BIOFREEDOM™

DRUG COATED CORONARY STENT SYSTEM

# INSTRUCTIONS FOR USE

**Caution:** Federal (USA) law restricts this product to sale by or on the order of a physician

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## 1. PRODUCT DESCRIPTION

The BioFreedom™ Drug Coated Coronary Stent System (BioFreedom™ DCS) is a combination product consisting of two key components: the stent coated abluminally with the active ingredient BA9 (Biolimus A9™), and the delivery system. The BioFreedom™ DCS is a polymer free drug-coated coronary stent system. The BioFreedom™ DCS is described in **Table 1-1** below.

**TABLE 1-1: BIOFREEDOM™ DCS PRODUCT DESCRIPTION**

| | | |
|---|---|---|
| **Stent Pattern:** | 6-crown model | 9-crown model |
| **Stent Diameters (mm):** | 2.25, 2.5, 2.75, 3.0 | 3.5, 4.0 |
| **Stent Lengths (mm):** | 8, 11, 14, 18, 24, 28 | |
| **Stent Material:** | Stainless Steel 316L | |
| **Drug Component:** | BA9 drug | |
| **Delivery System Design:** | Working length: 142 cm<br>Rapid Exchange (RX) compatible with guidewires ≤ 0.014” | |
| **Stent Delivery System** | Semi-compliant balloon with two radiopaque markers located on the catheter system balloon shaft to indicate balloon positioning and expanded stent length | |
| **Guiding Catheter compatibility:** | ≥ 6F (min. guide catheter ID of 0.070”/1.78mm) | |
| **Balloon Inflation Pressure:** | | |
| **Nominal Inflation Pressure (NP):** | 7 atm/ 709 kPa | |
| **Rated Burst Pressure (RBP):** | 16 atm/1621 kPa | 14 atm/1418 kPa |

**TABLE 1-2: STENT CROSSING PROFILES FOR BIOFREEDOM™**

| Balloon Diameter (mm) | Maximum Crossing Profile (inches) 8/11/14/18/24/28 mm |
|---|---|
| 2.25 | 0.044 |
| 2.50 | 0.045 |
| 2.75 | 0.045 |
| 3.00 | 0.045 |
| 3.50 | 0.048 |
| 4.00 | 0.050 |

### 1.1. DEVICE COMPONENT DESCRIPTION

The device is a balloon-expandable 316L stainless steel stent abluminally coated with the BA9 drug and pre-mounted onto a semi-compliant rapid exchange balloon delivery system. The delivery system has two radiopaque markers, which fluoroscopically mark the ends of the stent to facilitate proper stent placement. At the proximal end of the delivery system is a female luer lock connector hub. This hub connects to the balloon inflation lumen. The guidewire enters the distal tip of the catheter and exits approximately 22 cm proximal to the tip of the delivery system.

### 1.2. DRUG COMPONENT DESCRIPTION

BA9 (Biolimus A9, INN: umirolimus) is the active ingredient that is incorporated onto the BioFreedom™ DCS. The drug is a semi-synthetic sirolimus derivative with anti-proliferative and pharmacokinetic properties similar to those of sirolimus. BA9, delivered via the drug-coated stent, inhibits smooth muscle cell proliferation within the stent proximity. BA9 is coated abluminally onto the stent.

BA9 drug is approximately ten times (10x) more lipophilic than sirolimus and everolimus and is rapidly absorbed into local tissue in its intended use. Current understanding suggests that the BA9 mechanism of action on a molecular level is due to complex formation with cytoplasmic proteins that inhibit the cell cycle between the G0 and G1 phase. This results in the interruption of the cascade governing cell metabolism, growth, and proliferation, leading to a reversible inhibition of growth-factor-stimulated cell proliferation.

The chemical structure of BA9 is illustrated in **Figure 1**.

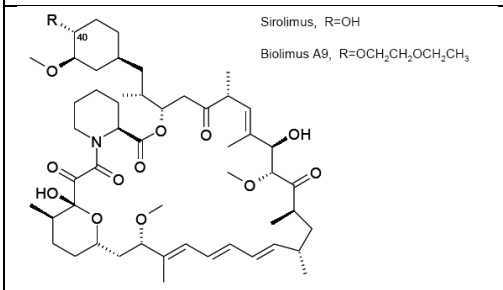


**Figure 1: Biolimus A9 Chemical Structure**

The product size matrix and the BA9 per product code content are presented in **Table 1-3** below.

**TABLE 1-3: BIOFREEDOM STENT SPECIFICATIONS AND NOMINAL BA9 DRUG DOSAGE**

| Product Code | Nominal Expanded Inner Diameter (mm) | Nominal Unexpanded Stent Length (mm) | Nominal Dose of BA9 drug (µg) |
|---|---|---|---|
| BFR2-2208 | 2.25 | 8 | 133 |
| BFR2-2211 | 2.25 | 11 | 178 |
| BFR2-2214 | 2.25 | 14 | 225 |
| BFR2-2218 | 2.25 | 18 | 292 |
| BFR2-2224 | 2.25 | 24 | 384 |
| BFR2-2228 | 2.25 | 28 | 453 |
| BFR2-2508 | 2.5 | 8 | 133 |
| BFR2-2511 | 2.5 | 11 | 178 |
| BFR2-2514 | 2.5 | 14 | 225 |
| BFR2-2518 | 2.5 | 18 | 292 |
| BFR2-2524 | 2.5 | 24 | 384 |
| BFR2-2528 | 2.5 | 28 | 453 |
| BFR2-2708 | 2.75 | 8 | 133 |
| BFR2-2711 | 2.75 | 11 | 178 |
| BFR2-2714 | 2.75 | 14 | 225 |
| BFR2-2718 | 2.75 | 18 | 292 |
| BFR2-2724 | 2.75 | 24 | 384 |
| BFR2-2728 | 2.75 | 28 | 453 |
| BFR2-3008 | 3.0 | 8 | 133 |
| BFR2-3011 | 3.0 | 11 | 178 |
| BFR2-3014 | 3.0 | 14 | 225 |
| BFR2-3018 | 3.0 | 18 | 292 |
| BFR2-3024 | 3.0 | 24 | 384 |
| BFR2-3028 | 3.0 | 28 | 453 |
| BFR2-3508 | 3.5 | 8 | 133 |
| BFR2-3511 | 3.5 | 11 | 178 |
| BFR2-3514 | 3.5 | 14 | 225 |
| BFR2-3518 | 3.5 | 18 | 292 |
| BFR2-3524 | 3.5 | 24 | 384 |
| BFR2-3528 | 3.5 | 28 | 453 |
| BFR2-4008 | 4.0 | 8 | 133 |
| BFR2-4011 | 4.0 | 11 | 178 |
| BFR2-4014 | 4.0 | 14 | 225 |
| BFR2-4018 | 4.0 | 18 | 292 |
| BFR2-4024 | 4.0 | 24 | 384 |
| BFR2-4028 | 4.0 | 28 | 453 |

**2. INDICATIONS FOR USE**

The BioFreedom™ DCS is indicated for improving coronary luminal diameter in patients at high risk for bleeding with symptomatic ischemic heart disease due to *de novo* lesions of length ≤ 32 mm in native coronary arteries with a reference diameter ranging between 2.25 mm and 4.0 mm.

High bleeding risk (HBR) includes patients with any of the following:

- ≥ 75 years old
- Oral anticoagulation use (including vitamin-K antagonists or Direct Oral Anticoagulants (DOACs)) planned for > 1 month post PCI
- Hemoglobin < 11 g/dL or anemia requiring transfusion in the previous month
- Platelet count < 100,000/$mm^3$ in the previous month
- Hospital admission for bleeding in the previous 12 months
- Stroke in the previous 12 months
- Any prior intracerebral hemorrhage
- Severe chronic liver disease defined to include the following diseases or symptoms: variceal hemorrhage, ascites, hepatic encephalopathy or jaundice
- Creatinine clearance < 40 mL/min in the previous month
- Cancer (non-skin) in the previous 3 years
- Major surgery planned in the 12 months post-PCI
- Glucocorticoids or NSAID planned to continue > 1 month post-PCI
- Other medical reasons that would preclude treatment with >1 month dual antiplatelet therapy which may include: congenital conditions, high risk of trauma, history of falling

**3. CONTRAINDICATIONS**

The BioFreedom™ DCS is contraindicated for use in:

- Patients who cannot receive the recommended antiplatelet therapy (aspirin/P2Y12 platelet inhibitor) and/or anticoagulation therapy (heparin or bivalirudin).
- Patients with lesion(s) that prevent(s) complete inflation of an angioplasty balloon.
- Patients with known hypersensitivity to the BA9 drug or its derivatives.
- Patients with known allergies to stainless steel, nickel or other metal ions found in 316L stainless steel.
- Patients with known sensitivity to contrast agents that cannot be controlled prophylactically prior to BioFreedom™ stent implantation.

