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Thin- versus thick-strut polymer-free biolimus-eluting stents: the BioFreedom QCA randomised trial

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KEYWORDS

- clinical trials
- drug-eluting stent
- QCA

Abstract

Background: The BioFreedom drug-coated stent with a stainless steel platform (BF-SS) has been demonstrated to be efficacious in patients at high bleeding risk and receiving only one-month dual antiplatelet therapy.

Aims: The aim of this study was to evaluate the efficacy of the new BioFreedom Ultra drug-coated stent with a thin-strut cobalt-chromium platform (BF-CoCr) compared to the BF-SS in an all-comers population undergoing percutaneous coronary intervention (PCI).

Methods: This was a prospective, multicentre, non-inferiority trial. The primary endpoint was in-stent late lumen loss (LLL) as determined by quantitative coronary angiography at nine-month follow-up. Clinical evaluation was performed at one year.

Results: A total of 200 patients were randomised (1:1) to either the BF-CoCr or the BF-SS stent at eight centres in Spain and Denmark. Baseline clinical and lesion characteristics were similar between the groups. Mean age was 66 years and 23% were female. The mean number of stents implanted per patient was 1.5. At nine-month follow-up, mean in-stent LLL was 0.34±0.49 mm in the BF-CoCr group versus 0.29±0.37 mm in the BF-SS group, p=0.005 for non-inferiority. At one year, target lesion failure was similar between the groups (7.3% in BF-CoCr vs 9.3% in the BF-SS group; p=0.60).

Conclusions: The BF-CoCr was non-inferior to the BF-SS in terms of in-stent LLL at nine months. Larger studies powered for clinical endpoints are warranted to compare the efficacy of this new platform with currently available DES.

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Abbreviations

BF-SS	BioFreedom stainless steel
BF-CoCr	BioFreedom cobalt-chromium
CI-TLR	clinically indicated target lesion revascularisation
CI-TVR	clinically indicated target vessel revascularisation
ITT	intention to treat
LLL	late lumen loss
MACE	major adverse cardiac events
MI	myocardial infarction
QCA	quantitative coronary angiography
TLF	target lesion failure

Introduction

The antirestenotic efficacy of drug-eluting stents (DES) has been demonstrated in large randomised trials. This has led to their widespread use in daily practice, making them the treatment of choice for patients undergoing percutaneous coronary intervention (PCI) in any clinical setting[1-4]. Since the approval of first-generation DES, stent design and several technical aspects have evolved, including the use of thinner stent struts, biodegradable polymers and the preferential use of cobalt-chromium (CoCr)-based alloys for the stent platform. The polymer-free biolimus-coated stent was originally developed to minimise the potential long-term adverse effects associated with polymer coatings. The first iteration had a stainless steel (SS) platform with a strut thickness of 112-120 µm and a micro-structured abluminal surface to optimise drug delivery. This enabled drug-to-vessel wall tissue transfer from the stent to be complete within 28 days of treatment leaving the implant behind as a bare metal stent. This rapid drug transfer to the vessel wall provided a rationale for an abbreviated dual antiplatelet therapy, which was an attractive treatment option for patients at high bleeding risk. The LEADERS FREE trial demonstrated the superior efficacy and safety of the BioFreedom™ SS (BF-SS; Biosensors Europe, Morges, Switzerland) platform compared to the bare metal comparator stent in patients at high bleeding risk and receiving only one-month dual antiplatelet therapy following stent implantation[5].

Since then, a second iteration of the BioFreedom device has been introduced with a thin-strut (84-88 µm) Co-Cr platform (BF-CoCr; Biosensors Europe) to improve the performance of the device further. This new platform allowed a reduction of the stent strut thickness while maintaining similar radial strength. Other design elements including the micro-structured abluminal surface, the Biolimus A9 drug, the drug dose and release kinetics are all identical to those of the previous BF-SS stent.

These features may provide the new iteration with additional advantages in terms of acute performance and antirestenotic efficacy. Therefore, we designed the BioFreedom QCA randomised clinical trial (ClinicalTrials.gov Identifier: NCT03307213) to evaluate the antirestenotic efficacy of the new BF-CoCr drug-coated stent in an all-comers population as compared to the first-generation BF-SS stent.

Methods

STUDY POPULATION

This trial enrolled adult patients with symptomatic coronary artery disease including chronic and acute coronary syndromes (ST-segment and non-ST-segment elevation myocardial infarction) who had an indication for PCI. As an angiographic inclusion criterion, the target lesion size should range between 2.5 and 3.5 mm to be covered by the available stent sizes. No other limitations on the number of lesions or vessels to be treated or lesion length were imposed. There were major exclusion criteria **(Supplementary Appendix 1)**.

STUDY DESIGN AND RANDOMISATION

The BioFreedom QCA trial was a prospective, multicentre, open-label, randomised study that compared the performance of the BF-SS versus the BF-CoCr stent in an all-comers population presenting with the full spectrum of coronary artery disease. Once the patient signed the informed consent and the above criteria were met, randomisation (1:1) was performed through an interactive web recognition system using random permuted blocks within strata of sizes 4 and 6 to receive either the BF-SS or the BF-CoCr stent. The randomisation schedule was computer generated and stratified by the presence or absence of diabetes mellitus.

PROCEDURES

PCI with the allocated stent was performed according to the local standard of care. Treatment of multiple target vessels (within the same procedure) and staged procedures within six weeks of the initial index procedure were permitted with the use of the assigned stent type as per randomisation. Therefore, any subsequent treatment of a lesion that was already present (but was not treated) at the time of the index procedure was considered as a staged procedure. Dual antiplatelet therapy was prescribed according to current clinical guideline recommendations.

