverse events and/or outcomes that are listed in the IFU and do not differ from other contemporary drug eluting stent implantation procedures.

Potential adverse events related to sirolimus (following oral administration) include but are not limited to: Abnormal liver function, anemia, arthralgia, diarrhea, hypercholesterolemia, hypersensitivity, including anaphylactic/ anaphylactoid type reactions, hypertriglyceridemia, hypokalemia, infections, interstitial lung disease, leukopenia, lymphoma and other malignancies, thrombocytopenia. Appropriate contraindications and warnings are included in the IFU provided with the study device.
For all subjects, quantitative coronary angiography including IVUS and OCT will

be performed at 6 and 12 months follow-up. Coronary angiography, IVUS and OCT are common medical tests. They rarely cause serious problems. However, complications can occur and include, but are not limited to:
Bleeding, infection, pain at the catheter insertion site, damage to blood vessels (including dissections), allergic reaction to contrast media or medication.
Other, less common complications include: arrhythmias, kidney damage, blot clots that can trigger a stroke, heart attack, or other serious problems, low blood pressure, pericardial effusion
The vasomotion test involves an infusion of acetylcholine, which can provoke a pathological narrowing of the vessel, which in turn may lead to chest pain, reduced blood supply to the heart, cardiac arrhythmia or an occlusion of the blood vessel. As the vasomotion test is performed during the coronary angiography, these side effects are generally easily controlled.
Benefits:
Coronary stents have improved significantly the immediate and long-term results of percutaneous coronary interventions. However, once the vessel has healed, the scaffolding function of the stent is no longer needed, and the presence of a permanent metallic stent poses important disadvantages.
One benefit of bioresorbable scaffolds is that the artery would not be permanently caged and late positive remodeling in response to physiological stimulus (restoration of vasomotion) would be possible. Persistent impairment of endothelial vasomotor function after treatment has been associated with adverse cardiovascular events at the long-term follow-up. Therefore, the restoration of coronary vasomotion is essential after percutaneous coronary intervention. In the BIOSOLVE II trial, angiographically discernible vasomotion was documented after implantation of the Magmaris (DREAMS 2G) scaffolds in 80% of the patients evaluated at 6 months.
The resorption of the scaffold would also allow future treatments in the vessels if needed (either percutaneous or surgical) and would facilitate the access to side branches initially jailed by the scaffold. Moreover it would avoid that subjects have several metal layers in their arteries. The resorbability of the scaffold also has important psychological implications. Many patients are concerned about having a permanent implant in their coronary arteries and would prefer a device that is able to disappear after a determined time.
The implantation of a resorbable device may also facilitate non-invasive imaging technologies, like CT or MRI, because they do not create any of the artefacts originating from permanent metallic stents.
Permanent stents are associated with a certain risk of stent thrombosis and in-stent restenosis. For bioresorbable scaffolds, the risks associated with stent thrombosis and in-stent restenosis would theoretically be removed once the scaffold has been fully degraded.
To determine its thrombogenicity, Magmaris was tested against the ABSORB in an ex-vivo arteriovenous porcine shunt model. Despite a similar scaffold strut thickness, the Magmaris scaffold was significantly less thrombogenic compared with the ABSORB .