**4. WARNINGS**

- The inner package should not be opened or damaged prior to use to maintain sterility.
- Patients who are unlikely to comply with the recommended antiplatelet therapy should not receive this product.
- The use of this DCS carries the risks associated with coronary artery stenting, including stent thrombosis, vascular complications, and/or bleeding events.
- Patients with known hypersensitivity to the product components (stainless steel, BA9 drug or its derivatives) may suffer an allergic reaction to this implant.
- This product is not intended or approved for use in peripheral applications.

**5. PRECAUTIONS**

**5.1 GENERAL PRECAUTIONS**

Stent implantation should only be performed by physicians who have received appropriate training.

Restenosis following stent implantation may require repeat dilatation of the arterial segment containing the stent. Long-term outcomes following repeat dilatation of the stent is presently not well characterized.

Risks and benefits should be considered in patients with severe reaction to contrast agents.

Care should be taken to control the guiding catheter tip during stent delivery, deployment, and balloon withdrawal. Before withdrawing the stent delivery system, visually confirm complete balloon deflation by fluoroscopy to avoid guiding catheter movement into the vessel and subsequent arterial damage.

Stent thrombosis is a low-frequency event that is frequently associated with myocardial infarction (MI) or death.

When DCS are used outside the specified indications for use, patient outcomes may differ from the results observed in the clinical trials.

Compared to use within the specified indications for use, the use of DCS in patients and lesions outside of the labeled indications, including more tortuous anatomy, may have an increased risk of adverse events, including stent thrombosis, stent embolization, MI, or death.

**5.2 PRE- AND POSTPROCEDURE ANTIPLATELET THERAPY RECOMMENDATIONS**

Dual antiplatelet therapy (DAPT) using a combination treatment of aspirin with a P2Y12 platelet inhibitor after percutaneous coronary intervention (PCI), reduces the risk of stent thrombosis and ischemic cardiac events, but increases the risk of bleeding complications. The BioFreedom DCS is intended for patients at high risk for bleeding, therefore the risks of significant bleeding related to DAPT therapy should be carefully balanced against the risk of serious ischemic events following early DAPT discontinuation.

The optimal duration of antiplatelet therapy is unknown and DES thrombosis may still occur despite continued therapy. Per 2021 ACC/AHA guidelines, a daily aspirin dose of 75-100 mg is recommended indefinitely after PCI. A P2Y12 platelet inhibitor should be given daily for at least 6 months in stable ischemic heart disease patients and for at least 12 months in patients with acute coronary syndrome (ACS). With regard to the antiplatelet therapy designed specifically for patients at high bleeding risk (HBR), and with the aim to avoid prolonged dual antiplatelet therapy (DAPT) in such patient populations, current ACC/AHA guidelines state that DAPT discontinuation “may be reasonable” after 3 months in stable patients or 6 months in ACS patients. The 2021 ACC/AHA guideline recommends that in selected patients undergoing PCI (underwent DES implantation or with ACS), shorter-duration DAPT (1–3 months) is reasonable, with subsequent transition to P2Y12 inhibitor monotherapy to reduce the risk of bleeding events. Now, based on the results of the LEADERS FREE II trial that demonstrate the efficacy and safety of the BioFreedom™ DCS versus a BMS (refer to **Section 7.3** for more details), physicians may choose a one month dual antiplatelet regimen following BioFreedom™ implantation in patients at high risk of bleeding.

Decisions about duration of DAPT are best made on an individual basis and should integrate clinical judgment, assessment of the benefit/risk ratio, and patient preference. Prior to PCI, if premature discontinuation of antiplatelet therapy is anticipated, physicians should carefully evaluate with the patient whether a DES and its associated recommended DAPT regimen is the appropriate PCI choice. Administration of appropriate anticoagulants as well as appropriate antiplatelet and coronary vasodilator therapy are critical for a favorable long-term result of the implantation. Following PCI, if elective noncardiac surgery requiring suspension of antiplatelet therapy is considered, the risks and benefits of the procedure should be weighed against the possible risk associated with interruption of antiplatelet therapy. Patients who require premature DAPT discontinuation should be carefully monitored for cardiac events. At the discretion of the patient’s treating physician(s), the antiplatelet therapy should be restarted as soon as possible.

In the LEADERS FREE trial, 36.7% of the patients received a loading dose of Aspirin, and 60.7% received a loading dose of a thienopyridine ADP antagonist (Clopidogrel/Prasugrel/Ticagrelor).

In the LEADERS FREE II trial, 37.2% of the patients received a loading dose of Aspirin, and 72.2% received a loading dose of a thienopyridine ADP antagonist (Clopidogrel/Prasugrel/Ticagrelor).

In the LEADERS FREE trial, DAPT was administered in 96.5% of the patients at discharge, in 95.2% at day 23 and in 9.5% at day 37 (lower and upper limit of the one-month visit window). At one year, DAPT was used in 7.7% of the patients.

In the LEADERS FREE II trial, DAPT was administered in 92.3% of the patients at one month, in 8.7% at two months and in 11.4% at one year. Also refer to the “Clinical” section for more information on DAPT usage in the LEADERS FREE and LEADERS FREE II Trials.

Patients who suffer a stent thrombosis during the first 30 days may be maintained on DAPT beyond 30 days if the treating physician considers that this is the safest option.

The clinical profile of HBR patients makes it unlikely that more potent antiplatelet agents than Clopidogrel will be used. However, should this be considered justified by the treating physician, the dose regimens of Prasugrel and Ticagrelor should be those recommended by the AHA/ACC/SCAI guidelines whenever possible.

Physicians should take into consideration information from clinical trials with BA9 DCS[1,2,3], other BA9 DES trials[4,5,6] as well as the most recently updated AHA/ACC/SCAI Guidelines for percutaneous coronary intervention and the specific needs of individual patients to determine the antiplatelet/anticoagulation regimen to be used for their patients.

Premature discontinuation or interruption of prescribed antiplatelet medication could result in a higher risk of stent thrombosis, MI or death.

**5.3 USE OF MULTIPLE STENTS**

When treating multiple lesions, distal lesions should be stented first followed by proximal lesion stenting. Stenting in this order obviates the need to cross the proximal stent in placement of the distal stent and reduces the chances for dislodging the proximal stent.

A patient's exposure to drug is proportional to the number and total length of implanted stents. In the LEADERS FREE trial, total stenting length was limited to 56 mm. When multiple stents are required, stent materials should be of similar composition. Placing multiple stents of different materials in contact with each other may increase potential for corrosion. To avoid the possibility of dissimilar metal corrosion, do not implant stents of different materials in tandem where overlap or contact is possible.

Potential interactions of the BioFreedom™ stent with other stents have not been evaluated and should be avoided whenever possible.

**5.4 USE IN CONJUNTION WITH OTHER PROCEDURES**

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters has not been established when used in conjunction with the BioFreedom stent. Also, please note that safety and effectiveness with Brachytherapy has not been established.

**5.5 USE IN SPECIAL POPULATIONS**

The safety and effectiveness of the BioFreedom™ DCS has not been established in the following patient populations:

- Pregnancy: There are no data available for the use of the BioFreedom™ stent in pregnant women or men intending to father children.
- During Lactation: The effects of the BA9 drug during lactation have not been evaluated.
- Pediatric use: The safety and efficacy of the BioFreedom™ stent has not been established in children.

Carefully consider whether it is appropriate to use the BioFreedom™ stent in the above patient populations.

**5.6 LESION/VESSEL CHARACTERISTICS**

The safety and effectiveness of the BioFreedom™ stent have not been established for the patient populations with the following clinical settings:

- Coronary artery reference vessel diameters < 2.25 mm or > 4.0 mm
- Cardiogenic shock
- STEMI patients
- Lesions with thrombus
- SVG
- UPLM
- CTO
- Bifurcation
- Ostial lesions
- 3V CAD
- Lesions in vascular territories other than coronary

**5.7 DRUG INTERACTION**

Consideration should be given to the potential for drug interactions when deciding to place a BioFreedom™ stent in a patient who is taking a drug that could interact with the BA9 drug or when deciding to initiate therapy with such a drug in a patient who has recently received a stent coated with BA9 drug. The effect of BioFreedom™ DCS drug interactions on safety or efficacy has not been determined.