ENDPOINTS

The primary endpoint of the study was in-stent late lumen loss (LLL) assessed by quantitative coronary angiography (QCA) at nine months. Secondary endpoints at all follow-up time points included all-cause and cardiac death, non-fatal myocardial infarction (MI), clinically indicated target lesion and target vessel revascularisation (CI-TLR; CI-TVR), major adverse cardiac events (MACE, defined as the composite of cardiac death, MI or CI-TLR), target lesion failure (TLF, defined as the composite of cardiac death, target vessel-related MI, CI-TLR), stent thrombosis per ARC definition[6], device success, procedure success, and lesion success. Definitions of these endpoints are available in **Supplementary Appendix 1**.

FOLLOW-UP

Patients were scheduled to be followed after hospital discharge at 30 days, 9, 12 and 24 months. In addition, at 9 months post index procedure, another angiography was performed for QCA analysis.

QCA ANALYSIS

Core lab QCA assessments (HCor, Sao Paolo, Brazil) were performed at baseline, post procedure and after the 9-month follow-up angiography to assess the primary endpoint. Additionally, the core lab assessed all cases of stent thrombosis and revascularisation. A technical description of the angiographic assessment is available in **Supplementary Appendix 1**.

STUDY COMMITTEES

Members of the Data Safety Monitoring Board and of the Clinical Events Committee are shown in **Supplementary Appendix 1**.

SAMPLE SIZE CALCULATION

The hypothesis of the study was that the BF-CoCr was non-inferior to the BF-SS with respect to in-stent LLL. Assuming true equivalence of the means between both stents, with a common standard deviation (SD) of 0.45 mm and a non-inferiority margin of 0.20 mm, 160 evaluable patients were needed in order to yield 80% power for non-inferiority using a one-sided, two-sample t-test with an alpha of 0.025. With an anticipated drop-out rate of 20%, we planned to enrol 200 patients. Statistical analysis and ethical considerations are detailed in **Supplementary Appendix 1**.

Results

BASELINE AND PROCEDURAL CHARACTERISTICS

Between June 2018 and March 2019, 200 patients were randomised in eight centres in Denmark and Spain. In five patients PCI was not performed. Therefore, the final sample size was 195 patients with 211 treated lesions (modified intention-to-treat [mITT] population). The institutions involved are presented in **Supplementary Appendix 1**. The flow chart of the trial is shown in **Figure 1**. Baseline demographics, clinical and procedural characteristics are presented in **Table 1** and **Table 2**. No major clinically relevant differences were observed between groups. The mean age was 66 years and 23% were female. Diabetes mellitus was present in one third of the patients and acute coronary syndromes in 40% of the recruited individuals. In terms of periprocedural variables, treatment of bifurcation lesions was significantly more often performed in the BF-CoCr group (16.3% vs 7.1% in the BF-SS arm; p=0.019).

PRIMARY ENDPOINT ANALYSIS

Baseline and post-procedure QCA data were similar between the groups **(Table 3)**. Follow-up angiography was performed in 90 patients (103 lesions) in the BF-CoCr group (92.8% of those allocated) and in 89 patients (108 lesions) in the BF-SS group (90.8%) **(Figure 1)**. Mean in-stent LLL was 0.34±0.49 mm in the BF-CoCr group versus 0.29±0.37 mm in the BF-SS group (p for non-inferiority=0.005). The per-protocol population yielded similar results with non-inferiority also reached. The cumulative frequency distribution curve for LLL of the two stent types is displayed in **Figure 2**. Mean LLL was similar between diabetic and non-diabetic patients (0.28±0.29 mm and 0.33±0.45 mm, p=0.23). Also, there were no differences between stent types both in diabetics and in non-diabetics (0.33±0.44 mm in BF-CoCr vs 0.24±0.35 mm in BF-SS, p=0.353, and 0.34±0.52 mm in BF-CoCr and 0.31±0.35 mm in BF-SS, p=0.745, respectively).

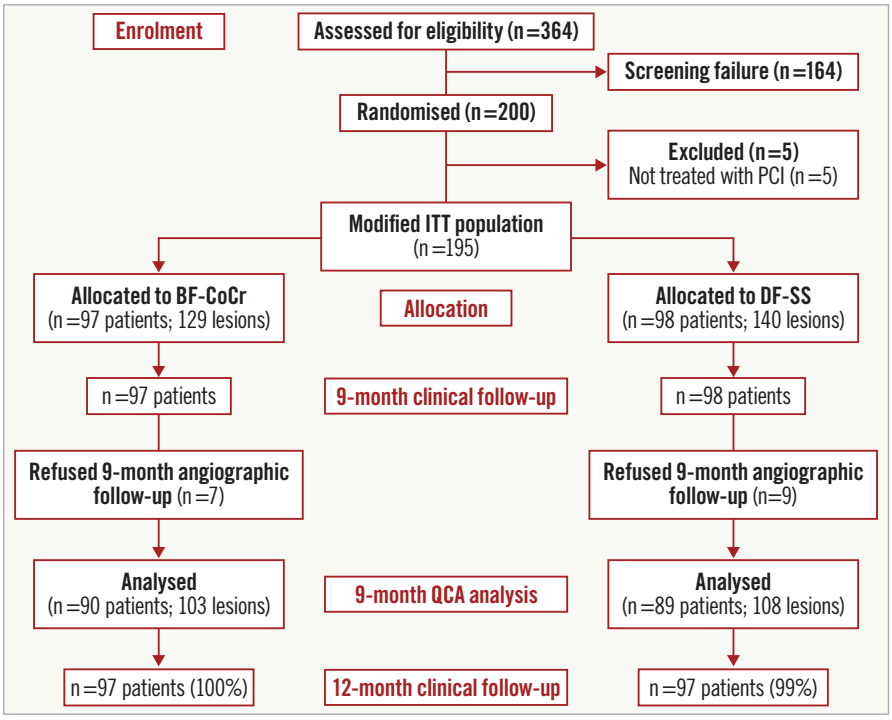

Figure 1. *Study flow chart.*

Table 1. Baseline clinical characteristics.