Similarly, a study in porcine and rabbit models showed an increased endothelialization and decreased thrombus formation for DREAMS 2G compared to ABSORB.
Clinical evidence from several trials associated the ABSORB BRS with an elevated thrombosis risk compared to DES and its commercial distribution was stopped. For Magmaris, no elevated thrombosis risk was identified in clinical experience. No definite or probable scaffold thrombosis was reported in the BIOSOLVE-II and BIOSOLVE-III studies up to 36 and 12 months, respectively. In the BIOSOLVE-IV study, the definite/probable scaffold thrombosis rate was 0.5%, whereby 4 of the 5 scaffold thrombosis cases were associated to early DAPT interruption, in the full cohort up to 12 months which is comparable to DES.
For DREAMS 3G, the scaffold structure design was adapted and a Magnesium alloy with increased mechanical strength was developed. Magnesium has superior mechanical properties with its higher tensile strength and greater % elongation-at-break compared with polymeric material. The Magnesium alloy used in the Magmaris offers higher deformation resistance and lighter weight as compared with pure Magnesium. The improved Magnesium alloy of DREAMS 3G scaffold contains Aluminum to support the required material characteristics regarding mechanical performance and resorption behavior. Accordingly, the DREAMS 3G scaffold alloy has an increased mechanical strength compared to the Magmaris alloy and provides a more uniform resorption. The improved scaffold acute mechanical properties are expected to support treatment of complex lesions with DREAMS 3G. In addition to higher mechanical strength, the improved Mg alloy of DREAMS 3G will provide an increased scaffolding period. At the same time, the Mg resorption period of 12 months is maintained. The increased scaffolding period is expected to further improve chronic luminal outcome for DREAMS 3G in comparison to Magmaris without compromising safety.
In comparison to Magmaris, the scaffold strut dimensions of DREAMS 3G were further decreased to further reduce the risk of thrombosis. Compared to the 150 µm strut thickness of Magmaris, the strut thickness of DREAMS 3G is 117 µm for scaffolds with a diameter of 3 and 3.5 mm. Additional sizes were added to the device portfolio of DREAMS 3G. The increased size range of the DREAMS 3G product portfolio will allow for treatment of smaller/larger vessels and longer/shorter lesions in comparison to Magmaris. The new Ø 2.5 mm DREAMS 3G scaffold has a strut thickness of 99 µm and the Ø 4 mm DREAMS 3G scaffold has a strut thickness of 147 µm.
The polymeric scaffolds ABSORB and DESolve have a strut thickness of 150 µm and a strut width of 190 µm and 165 µm, respectively. With a maximum strut thickness of 147 µm and strut width of 150 µm, DREAMS 3G will have a lower vessel coverage than the polymeric scaffolds.
The reduced scaffold strut dimensions will also contribute to improved deliverability of the device. In terms of deliverability, DREAMS does not require stepwise inflation as required for polymeric scaffolds. Which contributes to a better scaffold expansion and apposition. To further improve scaffold deliverability of DREAMS 3G, the profile of the crimped scaffold was further reduced to support deployment in challenging vessel anatomy. In preclinical testing, trackability/deliverability of DREAMS 3G was rated

excellent, same as the drug-eluting stent Orsiro.
To increase the scaffold marker x-ray visibility, the marker material density and marker dimensions were increased compared to Magmaris. This will support scaffold positioning and post-dilatation for DREAMS 3G.

Risk / Benefit Conclusion
Pre-clinical findings indicate that the Mg based scaffold is less thrombogenic, provokes less inflammatory response and reduces formation of new artherosclerosis when compared to other available scaffolds and DES which eventually results in improved endothelial integrity. Available data on DREAMS 2G on more than 1000 subjects with a low rate of target lesion failure and scaffold thrombosis further support these beneficial findings and show that the device is safe and efficient when used according to the instructions of use.
The iterations of the device from DREAMS 2G to DREAMS 3G have addressed potential disadvantages of DREAMS 2G while maintaining the characteristic features that are thought to be responsible for the beneficial pre-clinical and clinical findings. This FIM trial will provide further evidence of the safe use of bioresorbable Mg based scaffolds in the treatment of coronary artery lesions. The device will be used under controlled conditions and subjects will be closely monitored. Every precaution has been taken to protect the health and safety of the subjects.
Moreover, subjects will be closely monitored throughout the clinical investigation duration. They will be evaluated at pre-determined time points to assess their clinical status and follow-up angiographies (including additional imaging by IVUS and OCT) will be performed to assess the status of both target lesion and the scaffold.
An independent Data Monitoring Committee (DMC) will monitor safety throughout the clinical investigation. Stopping rules will be discussed with the DMC and applied for subject safety throughout enrollment.

Therefore we conclude that the benefits of the new DREAMS 3G device outweigh the risks that are involved within this study.