There is no specific clinical data available for the interactions of the BA9 drug with other drugs. However, drugs like tacrolimus that may act through the same binding proteins (FKBP) may interfere with the efficacy of the BA9 drug. Drug interaction studies have not been performed. The BA9 drug is metabolized by CYP3A4. Strong inhibitors of CYP3A4 (e.g. ketoconazol) might cause increased BA9 drug exposure to levels associated with systemic effects, especially if multiple stents are deployed. Systemic exposure of the BA9 drug should be taken into consideration if the patient is treated concomitantly with systemic immunosuppressive therapy.

The patient's exposure to the BA9 drug is directly related to number of stents used and length of the BioFreedom™ stent or any other BA9 coated stents implanted.

**5.8 MRI**

Non-clinical testing has demonstrated that the BioFreedom™ DCS is MR Conditional up to a total length of 58 mm. A patient with a BioFreedom™ DCS can be safely scanned, immediately after placement, in a MR system meeting the following conditions:

- Static magnetic field of 1.5 Tesla or 3.0 Tesla
- Spatial gradient field of ≤ 3000 gauss/cm

*[1] Urban P, Meredith IT, Abizaid A, et al. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. N Engl J Med. 2015;373(21):2038-2047. doi:10.1056/NEJMoa1503943*
*[2] Garot P, Morice MC, Tresukosol D, et al. 2-Year Outcomes of High Bleeding Risk Patients After Polymer-Free Drug-Coated Stents. J Am Coll Cardiol. 2017;69(2):162-171. doi:10.1016/j.jacc.2016.10.009*
*[3] Costa RA, Abizaid A, Mehran R, et al. Polymer-Free Biolimus A9-Coated Stents in the Treatment of De Novo Coronary Lesions: 4- and 12-Month Angiographic Follow-Up and Final 5-Year Clinical Outcomes of the Prospective, Multicenter BioFreedom FIM Clinical Trial. JACC Cardiovasc Interv. 2016;9(1):51-64. doi:10.1016/j.jcin.2015.09.008*
*[4] Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet. 2008;372(9644):1163-1173. doi:10.1016/S0140-6736(08)61244-1*
*[5] Stefanini GG, Kalesan B, Serruys PW, et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. Lancet. 2011;378(9807):1940-1948. doi:10.1016/S0140-6736(11)61672-3*
*[6] Serruys PW, Farooq V, Kalesan B, et al. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, noninferiority trial. JACC Cardiovasc Interv. 2013;6(8):777-789. doi:10.1016/j.jcin.2013.04.011*

- Maximum MR system reported whole-body-averaged specific absorption rate (SAR) of ≤ 2 W/kg (Normal Operating Mode)

**MRI-induced heating:**

Under the scanning conditions defined above, the BioFreedom™ DCS is expected to produce a maximum temperature rise of less than 1°C after 15 minutes of continuous scanning.

**Image Artifact:**

MR image quality may be compromised if the area of interest is in the same area or relatively close to the position of the BioFreedom™ DCS. Therefore it may be necessary to optimize MR imaging parameters for the presence of the stent.

In non-clinical testing, the image artifact caused by the device extends approximately 13 mm from the BioFreedom™ DCS when imaged with gradient echo pulse sequence and a 3.0 Tesla MRI system. The lumen is fully obscured.

**5.9 STENT HANDLING**

**For single use only.** Do not re-sterilize or reuse.

Do not use a product that has reached or exceeded its labeled expiration date.

Do not use if packaging has been damaged or opened. **The sterility and stability of the BioFreedom™ DCS cannot be guaranteed once the pouch has been opened** and hence the device MUST be used promptly. Un-used devices should be discarded or returned to Biosensors™ and should not be re-stocked.

**DO NOT RUB OR SCRAPE THE STENT COATING.**

Do not use if stent coating is subjected to abrasions beyond those of normal insertion and delivery.

Do not use if stent is exposed to abnormal rubbing or contact with objects other than the guide catheter or opened hemostasis valve prior to implantation.

Exposing the stent to fluids before implantation should be avoided. Exposure to fluids prior to implantation may result in premature release of drug.

Special care must be taken not to manipulate or mechanically disrupt the stent on the balloon in any way.

Do not "roll" the mounted stent with your fingers as this action may damage stent coating and loosen the stent from the balloon. Subsequently this could cause dislodgement, or some loss of drug coating.

Do not remove the stent from its delivery catheter as removal may damage the stent and/or lead to stent embolization. The BioFreedom™ DCS is intended to perform as a system.

The delivery system should not be used in conjunction with other stents.

Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.

Do not attempt to straighten the proximal shaft (hypotube) if it is accidentally bent as it may cause the catheter to break.

**IN THE EVENT THAT THE STENT IS NOT SUCCESSFULLY DEPLOYED, THE STENT AND DELIVERY SYSTEM SHOULD BE RETURNED TO BIOSENSORS IF POSSIBLE.**

**5.10 STENT PLACEMENT**

**Do not introduce negative pressure or pre-inflate the delivery system prior to stent deployment** other than as directed. Use the balloon purging technique described in Section 11.3 DELIVERY SYSTEM PREPARATION.

**The labeled stent diameter refers to the expanded inner stent diameter.**

Implanting a stent may lead to dissection of the vessel distal and/or proximal to the stent and may cause acute closure of the vessel requiring additional intervention (CABG, further dilatation, placement of additional stents, or other).

Do not expand the stent if it is not properly positioned in the vessel. (See Section 5.11 STENT SYSTEM REMOVAL)

Placement of a stent has the potential to compromise side branch patency.

**Do not exceed rated burst pressure as indicated on product label.** Use of pressures higher than specified on the product label may result in a ruptured balloon with possible intimal damage and dissection.

**In case of mechanical resistance, do not attempt to pull an unexpanded stent back through the guiding catheter as dislodgement of the stent from the balloon may occur. Remove as a single unit as described in Section 5.11 STENT SYSTEM REMOVAL.**

Stent retrieval methods (use of additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma or pseudoaneurysm.

**Do not torque the catheter more than two (2) full turns.**

**5.11 STENT SYSTEM REMOVAL**

Should unusual resistance be felt at any time during either stent advancement or removal of the stent delivery system prior to the stent being implanted, the entire system should be removed as a single unit.

**When removing the stent delivery system as a single unit:**

- Do not attempt to retract an unexpanded stent into the guiding catheter while engaged in the coronary arteries.
- Stent damage or dislodgement may occur. Advance the guidewire into the coronary anatomy as far distally as safely possible.
- Position the proximal balloon marker just distal to the tip of the guiding catheter.
- **NOTE:** If it is necessary to maintain guidewire position, the guidewire must either be converted to an exchange wire length using an elongation wire or a second guidewire must be inserted.
- Tighten the rotating hemostatic valve to secure the delivery system to the guiding catheter. Remove the guiding catheter and stent delivery system as a **single unit**.

Failure to follow these steps and/or applying excessive force to the stent delivery system can potentially result in stent dislodgement or damage to the stent and/or delivery system components.

**5.12 POSTPROCEDURE PRECAUTIONS**

- Care must be exercised when crossing a newly deployed stent with a coronary guidewire, IVUS catheter, an OCT catheter, balloon or another stent delivery system to avoid disrupting the stent geometry.
- Post-dilatation: All efforts should be made to assure that the stent is not under-dilated. If the deployed stent is not fully affixed to the vessel wall, the stent may be expanded further with a larger diameter balloon that is slightly shorter (about 2 mm) than the stent. The post-dilatation can be done using a low-profile, high pressure, non-compliant balloon catheter. The balloon should not extend outside of the stented region. Do not use the stent delivery balloon for post-dilatation.
- Antiplatelet therapy should be administered post-procedure (see Section 5.2).
- If the patient requires imaging, see Section 5.8 MRI.

**6. DRUG INFORMATION**

**6.1 MECHANISM OF ACTION**

Current understanding suggests that the mechanism of action of Biolimus A9™ drug on a molecular level is due to complex formation with cytoplasmic proteins that inhibit the cell cycle between the G0 and G1 phase. This results in interruption of the cascade governing cell metabolism, growth, and proliferation, leading to a reversible inhibition of growth-factor-stimulated cell proliferation.

It is believed that the mechanism of action of the "limus family" is to be similar, in which Biolimus A9™ drug shares a common internal 'rapamycin' ring structure. This rapamycin ring structure is known to bind with the intracellular receptor FKBP-12. The resulting macrolide/FKBP-12 complex subsequently binds to a specific target protein known as mTOR (mammalian target of rapamycin) which is critical for cell cycle progression. Interaction of the macrolide/FKBP-12 complex with mTOR inactivates mTOR resulting in suppression of several specific signal transduction pathways and arrest of the cell cycle at the G1 to S phase.