		BF-CoCr N=97	BF-SS N=98
Age, years, mean±SD		66.7±10.2	65.6±10.0
Female gender, n (%)		24 (24.7)	21 (21.4)
Body mass index, mean±SD		28.1±4.1	28.3±4.1
Coronary risk factors	Diabetes mellitus, n (%)	30 (30.9)	32 (32.7)
	Past or current smoker, n (%)	58 (61.7)	61 (64.9)
	Hypercholesterolaemia, n (%)	65 (67)	69 (70.4)
	Hypertension, n (%)	59 (60.8)	69 (70.4)
Comorbidities	Renal insufficiency, n (%)	4 (4.1)	6 (6.1)
	Liver disease, n (%)	3 (3.1)	1 (1)
	Chronic lung disease, n (%)	9 (9.3)	16 (16.3)
	Previous stroke, n (%)	5 (5.2)	11 (11.2)
	History of malignancy, n (%)	8 (8.2)	5 (5.1)
	Congestive heart failure, n (%)	5 (5.2)	6 (6.1)
	Previous MI, n (%)	20 (20.6)	22 (22.7)
	Previous PCI, n (%)	26 (26.8)	32 (32.7)
	Previous CABG, n (%)	2 (2.1)	6 (6.1)
Indication for PCI	Chronic coronary syndrome, n (%)	45 (46%)	50 (51%)
	Unstable angina, n (%)	13 (13.4)	7 (7.1)
	Non-STEMI, n (%)	21 (21.6)	25 (25.5)
	STEMI, n (%)	18 (18.6)	16 (16.3)

No significant differences were observed between groups except for bifurcation lesions (p=0.019). BF-CoCr: BioFreedom cobalt-chromium stent; BF-SS: BioFreedom stainless steel stent; CABG: coronary artery bypass graft; MI: myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

Table 2. Procedural characteristics.

		BF-CoCr N=129	BF-SS N=140
Procedure success*		102 (97.1)	101 (94.4)
Device success[y]		148 (99.3)	158 (99.4)
Lesion success[z]		126 (97.7)	137 (97.9)
De novo lesions, n (%)		127 (98.4)	136 (97.1)
Total stent length, mm (mean±SD)		29.6±15.7	34.1±23.3
Number of stents per patient (mean±SD)		1.46±0.7	1.53±0.8
Overlapping stent, n (%)		24 (22.9)	19 (17.6)
Target coronary vessel, n (%)	Left main	1 (0.8)	3 (2.1)
	Left anterior descending	61 (47.3)	59 (42.1)
	Circumflex	29 (22.5)	34 (24.3)
	Right coronary	38 (29.5)	44 (31.4)
ACC lesion classification, n (%)[¶]	A	11 (9.1)	12 (9.1)
	B1	27 (22.3)	34 (25.8)
	B2	49 (40.5)	45 (34.1)
	C	34 (28.1)	41 (31.1)
Bifurcation lesions[z], n (%)		21 (16.3)	10 (7.1)
Chronic total occlusions, n (%)		11 (8.5)	17 (12.1)
Multivessel PCI, n (%)		10 (9.5)	16 (14.8)

* Calculated from n=105 in BF-CoCr and n=107 in BF-SS. [y] Calculated from n=149 in BF-CoCr and n=159 in BF-SS. [z] Calculated from n=129 in BF-CoCr and n=140 in BF-SS. [¶] Data available in n=121 in the BF-CoCr group and in n=132 in the BF-SS group, respectively.

Table 3. Quantitative coronary angiography analysis (paired analysis baseline vs follow-up).

	BF-CoCr N=103	BF-SS N=108	p-value
Pre procedure			
Lesion length, mm	15.7±10.1	16.7±13.5	0.547
Reference diameter, mm	2.83±0.4	2.75±0.4	0.163
Minimal lumen diameter, mm	0.82±0.5	0.82±0.4	0.961
Diameter stenosis, %	71.4±14.7	70.4±14.7	0.642
Post procedure			
Reference diameter, mm	2.95±0.4	2.86±0.4	0.114
Minimal lumen diameter, mm	2.62±0.4	2.50±0.4	0.044
Diameter stenosis, %	10.3±7.0	10.9±7.2	0.355
Acute gain, mm	1.8±0.5	1.7±0.5	0.096
Follow-up			
Reference diameter, mm	2.89±0.4	2.80±0.4	0.128
Minimal lumen diameter, mm	2.29±0.6	2.21±0.5	0.361
Diameter stenosis, %	19.8±17.5	20.2±16.6	0.899
In-stent binary restenosis, n (%)	7 (6.8)	9 (8.3)	0.673
In-segment binary restenosis, n (%)	6 (5.9)	7 (6.5)	0.856
In-stent late lumen loss, mm*	0.34±0.49 0.16 (0.06:0.43)	0.29±0.37 0.17 (0.07:0.34)	0.444
In-segment late lumen loss, mm**	0.32±0.52 0.12 (0.04:0.33)	0.26±0.35 0.13 (0.05:0.34)	0.366

Values presented as mean±SD and median (interquartile range). * p-value for non-inferiority=0.0061; 95% two-sided confidence interval for the mean difference [-0.069 - 0.167]. ** p-value for non-inferiority= 0.0092; 95% two-sided confidence interval for the mean difference [-0.06 - 0.18].