NOTE: for a full risk - benefice information, please kindly see section 3. RISK-BENEFIT-ANALYSIS of the study protocol

Contacts

Public
BIOTRONIK AG

ACKERSTRASSE 6
BÜLACH 8180

CH
Scientific
BIOTRONIK AG

ACKERSTRASSE 6
BÜLACH 8180
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject is > 18 years and < 80 years of age
2. Written subject informed consent available prior to PCI
3. Subject eligible for PCI, according to the 2018 ESC/EACTS Guidelines on myocardial revascularization.
4. Subjects with a maximum of two single lesions in two separate coronary arteries which have to be de novo lesions and can be covered with 1 device each
5. Reference vessel diameter between 2.5-4.2 mm by visual estimation, depending on the scaffold size used
6. Target lesion length <= 28 mm by visual estimation, depending on the scaffold size used
7. Target lesion stenosis by visual estimation > 50% - < 100% and TIMI flow >=1 (assisted by e.g. QCA / IVUS /FFR).
8. Subjects with stable or unstable angina pectoris or documented silent ischemia or hemodynamically stable NSTEMI patients without angiographic evidence of
thrombus at target lesion
NOTE: patient with acute STEMI can not be included in the study (according to exclusion criteria 2)
9. Subject who has no contraindication for.Dual Anti Platelet Therapy (DAPT)

Exclusion criteria

1. Pregnant or breast-feeding females or females who intend to become pregnant during the time of the study
2. Subject has clinical symptoms and electrocardiogram (ECG) changes consistent with acute ST elevation myocardial infarction (STEMI) within 72 hours prior to the index procedure.
NOTE: after 72 hours, any lesion other than the one causing the acute STEMI (culprit lesion) in any other epicardial vessel, may be treated according to the inclusion and exclusion criteria
3. Left main coronary artery disease
4. Three-vessels with coronary artery disease requiring treatment at time of procedure, including: left main, left anterior descending artery (LAD) right coronary artery (RCA) and circumflex coronary artery (Cx)
5. Planned interventional treatment of any non-target vessel within 12-month post-procedure
6. Subjects on dialysis
7. Impaired renal function (serum creatinine > 2.5 mg/dl or 221 µmol/l, determined within 72 hours prior to intervention)
8. Planned future intervention of a second lesion within the target vessel.
9. Ostial target lesion (within 5.0 mm of vessel origin)
10.Target lesion involves a side branch >2.0 mm in diameter
11.Documented left ventricular ejection fraction (LVEF) <= 30% within the last 6 months
12.Heavily calcified lesion which can not be adequately pre-dilated by a non-compliant and/ or scoring balloon as described in exclusion criteria 15.
13.Target lesion is located in or supplied by an arterial or venous bypass graft
14.Target lesion requiring treatment with a device other than the non-compliant pre-dilatation balloon or scoring balloon prior to scaffold placement (including but not limited to rotational atherectomy, etc.)
15.Unsuccessful pre-dilatation, defined as a residual stenosis rate more than 20%, estimated by any
method and/or angiographic complications (e.g. distal embolization, side branch closure, extensive
dissections)
16.Known allergies or intolerances to: Acetylsalicylic Acid (ASA), P2Y12 inhibitors, Heparin, Contrast medium, Sirolimus, or similar drugs; or the scaffold material (Magnesium, Aluminium)
17.Subject is receiving an oral or intravenous immunosuppressive therapy (e.g., inhaled steroids are not excluded) or has a known life-limiting immunosuppressive or autoimmune disease (e.g.,
human immunodeficiency virus, systemic lupus erythematosus) diabetes mellitus is not excluded)
18.Life expectancy less than 1 year
19.Subjects under oral anticoagulation therapy (OAC) prior to implantation of DREAMS 3G unless DAPT can be maintained for a minimum of 6-month.

Recommendation: If a subject requires OAC after DREAMS 3G implantation, DAPT should be maintained until 6 months follow up. Afterwards DAPT can be downsized to either ASA or Clopidogrel alone together with OAC for the remaining time period up to 12 months. After this, OAC monotherapy can be prescribed if still required.
20.Planned surgery or dental surgical procedure within 6 months after index procedure unless DAPT will be maintained
21.In the investigators opinion, subject will not be able to comply with the follow-up requirements
22.Subject is currently participating in another study with an investigational device or an investigational drug and has not reached the primary endpoint yet

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-08-2021
Enrollment:	12
Type:	Actual

Medical products/devices used

Generic name:	DREAMS 3G
Registration:	No

Ethics review

Approved WMO

Date:	27-05-2020
Application type:	First submission

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-10-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-06-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-10-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-04-2022
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	NCT04157153
CCMO	NL72138.100.19