The Biolimus A9™ drug coated on the BioFreedom™ DCS has an ancillary function as anti-proliferative and anti-restenotic agent due to its ability to interrupt smooth muscle cell migration and proliferation. Available short and long term clinical data of Biolimus A9™ release from coronary stents demonstrate the safety and efficacy of Biolimus A9™ for the treatment of restenosis in coronary arterial disease.

**6.2 PHARMACOKINETICS**

Evaluation of pharmacokinetics (PK) of Biolimus A9™ drug as delivered via the BioFreedom™ DCS was demonstrated in the BIOFREEDOM PK study (data on file at Biosensors). The PK analysis was done on the whole blood samples collected from 15 patients with coronary artery disease (CAD) who were eligible for inclusions, received BioFreedom™ stents, and completed the trial following the stent implantation.

Biolimus A9™ was quantifiable in systemic human blood as early as 15 minutes after stent implantation. The median maximum blood concentration ($C_{max}$) of 6.60 ng/mL (interquartile range: 5.73 to 8.14 ng/mL) was reached after a median time (time to $C_{max}$) of 1.0 hour (interquartile range: 1.0 to 2.0 hours). The highest Biolimus A9™ blood concentration measured in any of the study participants at any sample collection time point was 12.90 ng/mL (patient 14; blood sample collected at 1 hour post implantation). In all study participants, Biolimus A9™ was still quantifiable 3 days after stent implantation with a median Biolimus A9™ concentration of 0.37 ng/mL (interquartile range: 0.26 to 0.51 ng/mL). The median area-under-the-concentration time curve (AUC) of Biolimus A9™ over the observation period was 86.0 ng/mL·h (interquartile range: 67.1 to 114.8 ng/mL·h).

In a single ascending dose trial, Steudel et al. (2011) identified the highest safe intravenous dose of Biolimus A9™, to evaluate the dose-dependent pharmacokinetics of Biolimus A9™ after intravenous administration in humans, and to characterize early clinical symptoms of Biolimus A9™ toxicity in healthy patients. At the highest Biolimus A9™ dose, which was considered safe (0.25 mg/kg), the $C_{max}$ was 79.4 ± 54.1 ng/mL (mean ± standard deviation) and the AUC over the observation period was 221.4 ± 94.6 ng/mL·h (mean ± standard deviation). This means that the mean (± standard deviation) $C_{max}$ (7.23 ± 2.83 ng/mL) in the BIOFREEDOM PK study was approximately 11.0-fold lower than the mean $C_{max}$ at the highest safe Biolimus A9™ dose in the single ascending dose trial, and the AUC in the BIOFREEDOM PK study (mean ± standard deviation: 95.3 ± 44.0 ng/mL·h) was approximately 2.3-fold lower than the AUC at the highest safe single Biolimus A9™ dose.

*Reference: Steudel W, Dingmann C, Zhang YL, Bendrick-Peart J, Clavijo C, Shulze J, Betts R, Christians U. Randomized, double-blind, placebo-controlled, single intravenous dose-escalation study to evaluate the safety, tolerability, and pharmacokinetics of the novel coronary smooth muscle cell proliferation inhibitor Biolimus A9 in healthy individuals. J Clin Pharmacol. 2011;51:29-39.*

**6.3 DRUG INTERACTIONS**

Please refer to Section 5.7.

**6.4 MUTAGENESIS, CARCINOGENICITY AND REPRODUCTIVE TOXICITY**

**6.4.1 Mutagenesis**

Biolimus A9™ drug was not genotoxic in the bacterial mutagenicity test (Ames assay), *in vitro* mouse lymphoma assay, or *in vivo* mouse micronucleus assay.

**6.4.2 Carcinogenicity**

No long-term studies in animals have been performed to evaluate the carcinogenic potential of Biolimus A9™. The likelihood of carcinogenetic risk is low based on the chemical characterization test data of the BioFreedom™ drug-coated stents.

**6.4.3 Reproductive Toxicity**

In a fertility and early embryonic development study in rats, intravenous administration of Biolimus A9™ decreased sperm count and motility, atrophy of seminiferous tubes, and degeneration of spermatocytes, and decreased fertility at a dose 34 times the maximum potential human dose of Biolimus A9™ in patients (the highest nominal drug dose of a 28-mm stent length is 453 µg Biolimus A9™; or a maximum potential dose of 7.55 µg/kg of Biolimus A9™, assuming an average 60 kg human).

**6.5 PREGNANCY**

There are no adequate and well-controlled Biolimus A9™ or BioFreedom™ DCS related studies in pregnant women or men intending to father children. In women of birth potential, effective contraception should be initiated before implanting a BioFreedom™ stent and continued for one year post-stent implantation. The BioFreedom™ stent should be used in pregnant women only if potential benefit outweighs the potential risk to the embryo/fetus.

Administration of Biolimus A9™ to pregnant female rats in an embryo-fetal development study at an intravenous dosage 0.4 times the maximum potential human dose resulted in embryo-lethality and lower fetal body weights. At doses 1.4 times the maximum potential human dose, a fetal malformation and early resorptions in utero were noted. There were no effects on rabbit embryo-fetal development at a dose similar to the maximum potential human dose of Biolimus A9™.

**6.6 LACTATION**

The effects of the Biolimus A9™ drug during lactation have not been evaluated and it is unknown whether Biolimus A9™ is distributed in human milk. The pharmacokinetic and safety profiles of Biolimus A9™ have also not been established in infants, and the potential adverse effects in nursing infants from Biolimus A9™ are not known. A decision to discontinue breastfeeding during the mother's exposure to Biolimus A9™ may be needed, taking into account the importance of the stent to the mother.

**7. CLINICAL STUDIES**

**7.1 BIOFREEDOM FIRST-IN-MAN (FIM) CLINICAL TRIAL**

| | |
|---|---|
| **STUDY DESIGN** | Prospective, randomized, single-blinded, multicenter study |
| **STUDY SIZE** | 182 (122 BioFreedom patients with half the BioFreedom Patients receiving the standard dose and half receiving a low dose device) |
| **SITE LOCATION** | 4 sites in Germany |
| **PATIENT POPULATION** | Patients with *de novo* coronary lesions |
| **POST PROCEDURAL ANTIPLATELET THERAPY** | 6 Month DAPT |
| **FOLLOW UP DURATION** | 5 Years |
| **STATUS** | This FIM study met the primary efficacy endpoint and demonstrated sustained safety throughout the study. |

The BioFreedom First In Man (FIM) trial was a prospective, single blinded, randomized clinical trial to evaluate the safety and effectiveness of a low and standard dose BioFreedom™ Biolimus A9 Drug-Eluting Coronary Stent Delivery System compared with a Taxus® Liberté® control arm for the treatment of stenotic lesions in native coronary arteries.

The BioFreedom FIM trial documented, that the standard dose BioFreedom™ (BFD) stent was non inferior to the CE-mark approved Taxus® Liberté® Paclitaxel Eluting stent (PES) for the angiographic endpoint “in-stent late lumen loss” at 12 months (BFD 0.17mm vs. PES 0.35mm; p=0.001 for non-inferiority; p=0.11 for superiority). Despite a numerically better late lumen loss for the BFD, superiority was not reached. Both stents showed similar clinical outcomes at 12 months with MACE rates of 6.1% (BFD) vs. 5.5% (PES) (p=0.98), and of 23.8% (BFD) vs. 20.3% (PES) at 5 years (p=0.67). No ARC definite/probable stent thrombosis occurred in either arm. These results demonstrated that the BFD stent has comparable angiographic efficacy at 1 year and similar long-term safety outcomes as the PES out to 5 years.

*Reference: Costa RA, Abizaid A, Mehran R, et al. Polymer-Free Biolimus A9-Coated Stents in the Treatment of De Novo Coronary Lesions. 4- and 12-Month Angiographic Follow-Up and Final 5-Year Clinical Outcomes of the Prospective, Multicenter BioFreedom FIM Clinical Trial. JACC Cardiovasc Interv 2016; 9:51-64; DOI: 10.1016/j.jcin.2015.09.008*

**7.2 EGO BIOFREEDOM STUDY**

| | |
|---|---|
| **STUDY DESIGN** | Prospective, single-center, single-arm study |
| **STUDY SIZE** | 100 BioFreedom Patients |
| **SITE LOCATION** | 1 site in Hong Kong |
| **PATIENT POPULATION** | Patients with *de novo* coronary lesions |
| **POST PROCEDURAL ANTIPLATELET THERAPY** | 9 Month DAPT |
| **FOLLOW UP DURATION** | 1 Year |
| **STATUS** | Longitudinal sequential OCT assessments confirmed rapid healing and healthy neointimal transformation of the BioFreedom Stent and established, in coincidence with angiographic QCA assessment, its anti-proliferation efficacy at 9 months. |

The EGO BioFreedom study was a prospective, single center, open-label study using BioFreedom™ stents. All patients received baseline optical coherence tomography (OCT) for best optimization of stenting. Patients were then randomly assigned to 5 monthly groups (each group consisted of 20 patients) to be followed up by OCT at 1, 2, 3, 4, or 5 months and then all patients had OCT at 9 months. All patients were followed up clinically to 12 months. The primary objective was the percentage of strut coverage from 1 to 9 month, as determined by independent OCT core laboratory analysis. A total of 104 patients with coronary artery disease, who qualify for percutaneous coronary intervention and without contraindications to implantation of drug eluting stents were enrolled in the study in Hong Kong.