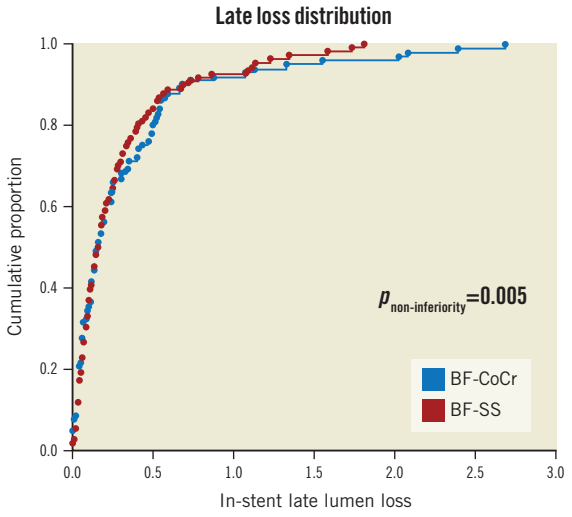

Figure 2. *Cumulative distribution curves of the LLL between the BF-CoCr and BF-SS groups. LLL: late lumen loss*

CLINICAL FOLLOW-UP

Rates of procedure, lesion, and device success were comparable between groups **(Table 2)**. At 12 months, clinical events could be obtained in all patients included **(Figure 1)**; no significant differences

were apparent between the two stent groups **(Supplementary Table 1)**. The antithrombotic therapy regimen up to 12 months is presented in **Supplementary Table 2** and **Supplementary Table 3**. Overall, at 12 months, the proportion of patients on dual antiplatelet therapy was 59.2%, with similar proportions in both arms (64.6% in the BF-SS arm vs 53.7% in the BF-CoCr arm; p=0.125). A total of 17.3% of patients received oral anticoagulation therapy without differences between groups. In patients with acute coronary syndromes on admission, the rate of dual antiplatelet therapy at 12 months was higher (67.1%) than that of patients with chronic coronary syndromes (53.6%), with no differences between groups.

Discussion

This study represents the first-in-human clinical experience of the new BF-CoCr stent in an all-comers cohort of patients presenting with the entire spectrum of coronary artery disease. This new platform demonstrated non-inferiority for LLL at nine-month angiographic follow-up compared with its market-approved precursor, the BF-SS. The main difference between the two stents is the cobalt-chromium alloy that allowed a reduction in strut thickness from 120 µm of the BF-SS to approximately 84-88 µm for this new platform. All other design elements, including the polymer-free design, the antiproliferative drug, the dose, the release kinetics and the achieved target tissue drug concentrations, were not different between the stents.

IN-STENT LATE LUMINAL LOSS AS SURROGATE ENDPOINT

In-stent LLL is calculated as the difference in minimal luminal diameter inside the boundaries of the stent between that achieved post index procedure and that observed at angiographic follow-up. This parameter has been widely used to assess the antirestenotic efficacy of various angioplasty techniques such as balloon angioplasty, atherectomy, intracoronary brachytherapy, bare metal stents, DES, and bioresorbable scaffolds, among others[1-4,7-11]. As a continuous variable, the required sample size for a trial would be smaller than that required for a binary angiographic parameter such as restenosis rate or a clinical parameter such as TLR. Consequently, LLL has been routinely used as the reference standard for stent efficacy comparisons and for device approval by regulatory bodies. In the bare metal stent era, restenosis was the major limitation for stenting, with values of LLL commonly ranging between 0.8 and 1.2 mm[12]. With the advent of first-generation DES, neointimal proliferation was dramatically suppressed with a subsequent reduction in LLL values to <0.2 mm[1]. Although these low values of LLL were initially associated with negligible rates of TLR, safety concerns in terms of stent thrombosis or late restenotic catch-up phenomenon started to appear in the long term[13]. Consequently, the lower the better concept as it referred to LLL became debatable. Clearly, LLL has good discriminating capability for clinical outcomes in patients treated with devices or techniques with rather poor antirestenotic efficacy[14]. However, below a certain threshold, this parameter may lose the ability to predict the occurrence of clinical events such as TLR. Other vascular factors such as completeness of the healing process, the occurrence of late acquired stent malapposition or inflammatory and hypersensitivity reactions[15] may be more relevant for a patient's long-term outcomes than the angiographic quantification of their lumen loss.

CLINICAL CORRELATES OF LATE LUMINAL LOSS

In data from a pooled analysis of trials using bare metal and first-generation DES, Pocock et al demonstrated an exponential relationship between LLL and TLR, suggesting that low values for LLL were not associated with an appreciably increased incidence of TLR at one year[16]. Recently, Asano et al investigated the relationship between LLL and clinical outcomes with newer-generation DES. In a patient-level meta-analysis of seven trials (2,426 patients) and study-level meta-analysis involving 40 trials (19,199 patients), the exponential relationship between in-stent LLL and the incidence of TLR was confirmed with an optimal cut-off value of LLL for a TLR event of 0.50 mm[17]. The authors suggested that this cut-off value could be used as the upper limit non-inferiority boundary of LLL when objective performance criteria are used for device efficacy assessment.

In terms of safety, a mild or moderately increased LLL might be favourable regarding completeness of stent coverage. Indeed, a very low LLL may reflect a delayed and incomplete healing process with uncovered and malapposed struts, only seen on optical coherence tomography[18].

Mean values of LLL evidenced in this trial for both arms were well below the 0.5 mm threshold but higher than other currently available DES that typically present values <0.20 mm. Variations in LLL values across trials can be related to variability of core lab analyses and different timing of the angiographic follow-up. Interestingly, a broad SD and non-normal distribution of LLL are typically seen with DES[8]. As such, comparison of medians rather than means could be more accurate. In this regard, both the BF-CoCr and BF-SS showed median values of LLL in the range of 0.16-0.17 mm **(Table 2)**.