One conclusion of the study was that the in-stent LLL at 9 months was 0.21 ± 0.30 mm. This was comparable with the results of the BioFreedom FIM study at 12 months, where the median LLL was 0.17 [0.09, 0.39] mm in the BioFreedom™ arm, compared to 0.35 [0.22, 0.57] mm in the Taxus Liberté arm. It was further stated, the BioFreedom™ stent showed a favorable early healing profile, and near complete strut coverage at 9 months, as confirmed by the OCT core-laboratory of the study. Clinical outcomes were a total MACE rate of 4.0% at 1 year, including the rate of TLR of 2.0%. There were no stent thrombosis events observed.

*Reference: Lee SWL, Tam FCC, Chan KKW, et al. Establishment of healing profile and neointimal transformation in the new polymer-free biolimus A9-coated*

*coronary stent by longitudinal sequential optical coherence tomography assessments: The EGO-BioFreedom study. EuroIntervention 2018; 14:780-788; DOI: 10.4244/EIJ-D-18-00061*

**7.3 LEADERS FREE TRIAL**

| | |
|---|---|
| **STUDY DESIGN** | Prospective, randomized, double-blinded, multicenter study |
| **STUDY SIZE** | 2,466 Patients (1,239 BioFreedom Patients) |
| **SITE LOCATION** | 68 sites across 20 regions (France, United Kingdom, Germany, Spain, Italy, Switzerland, Singapore, Denmark, Hong Kong, Malaysia, Australia, Thailand, Belgium, Israel, Latvia, Norway, The Netherlands, Canada, Ireland, and Austria). |
| **PATIENT POPULATION** | Patients with coronary artery disease at high risk of bleeding |
| **POST PROCEDURAL ANTIPLATELET THERAPY** | 1 Month DAPT |
| **FOLLOW UP DURATION** | 2 Years |
| **STATUS** | The authors concluded that the BioFreedom stent was superior to a BMS with respect to the primary safety endpoint and demonstrated a significantly lower incidence of the primary efficacy endpoint, when used with a 1-month regimen of dual antiplatelet therapy in patients with high bleeding risk following PCI. |

LEADERS FREE was a prospective, randomized, double-blind study to evaluate the safety and efficacy of the BioFreedom™ polymer-free stent compared with a bare-metal stent (BMS) in patients with high bleeding risk (HBR). A total of 2,466 patients were enrolled (including 659 patients with ACS) and treated with one month of dual antiplatelet therapy. Inclusion criteria were designed to create a patient population at high bleeding risk. Patients with coronary artery disease and a clinical indication for PCI were eligible for inclusion.

The HBR Definition utilized in LEADERS FREE was as follows:

1. Adjunctive oral anticoagulation treatment planned to continue after PCI
2. Age ≥75 years old
3. Baseline Hgb <11 g/dl (or anemia requiring transfusion during the 4 weeks prior to randomization)
4. Any prior intracerebral bleed
5. Any stroke in the last 12 months
6. Hospital admission for bleeding during the prior 12 months
7. Non skin cancer diagnosed or treated <3 years
8. Planned daily NSAID (other than aspirin) or steroids for >30 days after PCI
9. Planned surgery that would require interruption of DAPT (within next 12 months)
10. Renal failure defined as: Creatinine clearance <40 ml/min
11. Thrombocytopenia (PLT <100,000/$mm^3$)
12. Severe chronic liver disease defined as: patients who have developed any of the following: variceal hemorrhage, ascites, hepatic encephalopathy or jaundice
13. Expected non-compliance to prolonged DAPT for other medical reasons

The primary safety endpoint was the composite of cardiac death, MI, and definite or probable stent thrombosis at 390 days. The primary efficacy endpoint was the incidence of clinically-driven target-vessel revascularization (CI-TLR) at 390 days. The study was powered to determine whether the BioFreedom™ stent was non-inferior to the bare-metal stent for the primary safety endpoint. If non-inferiority was shown, the safety endpoint would then be tested for superiority. The 1-year period was extended to 390 days in order to capture events and revascularizations occurring soon after the 1-year follow-up visit.

At 1 year. the primary safety endpoint occurred in 112 patients (9.4%) in the BioFreedom™ group, and 154 patients (12.9%) in the BMS group ($P < 0.001$ for non-inferiority, $P = 0.005$ for superiority). The significantly lower incidence of the composite safety endpoint in the BioFreedom™ group was driven by a reduction of MI events, observed in 72 patients (6.1%) vs. 104 patients (8.9%) ($P = 0.01$).

At 1 year, the primary efficacy endpoint (CI-TLR through 390 days) occurred in 59 patients (5.1%) in the BioFreedom™ group and 113 patients (9.8%) in the BMS group (P <0.001). Bleeding (category BARC 3-5) was high in both groups, as expected, with 85 BioFreedom™ patients (7.2%) vs. 85 BMS patients (7.3%) experiencing bleeding at 1 year.

In the BioFreedom™ group, 50 patients (4.2%) died from cardiac causes compared with 63 cardiac deaths (5.3%) in the BMS group. Rates of stent thrombosis (definite/probable) were similar in the two groups, with 24 patients (2.0%) vs. 26 patients (2.2%) through 390 days.

At 2 years of follow-up, the composite safety endpoint occurred in 147 patients (12.6%) in the DCS group and in 180 patients (15.3%) in the BMS group. Clinically driven TLR occurred in 77 patients (6.8%) in the DCS group and in 136 patients (12%) in the BMS group. Further, significant differences between the two stent groups continued to be observed for the secondary endpoints in favour of the DCS group.

In line with the primary efficacy endpoint, significant differences between groups were also sustained for the primary efficacy endpoint which occurred in 77 patients (6.8%) in the BioFreedom™ arm, vs 136 patients (12.0%) in the BMS arm at 24 months.

Rates of death (all types), cardiac death, stent thrombosis and major bleeding did not differ significantly between the BMS and DCS groups.

Importantly, the trial did not find a difference in stent thrombosis at 1 year, and virtually no increment from 1 year to 2 years, confirming that the risk for late stent thrombosis associated with the DCS is very low and similar to that of BMS.

The authors concluded that the BioFreedom™ stent was safer and more effective than a bare-metal stent when used with a 1-month regimen of dual antiplatelet therapy in patients at high bleeding risk.

*References:*

*Urban P, Meredith IA, Abizaid A, et al. Polymer-free Drug-Coated Coronary Stents in patients at High Bleeding Risk. N Engl J Med 2015. 373:2038-47; DOI: 10.1056/NEJMoa1503943*

*Garot P, Morice MC, Tresukosol D, et al. 2-Year Outcomes of High Bleeding Risk Patients After Polymer-Free Drug-Coated Stents. J Am Coll Cardiol. 2017;69(2):162-171; Doi:10.1016/j.jacc.2016.10.009*

**7.4 LEADERS FREE II TRIAL**

| | |
|---|---|
| **STUDY DESIGN** | Prospective, multi-center, multi-national, open label, single-arm study |
| **STUDY SIZE** | 1,203 BioFreedom Patients |
| **SITE LOCATION** | 66 sites in North America and Europe |
| **PATIENT POPULATION** | Patients with coronary artery disease at high risk of bleeding |
| **POST PROCEDURAL ANTIPLATELET THERAPY** | 1 Month DAPT |
| **FOLLOW UP DURATION** | 3 Years |
| **STATUS** | One-year data confirmed the results from LEADERS FREE and demonstrated further generalizability of the treatment benefits of BioFreedom over a BMS for clinical practice in North America when a 1 month DAPT regimen is applied. The trial is currently on-going to 3 years of follow-up. |

LEADERS FREE II was a prospective, non-randomized single arm open-label clinical study to evaluate the safety and efficacy of the BioFreedom™ polymer-free stent in a high bleeding risk patient population in North America and Europe. The rationale for conducting the study in a single arm design was the absence of equipoise for randomization against a bare metal stent following publication of the LEADERS FREE study results. The study was conducted in close similarity to LEADERS FREE and used identical patient selection criteria, identical outcome endpoints, identical event adjudication processes, an identical angiographic core laboratory and identical case report forms. An important objective of the LEADERS FREE II study was to demonstrate that the outcomes of LEADERS FREE were reproducible and generalizable to the clinical practice in the United States. The bare-metal stent arm (Gazelle) from LEADERS FREE served as the historical control. Though the Gazelle stent is not currently commercially approved in the US, it was considered the most appropriate comparator for the new study because of its use in the LEADERS FREE study and the fact that the Gazelle is identical to the BioFreedom™ stent, with the exception that Gazelle has no drug coating. The Gazelle stent has also demonstrated clinical outcomes very similar to other BMS on the US market.[7] Additionally at the time that the LEADERS FREE II trial was initiated there were no drug-eluting stents in the United States approved for use in patients at high risk for bleeding, therefore use of a control DES with one month DAPT in the LEADERS FREE II trial would have constituted the use of an off-label control group. The Gazelle BMS thus constituted the most meaningful control reference cohort for the LEADERS FREE II trial.