CLINICAL RELEVANCE OF STRUT THICKNESS

The importance of the strut thickness was demonstrated in the bare metal stent era. Kastrati et al compared the angiographic performance of otherwise identical ultra-thin (50 µm) versus thick-strut (140 µm) bare metal stents manufactured by the same company. Rates of angiographic restenosis and LLL were significantly lower in the thin-strut device group (15% vs 25.6%; p=0.003, and 0.94±0.74 mm vs 1.17±0.78 mm, p=0.001; thin-strut vs thick-strut, respectively)[12]. However, in the DES era, the importance of strut thickness to prevent restenosis may be less relevant. As mentioned above, the antirestenotic efficacy of the first-generation sirolimus-eluting stent (CYPHER®; Cordis, Cardinal Health, Milpitas, CA, USA) with a 140 µm strut thickness was the highest (LLL nearly 0 mm) among other comparable first-generation DES – the paclitaxel-eluting DES TAXUS™ Liberté™ (Boston Scientific, Marlborough, MA, USA) with 96 µm and LLL around 0.40 mm;

the zotarolimus-eluting DES Endeavor® (Medtronic, Minneapolis, MN, USA) with 91 µm and LLL around 0.60 mm[19,20]. Thick rectangular struts may be associated with stent restenosis and thrombogenicity through creating areas of recirculation with low endothelial shear stress that increase local concentration of activated platelets, retard re-endothelialisation, and attenuate the production of natural anticoagulants[21]. Therefore, the development of new platform alloys for current-generation DES capable of reducing strut thickness may be more influential in the device's acute performance in complex anatomical scenarios than in their ability to reduce TLR *per se*[22]. The latter may probably be inherent to the biocompatibility of the device coating, type of antirestenotic drug and release kinetics. In addition, the clinical benefit of thin-strut devices may also derive from a long-term reduction of the rates of stent thrombosis and myocardial infarction[23].

Limitations

The major limitation of the study is the small sample size that does not provide sufficient power to confirm non-inferiority for the clinical endpoints. However, this is a typical feature of clinical studies powered for surrogate endpoints. Secondly, the study was not designed to use intracoronary imaging techniques to assess the healing process of both stent types. In addition, a non-inferiority margin of 0.20 mm represents 44% of the SD. This might represent a potential limitation of the trial. However, this margin has been chosen in similar head-to-head trials. Longer follow-up is needed to confirm the safety profile of this new platform after discontinuation of dual antiplatelet therapy. Finally, we cannot infer the safety of this new platform for patients receiving only a one-month dual antiplatelet regimen.

Conclusions

In summary, this study documents non-inferiority for the new BF-CoCr stent in comparison with its precursor, the BF-SS stent, for the primary angiographic endpoint of in-stent LLL. Larger studies powered for clinical endpoints are warranted to compare the efficacy of this new platform with currently available DES.

Impact on daily practice

The results of this first-in-human trial support the use of the new cobalt-chromium platform of the BioFreedom stent in patients with a wide spectrum of coronary artery disease. This new platform will improve the performance of the currently available stainless steel BioFreedom stent.

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Conflict of interest statement

M. Sabaté has received consultant fees from Abbott Vascular and iVascular outside the submitted work. A. Perez de Prado has received consultant fees from B. Braun, Boston Scientific and iVascular outside the submitted work. A. Cequier has received consultant fees from Abbott Vascular, Biotronik and Medtronic outside the submitted work. J. Flensted Lassen has received consultant fees from Abbott Vascular, Boston Scientific and Medtronic outside the submitted work. D. Schütte and H.-P. Stoll are employees of Biosensors. The other authors have no conflicts of interest to declare.

References

1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnàr F, Falotico R; RAVEL Study Group. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med.* 2002;346:1773-80.

2. Sabaté M, Brugaletta S, Cequier A, Iñiguez A, Serra A, Jiménez-Quevedo P, Mainar V, Campo G, Tespili M, den Heijer P, Bethencourt A, Vazquez N, van Es GA, Backx B, Valgimigli M, Serruys PW. Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. *Lancet.* 2016;387:357-66.

3. Smits PC, Hofma S, Togni M, Vázquez N, Valdés M, Voudris V, Slagboom T, Goy JJ, Vuillomenet A, Serra A, Nouche RT, den Heijer P, van der Ent M. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. *Lancet.* 2013;381:651-60.

4. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbaek H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med.* 2010;363:136-46.

5. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrié D, Naber C, Lipiecki J, Richardt G, Iñiguez A, Brunel P, Valdes-Chavarri M, Garot P, Talwar S, Berland J, Abdellaoui M, Eberli F, Oldroyd K, Zambahari R, Gregson J, Greene S, Stoll HP, Morice MC; LEADERS FREE Investigators. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. *N Engl J Med.* 2015;373:2038-47.

6. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.

7. Romaguera R, Gómez-Hospital JA, Gomez-Lara J, Brugaletta S, Pinar E, Jiménez-Quevedo P, Gracida M, Roura G, Ferreiro JL, Teruel L, Montanya E, Fernandez-Ortiz A, Alfonso F, Valgimigli M, Sabate M, Cequier A. A Randomized Comparison of Reservoir-Based Polymer-Free Amphilimus-Eluting Stents Versus Everolimus-Eluting Stents With Durable Polymer in Patients With Diabetes Mellitus: The RESERVOIR Clinical Trial. *JACC Cardiovasc Interv.* 2016;9:42-50.

8. Sabaté M, Jiménez-Quevedo P, Angiolillo DJ, Gómez-Hospital JA, Alfonso F, Hernández-Antolín R, Goicolea J, Bañuelos C, Escaned J, Moreno R, Fernández C, Fernández-Avilés F, Macaya C; DIABETES Investigators. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the diabetes and sirolimus-eluting stent (DIABETES) trial. *Circulation.* 2005;112:2175-83.