The primary safety endpoint was the composite of cardiac death and myocardial infarction. The primary efficacy endpoint was the incidence of clinically-driven target-vessel revascularization (CD-TLR). The study was powered to determine whether the BioFreedom™ stent in LEADERS FREE II was non-inferior to the bare-metal stent in LEADERS FREE for the primary safety endpoint. If non-inferiority was shown, the safety endpoint would then be tested for superiority.

A total of 1,203 patients were enrolled from February to September 2017 (including 544 patients with acute coronary syndromes) and were mandatorily treated with 1 month of dual antiplatelet therapy. The mean age of patients was 74.6 years with 68.7% being male. The most common comorbidities were hypertension (79.6%, 961/1208) and hypercholesterolemia (74.4%, 892/1199). Approximately 22% (265/1208) of patients received previous PCI and around 62% (738/1198) of patients had multiple vessel disease. Target lesions were restenotic in 8.2% of the lesions (160/1945). Total occlusions were found in 5.0% (98/1945) of target lesions and lesions were at bifurcations in 13.4% (261/1945). Target lesion lengths averaged 18.6±10.6 mm and the mean reference vessel diameter was 3.0±0.5 mm. Target lesion stenoses averaged 83.7±12.4%.

There were 1287 procedures in total, 93.5% index procedures and 6.5% were staged procedures. Multi vessel treatment occurred in 22.1% (284/1287) of the procedures and multiple lesions were treated in 35.9% (461/1284) of the procedures. 49.9 % (641/1284) of the lesions treated were in the LAD. Femoral access was utilized in 36.3% (467/12876) of the procedures and 63.7% (820/1287) used radial access.

At discharge, 84.6% of patients (1018/1203) were on aspirin and 93.1% (1120/1203) were on an ADP antagonist, with 78.9% (949/1203) of patients taking clopidogrel 84.1% of patients (1012/1203) were on DAPT at the time of discharge, most frequently aspirin and clopidogrel (70.2%, 845/1203) followed by aspirin and ticagrelor (12.6%, 151/1203). At discharge, 33.5% of patients (403/1203) were on oral anticoagulants. Among these, warfarin or another anti-vitamin K (AVK) agent was used in 13.0% (156/1203) while another (unspecified) oral agent was used in 20.6% (248/1203).

At 1 month, the proportion of patients receiving DAPT increased to 92.3% (1086/1177), most commonly aspirin and clopidogrel (79.1%, 931/1177) followed by aspirin and ticagrelor (12.1%, 143/1177). The use of oral anticoagulants was 36.7% (432/1177) at 1 month, the most frequent of which was warfarin or another AKV agent (13.8%, 162/1177), followed by apixaban (13.1%, 154/1177), rivaroxaban (8.2%, 97/1177), and dabigatran (1.5%, 18/1177). The proportion of patients on oral anticoagulation and the ratio of the various oral anticoagulants remained relatively constant through 12-month follow-up.

The proportion of patients on DAPT dropped precipitously at 2 months, with only 8.7% of patients (101/1162) on DAPT, most commonly aspirin and clopidogrel (7.6%, 88/1162). Single antiplatelet therapy (SAPT) was utilized in 89.0% of patients (1034/1162) at 2 months; primarily aspirin (66.4%, 771/1162), followed by clopidogrel (20.4%, 237/1162). These ratios remained similar at 6 months, with DAPT in 8.6% of patients (95/1110) and SAPT in 88.3% (980/1110). At 12 months, the proportion of patients on DAPT increased slightly to 12.0% (130/1083), while SAPT decreased to 83.1% (900/1083).

Safety: At 6-month follow-up, the composite safety endpoint (cardiac death, MI) occurred in 78/1,203 patients (6.5% KM estimate) in the BioFreedom™ group, and in 116/1,211 patients (9.7%) in the BMS group (log-rank *P*<0.001). After testing the primary efficacy endpoint and confirming noninferiority, superiority was tested for the primary safety endpoint. The 6-month primary safety endpoint was significantly lower in the DCS group (P=0.0033), confirming superiority for the primary safety endpoint in favor of DCS over BMS through 6 months. At one year follow-up, the composite safety endpoint (cardiac death, MI) occurred in 110/1,203

[7] Valgimigli, Marco, et al. "Zotarolimus-eluting versus bare-metal stents in uncertain drug-eluting stent candidates." *Journal of the American College of Cardiology* 65.8 (2015): 805-815.

patients (9.3% KM estimate) in the BioFreedom™ group, and in 148/1,013 patients (12.4%) in the BMS group.

Efficacy: At 6-month follow-up, a total of 43/1,203 patients (3.7%) in the BioFreedom™ group and 71/1211 patients (6.1%) in the BMS group (log-rank *P*<0.0001) experienced clinically indicated target lesion revascularization (CD-TLR). Once noninferiority was met for the primary efficacy endpoints, superiority was tested. The -2.2% difference (95% CI -4.1%, -0.4%) was statistically significant in favor of the LFII DCS group (P=0.0175), confirming superiority of the LFII DCS over the LFI BMS control with respect to the primary efficacy endpoint of 6-month CD-TLR through 6-months. At one-year follow-up, a total of 82/1,203 patients (7.2%) in the BioFreedom™ group and 107/999 patients (9.2%) in the BMS group experienced CD-TLR.

ARC definite/probable stent thrombosis occurred in 21 patients (1.8%) receiving BioFreedom™ stents, versus 26 patients (2.2%) in the BMS reference arm .

The investigators concluded after the 1 year follow up that the LEADERS FREE II trial reconfirmed the results from LEADERS FREE and demonstrated further generalizability of the treatment benefits for BioFreedom™ over a BMS for the clinical practice in North America when a 1 month DAPT regimen is applied.

## 8. ADVERSE EVENTS

### 8.1 OBSERVED ADVERSE EVENTS

Principal adverse event information is derived from the pivotal LEADERS FREE and LEADERS FREE II trials and is shown in **Table 8-1** and **Table 8-2**.