9. Stone GW, Midei M, Newman W, Sanz M, Hermiller JB, Williams J, Farhat N, Mahaffey KW, Cutlip DE, Fitzgerald PJ, Sood P, Su X, Lansky AJ; SPIRIT III Investigators. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. *JAMA.* 2008;299:1903-13.

10. Sabaté M, Pimentel G, Prieto C, Corral JM, Bañuelos C, Angiolillo DJ, Alfonso F, Hernández-Antolín R, Escaned J, Fantidis P, Fernández C, Fernández-Ortiz A, Moreno R, Macaya C. Intracoronary brachytherapy after stenting de novo lesions in diabetic patients: results of a randomized intravascular ultrasound study. *J Am Coll Cardiol.* 2004;44:520-7.

11. Sabaté M, Alfonso F, Cequier A, Romaní S, Bordes P, Serra A, Iñiguez A, Salinas P, García Del Blanco B, Goicolea J, Hernández-Antolín R, Cuesta J, Gómez-Hospital JA, Ortega-Paz L, Gomez-Lara J, Brugaletta S. Magnesium-Based Resorbable Scaffold Versus Permanent Metallic Sirolimus-Eluting Stent in Patients With ST-Segment

Elevation Myocardial Infarction: The MAGSTEMI Randomized Clinical Trial. *Circulation.* 2019;140:1904-16.

12. Kastrati A, Mehilli J, Dirschinger J, Dotzer F, Schühlen H, Neumann FJ, Fleckenstein M, Pfafferott C, Seyfarth M, Schömig A. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. *Circulation.* 2001;103:2816-21.

13. Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, Menichelli M, Sabaté M, Suttorp MJ, Baumgart D, Seyfarth M, Pfisterer ME, Schömig A. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med.* 2007;356:1030-9.

14. Moreno R, Fernandez C, Sanchez-Recalde A, Galeote G, Calvo L, Alfonso F, Hernandez R, Sánchez-Aquino R, Angiolillo DJ, Villarreal S, Macaya C, Lopez-Sendon JL. Clinical impact of in-stent late loss after drug-eluting coronary stent implantation. *Eur Heart J.* 2007;28:1583-91.

15. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol.* 2006;48:193-202.

16. Pocock SJ, Lansky AJ, Mehran R, Popma JJ, Fahy MP, Na Y, Dangas G, Moses JW, Pucelikova T, Kandzari DE, Ellis SG, Leon MB, Stone GW. Angiographic surrogate end points in drug-eluting stent trials: a systematic evaluation based on individual patient data from 11 randomized, controlled trials. *J Am Coll Cardiol.* 2008;51:23-32.

17. Asano T, Serruys PW, Collet C, Miyazaki Y, Takahashi K, Chichareon P, Katagiri Y, Modolo R, Tenekecioglu E, Morel MA, Garg S, Wykrzykowska J, Piek JJ, Sabate M, Morice MC, Chevalier B, Windecker S, Onuma Y. Angiographic late lumen loss revisited: impact on long-term target lesion revascularization. *Eur Heart J.* 2018;39:3381-9.

18. Matsumoto D, Shite J, Shinke T, Otake H, Tanino Y, Ogasawara D, Sawada T, Paredes OL, Hirata K, Yokoyama M. Neointimal coverage of sirolimus-eluting stents at 6-month follow-up: evaluated by optical coherence tomography. *Eur Heart J.* 2007;28:961-7.

19. Kandzari DE, Leon MB, Popma JJ, Fitzgerald PJ, O'Shaughnessy C, Ball MW, Turco M, Applegate RJ, Gurbel PA, Midei MG, Badre SS, Mauri L, Thompson KP, LeNarz LA, Kuntz RE; ENDEAVOR III Investigators. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. *J Am Coll Cardiol.* 2006;48:2440-7.

20. Mahmud E, Ormiston JA, Turco MA, Popma JJ, Weissman NJ, O'Shaughnessy CD, Mann T, Hall JJ, McGarry TF, Cannon LA, Webster MW, Mandinov L, Baim DS. TAXUS Liberté attenuates the risk of restenosis in patients with medically treated diabetes mellitus: results from the TAXUS ATLAS program. *JACC Cardiovasc Interv.* 2009;2:240-52.

21. Koskinas KC, Chatzizisis YS, Antoniadis AP, Giannoglou GD. Role of endothelial shear stress in stent restenosis and thrombosis: pathophysiologic mechanisms and implications for clinical translation. *J Am Coll Cardiol.* 2012;59:1337-49.

22. Foin N, Lee RD, Torii R, Guitierrez-Chico JL, Mattesini A, Nijjer S, Sen S, Petraco R, Davies JE, Di Mario C, Joner M, Virmani R, Wong P. Impact of stent strut design in metallic stents and biodegradable scaffolds. *Int J Cardiol.* 2014;177:800-8.

23. Iantorno M, Lipinski MJ, Garcia-Garcia HM, Forrestal BJ, Rogers T, Gajanana D, Buchanan KD, Torguson R, Weintraub WS, Waksman R. Meta-Analysis of the Impact of Strut Thickness on Outcomes in Patients With Drug-Eluting Stents in a Coronary Artery. *Am J Cardiol.* 2018;122:1652-60.

Supplementary data

Supplementary Appendix 1. Supplementary information including:
– Inclusion/exclusion criteria
– Endpoint definitions
– QCA analysis
– Statistical analysis
– Ethical considerations
– Study committees
– Institutions involved in the trial
– Description of device, lesion and procedural failures
– In-stent late loss according to relevant clinical variables
– Study protocol
– CONSORT 2010 checklist.

Supplementary Table 1. Clinical outcomes at 12 months.

Supplementary Table 2. Antithrombotic therapy up to 9 months.

Supplementary Table 3. Antithrombotic therapy according to clinical presentation.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-01162

Supplementary data

Supplementary Appendix 1. Supplementary information including:

1. INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria

1. Age ≥18 years;
2. Symptomatic coronary artery disease including patients with chronic stable angina, unstable angina, silent ischemia, and acute coronary syndromes including non-ST elevation myocardial infarction and ST-elevation myocardial infarction;
3. Presence of one or more coronary artery stenosis >50% in a native coronary artery or a saphenous bypass graft from 2.50 to 3.5 mm in diameter that can be covered with one or multiple stents (angiographic inclusion);
4. No limitation on the number of treated lesions, and vessels, and lesion length

Exclusion Criteria

1. Individual is pregnant, nursing or planning to be pregnant;
2. Known intolerance to aspirin, clopidogrel, heparin, stainless steel, cobalt chromium, Biolimus A9^{TM} or its analogues (e.g. sirolimus, everolimus, zotarolimus) or contrast material
3. Inability to provide informed consent;
4. Currently participating in another trial before reaching primary endpoint;
5. Planned surgery within 6 months of percutaneous coronary intervention (PCI)
6. Patient requires a stent <2.5mm (angiographic exclusion)
7. Patient requires a stent >3.5mm (angiographic exclusion)
8. Patient requires a non-study stent during the index or staged procedure
9. Use of a drug coated balloon planned at the index or staged procedure

2. ENDPOINTS DEFINITIONS

ABRUPT CLOSURE

Abrupt Closure. Defined as the occurrence of new (during the index procedure) severely reduced flow (TIMI grade 0-2) within the target vessel that persisted and required rescue by stenting or other treatment, or resulted in myocardial infarction or death. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus, or severe spasm. Abrupt closure does not connote "no reflow" (due to microvascular flow limitation), in which the epicardial artery is patent but had reduced flow. Abrupt closure also does not connote transient closure with reduced flow in which the index treatment application does reverse the closure.

Threatened Abrupt Closure. Defined as a grade B dissection and ≥ 50% diameter stenosis or any dissection of grade C or higher.

BINARY ANGIOGRAPHIC RESTENOSIS

Defined as >50% in-stent diameter stenosis at the follow-up angiogram. If an in-stent measurement is not available, the in-lesion diameter will be used.

BLEEDING COMPLICATIONS (AS PER BARC DEFINTIONS)

Bleeding Academic Research Consortium Definition for bleeding[25]

Type 0 no bleeding

Type 1 bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalisation, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2 any overt, actionable sign of hemorrhage (e.g. More bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4 or 5 but does meet at least one of the following criteria:

1) requiring nonsurgical, medical intervention by a healthcare professional,
2) leading to hospitalization or increased level of care, or
3) prompting evaluation.

Type 3a

- overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin a drop is related to bleed
- any transfusion with overt bleeding

Type 3b

- overt bleeding plus hemoglobin drop≥ 5 g/dl (provided hemoglobin drop is related to bleed)
- cardiac tamponade
- bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
- bleeding requiring intravenous vasoactive agents

Type 3c	• intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) • subcategories confirmed by autopsy or imaging or lumbar puncture • intraocular bleed compromising vision
Type 4 **CABG related**	• perioperative intracranial bleeding within 48 h • reoperation after closure of sternotomy for the purpose of controlling bleeding • transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period • chest tube output ≥2L within a 24-h period
Type 5	• fatal bleeding
Type 5a	• probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b	• definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood =1g/dL hemoglobin).

CLINICALLY DRIVEN
Stenosis >70% (by QCA), or stenosis >50% + ischemic symptoms, or stenosis >50% + positive Fractional Flow Reserve (FFR) measurement

DEATH
Death is divided into 2 categories:

- Cardiac death is defined as death due to any of the following:
- Acute myocardial infarction.
- Cardiac perforation/pericardial tamponade.
- Arrhythmia or conduction abnormality.
- Stroke within 30 days of the procedure or stroke suspected of being related to the procedure.
- Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery.
- Any death in which a cardiac cause cannot be excluded.

Non-cardiac death is defined as a death not due to cardiac causes (as defined above).

DEVICE SUCCESS

The attainment of < 20% residual stenosis by visual assessment AND either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, using the assigned device only.

DISSECTION, NHLBI (National Heart, Lung, and Blood Institute) CLASSIFICATION

Type A Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.

Type B Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles.

Type C Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material.

Type D Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow.

Type E Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen.

Type F Filling defect accompanied by total coronary occlusion.

DISTAL EMBOLIZATION

Defined as a new abrupt cut off of contrast column or filling defect distal to the treated lesion.

EMERGENT BYPASS SURGERY

Defined as coronary bypass surgery performed on an urgent or emergent basis for severe vessel **dissection or closure, or treatment failure resulting in new ischemia.**

LESION CLASS (AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION CLASS)

Type A Lesions: Minimally complex, discrete (length <10 mm), concentric, readily accessible, non-angulated segment (<45°), smooth contour, little or no calcification, less than totally occlusive, not ostial in location, no major side branch involvement, and an absence of thrombus.

Type B Lesions: Moderately complex, tubular (length 10 to 20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (>45°, <90°), irregular contour, moderate or heavy calcification, total occlusions <3 months old, ostial in location, bifurcation lesions requiring double guidewires, and some thrombus present.

Type B1: One adverse characteristic

Type B2: Two or more adverse characteristics

Type C Lesions: Severely complex, diffuse (length >2 cm), excessive tortuosity of proximal segment, extremely angulated segments >90°, total occlusions >3 months old and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions.

LESION SUCCESS

The attainment of < 20% residual stenosis by visual estimate AND either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, using any percutaneous method.