**TABLE 8-1: LEADERS FREE ADVERSE EVENTS**

| Event | Statistics | BioFreedom (N=1221) | Gazelle (N=1211) |
|---|---|---|---|
| **In-hospital Events** | | | |
| Primary safety endpoint (PSE) | % (n/N) | 1.15%(28/1221) | 0.99%(24/1210) |
| MACE | % (n/N) | 1.11%(27/1221) | 0.95%(23/1210) |
| All-cause mortality | % (n/N) | 0.29%(7/1221) | 0.21%(5/1210) |
| Cardiac Death | % (n/N) | 0.29%(7/1221) | 0.16%(4/1210) |
| Non-Cardiac Death | % (n/N) | 0.0%(0/1221) | 0.04%(1/1210) |
| Myocardial infarction (MI) | % (n/N) | 0.82%(20/1220) | 0.82%(20/1210) |
| Q-wave | % (n/N) | 0.08%(2/1221) | 0.08%(2/1210) |
| Non Q-wave | % (n/N) | 0.66%(16/1221) | 0.58%(14/1210) |
| Target-vessel MI | % (n/N) | 0.82%(20/1221) | 0.78%(19/1210) |
| Q-wave | % (n/N) | 0.08%(2/1221) | 0.08%(2/1210) |
| Non Q-wave | % (n/N) | 0.66%(16/1221) | 0.53%(13/1210) |
| Clinically-driven TLR | % (n/N) | 0.21%(5/1221) | 0.16%(4/1210) |
| Clinically-driven TVR | % (n/N) | 0.21%(5/1221) | 0.16%(4/1210) |
| Definite/Probable stent thrombosis (ARC) | % (n/N) | 0.37%(9/1221) | 0.33%(8/1210) |
| Major Bleeding (BARC 3-5) | % (n/N) | 0.86%(21/1220) | 0.74%(18/1209) |
| **Post-procedure Events** | | | |
| 30-day PSE | KM Estimate n(%) | 39 (3.22%) | 38 (3.12%) |
| 30-day MACE | KM Estimate n(%) | 38 (3.14%) | 37 (3.04%) |
| 6-month PSE | KM Estimate n(%) | 118 (9.83%) | 79 (6.55%) |
| 6-month MACE | KM Estimate n(%) | 141 (11.76%) | 90 (7.48%) |
| **12-Months Events** | | | |
| Primary safety endpoint (PSE) | KM Estimate n(%) | 151 (12.65%) | 110 (9.2%) |
| MACE | KM Estimate n(%) | 205 (17.22%) | 138 (11.57%) |
| All-cause mortality | KM Estimate n(%) | 105 (8.73%) | 91 (7.54%) |
| Cardiac Death | KM Estimate n(%) | 61 (5.12%) | 49 (4.12%) |
| Non-Cardiac Death | KM Estimate n(%) | 44 (3.8%) | 42 (3.57%) |
| Myocardial infarction (MI) | KM Estimate n(%) | 103 (8.77%) | 70 (5.9%) |
| Q-wave | KM Estimate n(%) | 7 (0.6%) | 6 (0.5%) |
| Non Q-wave | KM Estimate n(%) | 78 (6.67%) | 55 (4.65%) |
| Target-vessel MI | KM Estimate n(%) | 89 (7.57%) | 60 (5.05%) |
| Q-wave | KM Estimate n(%) | 7 (0.6%) | 6 (0.5%) |

| | | | |
|---|---|---|---|
| Non Q-wave | KM Estimate n(%) | 66 (5.65%) | 44 (3.72%) |
| Clinically-driven TLR | KM Estimate n(%) | 115 (9.97%) | 64 (5.5%) |
| Clinically-driven TVR | KM Estimate n(%) | 107 (9.27%) | 57 (4.9%) |
| Definite/Probable stent thrombosis (ARC) | KM Estimate n(%) | 26 (2.19%) | 24 (2%) |
| Major Bleeding (BARC 3-5) | KM Estimate n(%) | 85 (7.26%) | 85 (7.16%) |

**TABLE 8-2: LEADERS FREE II ADVERSE EVENTS**

| Event | Statistics | BioFreedom (N=1203) |
|---|---|---|
| **In-hospital Events** | | |
| Primary safety endpoint (PSE) | % (n/N) | 1.83%(22/1203) |
| MACE | % (n/N) | 1.91%(23/1203) |
| All-cause mortality | % (n/N) | 0.33%(4/1203) |
| Cardiac Death | % (n/N) | 0.33%(4/1203) |
| Non-Cardiac Death | % (n/N) | 0.0%(0/1203) |
| Myocardial infarction (MI) | % (n/N) | 1.5%(18/1203) |
| Q-wave | % (n/N) | 0.08%(1/1203) |
| Non Q-wave | % (n/N) | 1.25%(15/1203) |
| Target-vessel MI | % (n/N) | 1.5%(18/1203) |
| Q-wave | % (n/N) | 0.08%(1/1203) |
| Non Q-wave | % (n/N) | 1.25%(15/1203) |
| Clinically-driven TLR | % (n/N) | 0.5%(6/1203) |
| Clinically-driven TVR | % (n/N) | 0.42%(5/1203) |
| Definite/Probable stent thrombosis (ARC) | % (n/N) | 0.42%(5/1203) |
| Major Bleeding (BARC 3-5) | % (n/N) | 1.83%(22/1203) |
| **Post-procedure Events** | | |
| 30-day PSE | KM Estimate n(%) | 33 (2.74%) |
| 30-day MACE | KM Estimate n(%) | 35 (2.91%) |
| 60-day PSE | KM Estimate n(%) | 79 (6.64%) |
| 60-day MACE | KM Estimate n(%) | 101 (8.5%) |
| **12-Months Events** | | |
| Primary safety endpoint (PSE) | KM Estimate n(%) | 111 (9.4%) |
| MACE | KM Estimate n(%) | 159 (14.08%) |
| All-cause mortality | KM Estimate n(%) | 91 (7.7%) |
| Cardiac Death | KM Estimate n(%) | 41 (3.5%) |
| Non-Cardiac Death | KM Estimate n(%) | 50 (4.31%) |
| Myocardial infarction (MI) | KM Estimate n(%) | 75 (6.54%) |
| Q-wave | KM Estimate n(%) | 2 (0.17%) |
| Non Q-wave | KM Estimate n(%) | 66 (5.7%) |
| Target-vessel MI | KM Estimate n(%) | 52 (4.53%) |
| Q-wave | KM Estimate n(%) | 2 (0.17%) |
| Non Q-wave | KM Estimate n(%) | 46 (4.03%) |
| Clinically-driven TLR | KM Estimate n(%) | 88 (7.7%) |
| Clinically-driven TVR | KM Estimate n(%) | 82 (7.2%) |
| Definite/Probable stent thrombosis (ARC) | KM Estimate n(%) | 21 (1.8%) |
| Major Bleeding (BARC 3-5) | KM Estimate n(%) | 85 (7.2%) |

**8.2 POTENTIAL ADVERSE EVENTS**

Adverse events (in alphabetical order) which may be associated with percutaneous coronary and treatment procedures, where coronary stents are used in native coronary arteries include but are not limited to:

- Access site complications (incl. arteriovenous fistula, hematoma, infection, nerve injury, pain, peripheral ischemia, phlebitis, pseudoaneurysm)
- Acute myocardial infarction
- Allergic reaction or hypersensitivity to anti-coagulation and/or anti-thrombotic therapy, contrast media, or stent components and/or delivery system materials
- Aneurysm
- Angina pectoris (stable or unstable)
- Anxiety
- Bleeding complications which may require transfusions or surgical repair
- Cardiac arrhythmias, including ventricular fibrillation and ventricular tachycardia
- Cardiac failure
- Cardiac tamponade
- Cardiogenic shock
- Coronary artery complications (incl. abrupt closure, dissection, embolism, injury, perforation, plaque rupture/shift, restenosis, rupture, spasm, thrombosis, total occlusion)
- Death
- Delayed endothelialization
- Distal emboli
- Endocarditis
- Failure to deliver the stent to the intended site
- Need for emergent or non-emergent coronary artery bypass grafting (CABG)
- Fever or pyrogenic reactions
- Hypotension/hypertension
- Infections
- Myocardial ischemia
- Nausea and vomiting
- Palpitations
- Perforation of the heart or great vessels
- Pericardial effusion
- Pulmonary failure
- Renal failure
- Stent compression
- Stent misplacement/migration/ embolization
- Stent thrombosis
- Stroke/Cerebrovascular Accident (CVA)/ Transient Ischemic Attack (TIA)
- Vasovagal reaction
- Vessel spasm
- Volume overload

**Potential adverse events that may be associated with exposure of BA9 drug include but are not limited to:**

- Chest heaviness
- Lymphadenopathy
- Nausea
- Mouth ulcers

BA9 drug administration experience is limited to intra-coronary stent delivery. Patient exposure to BA9 is directly related to the total surface area of stents implanted. Consequently, the adverse drug effects have not been fully characterized especially at significantly higher systemic doses than what would be delivered via the BioFreedom™ DCS.

For the specific adverse events that occurred in the clinical studies, please see Section 8.1 OBSERVED ADVERSE EVENTS.

**9. PATIENT SELECTION AND TREATMENT**

The risks and benefits of drug-coated stents should be considered for each patient before use of the BioFreedom™ stent. Physicians are responsible for assessing patient appropriateness for stent implantation prior to procedure.

**10. PATIENT COUNSELING INFORMATION**

Physicians should consider the following in counselling patients about this product:

- Discuss the risks associated with stent placement
- Discuss the risks associated with an BA9-coated stent

- Discuss the risks of early discontinuation of the antiplatelet therapy
- Discuss the risks of late stent thrombosis with DCS use in higher risk patient subgroups
- Discuss the risk/benefit issues for this particular patient
- Discuss alternation to current life style immediately following the procedure and over the long term

**11. DIRECTIONS FOR USE (OPERATOR'S MANUAL)**

**11.1. INSPECTION PRIOR TO USE**

1. Inspect the stent delivery system package for damage to the sterile barrier.
2. Carefully remove the system from the package and inspect the delivery catheter for bends, kinks, and other damage.
3. Carefully remove the stent guard covering the stent /balloon. The pre-attached stylet is automatically removed.
4. Inspect the stent to ensure that it has not been damaged or displaced from its original position on the balloon. Verify that the stent is positioned between the proximal and distal balloon markers.
5. Note the position of the stent relative to the proximal and distal marker bands for use as reference under fluoroscopy.

Do not use if any defects are noted.

**11.2. MATERIALS REQUIRED**

| | |
|---|---|
| 1 | A guiding catheter with a minimum inner diameter of 0.070" |
| 1 | Pre-dilatation balloon catheter |
| 1 | 10-20 cc syringe |
| 1000 IU | Heparin per 500 cc Normal Saline (HepNS) |
| 1 | 0.014 inch guidewire ≥ 175 cm |
| 1 | Rotating hemostatic valve |
| N/A | Contrast diluted 1 : 1 with normal saline |
| 1 | Inflation device |
| 1 | Three-way stopcock |
| 1 | Guidewire introducer |
| 1 | Appropriate arterial access sheath |

**11.3. DELIVERY SYSTEM PREPARATION**

1. Prepare the inflation device/syringe with diluted contrast medium.
2. Attach the inflation device to the three-way stopcock; attach to the balloon inflation port hub.
3. Open the stopcock to the stent delivery system.
4. Leave on neutral.

**11.4. STENT DELIVERY PROCEDURE**

1. Prepare vascular access site according to standard PTCA practice.
2. Pre-dilate lesion with a balloon diameter 0.5 mm smaller than the stent, and a balloon length equal to or shorter than the target lesion length, and shorter than the length of the stent to be implanted.

**NOTE:** Stent contact with fluid has the possibility of initiating drug release. Fluid contact time should be limited to immediately prior to loading the delivery catheter on the guidewire. When flushing the delivery catheter, ensure that damage to the stent does not occur.

1. Backload stent delivery system onto the proximal portion of the guidewire while maintaining guidewire position across target lesion.
2. Open the rotating hemostatic valve on the guiding catheter hub as widely as possible, and close when the stent has been advanced safely inside the guide catheter.
3. Advance the stent delivery system over the guidewire to the target lesion under fluoroscopic guidance. Utilize the radiopaque balloon markers to position the stent across the lesion. Perform angiography to confirm stent position.

**NOTE:** If resistance is felt, DO NOT FORCE PASSAGE. Resistance may indicate a problem and may result in damage to the vessel or stent, or in stent dislodgement if it is forced. Remove the stent delivery system and the guiding catheter as a single unit, if possible (see Section 5.11 STENT SYSTEM REMOVAL).

**11.5. STENT DEPLOYMENT PROCEDURE**

1. Consult the balloon compliance chart on the compliance card or at the back of the product box in order to determine the balloon inflation pressure appropriate for the target vessel diameter.
2. Before deployment, reconfirm the correct position of the stent relative to the target lesion via the balloon markers.
3. Ensure that the three-way stopcock on the stent delivery system is open to the inflation device and apply negative pressure to purge the balloon of air.
4. Turn the three-way stopcock on the stent delivery catheter off to the balloon port and purge the inflation device of air. Open the side port of the three-way stopcock to the delivery system.

5. Under fluoroscopic visualization, inflate the balloon to at least 7 atm to deploy the stent at nominal diameter, but do not exceed the labeled rated burst pressure (RBP). Optimal expansion requires the stent to be in full contact with the artery wall with the stent internal diameter matching the size of the reference vessel diameter. **ENSURE THAT THE STENT IS NOT UNDERDILATED**.

6. Deflate the balloon with appropriate time reported below by pulling a vacuum with the inflation device. Make sure the balloon is fully deflated before attempting any movement of the system.

| Balloon Diameter (mm) / Balloon length (mm) | Time for Deflation |
|---|---|
| 2.25 to 2.75 / all lengths<br>3.0 up to 25 mm lengths | maximum 15 seconds |
| 3.0 of 30 mm length<br>3.5 to 4.0 / all lengths | maximum 20 seconds |

7. Confirm adequate stent expansion and balloon deflation by angiographic injection through the guiding catheter.

8. If more than one stent is needed to cover the lesion and balloon treated area, adequately overlap the stents (at least 2 mm) to avoid potential gap stenosis.

**11.6. REMOVAL PROCEDURE**

1. Ensure that the balloon is fully deflated.
2. Fully open the rotating hemostatic valve.
3. While maintaining guidewire position and negative pressure on inflation device, withdraw the delivery system.
4. Tighten rotating hemostatic valve.
5. Repeat angiography to assess the stented area.

**11.7. FURTHER DILATATION OF STENT SEGMENTS**

1. If an adequate expansion has not been obtained, re-advance the stent delivery system or exchange for another balloon catheter of appropriate balloon diameter to achieve proper stent apposition to the vessel wall.

**NOTE:** Post-dilatation should be performed within the stented segment. DO NOT dilate beyond the stent edges.

2. Reconfirm the stent position and the angiographic result. Repeat inflations until optimal stent deployment is achieved. Final stent diameter should match reference vessel.

**12. COMPLIANCE CHART**

The Nominal Pressure for each diameter is indicated by bold font.

**TABLE 12-1: BIOFREEDOM™ DCS STENT COMPLIANCE**

| PRESSURE | STENT ID by DIAMETER (mm) | | | | | |
|---|---|---|---|---|---|---|
| **atm** | **2.25** | **2.50** | **2.75** | **3.00** | **3.50** | **4.00** |
| 6 | 2.19 | 2.44 | 2.70 | 2.96 | 3.45 | 3.94 |
| **7 (Nominal Pressure)** | 2.24 | 2.49 | 2.75 | 3.03 | 3.52 | 4.02 |
| 8 | 2.28 | 2.54 | 2.81 | 3.08 | 3.58 | 4.10 |
| 9 | 2.32 | 2.58 | 2.85 | 3.13 | 3.64 | 4.16 |
| 10 | 2.35 | 2.61 | 2.89 | 3.18 | 3.68 | 4.22 |
| 11 | 2.38 | 2.64 | 2.92 | 3.21 | 3.73 | 4.27 |
| 12 | 2.41 | 2.67 | 2.95 | 3.25 | 3.77 | 4.32 |
| 13 | 2.44 | 2.70 | 2.99 | 3.29 | 3.82 | 4.38 |
| 14 (RBP)* | 2.46 | 2.73 | 3.02 | 3.33 | 3.87 | 4.44 |
| 15 | 2.50 | 2.77 | 3.06 | 3.37 | | |
| 16 (RBP)** | 2.53 | 2.81 | 3.10 | 3.41 | | |

* RBP for 3.50 mm and 4.00 mm
** RBP for 2.25 mm, 2.50 mm, 2.75 mm and 3.00 mm

**13. PATIENT MATERIALS**

Refer to a separate document for patient information leaflet.

**14. HOW SUPPLIED**

STERILE, NON-PYROGENIC. This device is sterilized via e-beam sterilization.

CONTENTS: One Biosensors BioFreedom™ Drug Coated Coronary Stent System.

STORAGE: Store in a cool dark dry place. Do not store above 25°C.

DISPOSAL: Dispose device in accordance with local regulations.

NOTE: This product does not contain phthalates

**15. SYMBOLS USED IN LABELING**

| | | | |
|---|---|---|---|
|  | Legal Manufacturer |  | Keep away from sunlight or heat |

| | | | |
|---|---|---|---|
|  | Date of Manufacture |  | Keep Dry |
| REF | Catalog number |  | Do not use if package is damaged or open |
| LOT | Batch code |  | Stent Length |
|  | Caution, consult accompanying documents |  | Stent Diameter |
|  | Do not re-sterilize |  | Maximum Guidewire Outer Diameter (OD) |
|  | Do not reuse |  | Minimum Guiding Catheter Inner Diameter (ID) |
| STERILE R | This device has been sterilized using irradiation |  | Do not store above 25°C |
|  | Use by date<br>Do not use this device after the indicated date (Year-month-day): |  | Consult Instruction for use |
|  | MR conditional | RBP | Rated Burst Pressure |
| NP | Nominal Pressure | | |

**16. WARRANTY**

Biosensors International warrants that its products are manufactured to the specifications set forth on its packaging, instructions for use and related literature.

This warranty is in lieu of and excludes all other warranties not expressly set forth herein, whether express or implied, by operation of law or otherwise, including, but not limited to, any implied warranties of merchantability or fitness for a particular purpose.

Biosensors International neither assumes, nor authorizes any other person to assume for it, any other or additional liability or responsibility in connection with this product.

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|---|---|
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