MYOCARDIAL INFARCTION

Criteria for acute myocardial infarction[26]

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
- Symptoms of ischaemia.
- New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
- Development of pathological Q waves in the ECG.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft

or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Table 5. Classification of myocardial infarction

Type 1: Spontaneous myocardial infarction
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.
Type 2: Secondary myocardial infarction
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.
Type 3: Myocardial infarction related to sudden cardiac death
Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)
Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (≤99thpercentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
Type 4b: Myocardial infarction related to stent thrombosis
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.
Type 4c: Myocardial infarction related to restenosis
Myocardial infarction associated with restenosis is arbitrarily defined as ≥50% stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of cTn values >99th percentile URL and no other significant obstructive CAD of

greater severity following: (i) initially successful stent deployment or (ii) dilatation of a coronary artery stenosis with balloon angioplasty (<50%).
Type 5: Myocardial infarction related to coronary artery bypass graft surgery (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a prior MI.

NO REFLOW
Defined as a sustained or transient reduction in antegrade flow that is not associated with an obstructive lesion at the treatment site.

PERCUTANEOUS CORONARY INTERVENTION (PCI) PROCEDURE
A PCI procedure will be considered to have commenced at the time the guidewire crosses the first lesion to be treated.

PERFORATION
Perforations will be classified as follows:

Angiographic perforation: perforation detected by the clinical site or the core laboratory at any point during the procedure.

Clinical perforation: perforation requiring additional treatment (including efforts to seal the perforation or pericardial drainage), or resulting in significant pericardial effusion, abrupt closure, myocardial infarction, or death.

Pericardial hemorrhage/tamponade: perforation resulting in cardiac tamponade.

PROCEDURE SUCCESS
The attainment of < 20% residual stenosis by visual estimate AND either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, using any percutaneous method without the occurrence of death, MI, or repeat revascularization of the target vessel during the hospital stay.

PROTOCOL DEVIATION

An incident where the investigator or site personnel did not conduct the study according to the investigational plan, protocol or the investigator agreement.

Major deviation:

Any deviation from patient inclusion and exclusion criteria or patient informed consent procedures.

- Failure to obtain informed consent prior to conducting study specific activities
- Inclusion/exclusion criteria not met
- Non-study stents are implanted at the index or staged procedure
- Study stent implanted not in accordance with the randomization procedure
- Incorrect version of the PIC used
- Adverse Events not reported by investigators in the required timeframe as specified in the protocol
- Source data permanently lost

Minor deviation:

Deviation from a protocol requirement such as incomplete/inadequate patient testing procedures, follow-ups performed outside specified time windows, etc.

REFERENCE VESSEL DIAMETER (RVD)
Defined as the average diameter of normal segments within 10 mm proximal and distal to the target lesion from 2 orthogonal views by visual estimate.

STENT THROMBOSIS (ARC definition)
Stent Thrombosis should be reported as a cumulative value over time and at the various individual time points as specified below. ***Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the Cath lab.***

Type	Timing
Acute stent thrombosis (*):	0 – 24 hours post stent implantation
Subacute stent thrombosis (*):	> 24 hours – 30 days post stent implantation
Late stent thrombosis (**):	> 30 days – 1 year post stent implantation
Very late stent thrombosis (**):	> 1 year post stent implantation

(*) Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 – 30 days) will be used in the remainder of this document.

(**) including ‘primary’ as well as ‘secondary’ late stent thrombosis; ‘secondary’ late stent thrombosis is a stent thrombosis after a target segment revascularization.

We recognize three categories of evidence in defining stent thrombosis.

Definite stent thrombosis:

Definite stent thrombosis is considered to have occurred by either

a. angiographic or
b. pathologic confirmation.

a. Angiographic confirmation of stent thrombosis:	Thrombolysis In Myocardial Infarction (TIMI) flow is: a) TIMI flow grade 0 with occlusion originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of a thrombus (*). b) TIMI flow grade 1, 2, or 3 with occlusion originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of a thrombus (*). **AND** at least one of the following criteria has been fulfilled within a 48-hours-time window: 1. New acute onset of ischemic symptoms at rest (typical chest pain with duration >20 minutes) 2. New ischemic ECG changes suggestive of acute ischemia 3. Typical rise and fall in cardiac biomarkers (refer to definition non-procedural related MI).

Comment: the incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

(*) Intracoronary thrombus[27-29]

Non-occlusive thrombus:

Intracoronary thrombus is defined as a (spheric, ovoid or irregular) non-calcified filling defect or lucency surrounded by contrast material (on three sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

Occlusive thrombus:

A TIMI 0 or TIMI 1 intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originating from the side branch).

b. Pathologic confirmation of stent thrombosis	Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable stent thrombosis:

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

Any unexplained death within the first 30 days.

Irrespective of the time after the index procedure any MI, which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.
Possible stent thrombosis:
Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow-up.

STROKE
Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.

TARGET SITE
Defined as the stented site plus 5mm on either side of the stent margins.

TARGET LESION (TL)
The target lesion is the treated lesion starting 5 mm proximal of the stented lesion and to end 5 mm distal of the stented lesion.

TARGET VESSEL (TV)
The TV is defined as the index coronary artery which was in physical contact with any component (guiding catheter, guide wire, balloon catheter, etc.) of the angioplasty hardware during the initial procedure.

TARGET LESION FAILURE (TLF)
Cardiac death, target-vessel myocardial infarction, or ischemia-driven target-lesion revascularization.

TARGET LESION REVASCULARIZATION (TLR)
Defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel.

Clinically-driven revascularizations are those in which the patient has a positive functional study, ischemic ECG changes at rest in a distribution consistent with the target vessel, or ischemic symptoms. Revascularization of a target lesion with an in-lesion diameter stenosis ≥70% (by QCA) in the absence of the above-mentioned ischemic signs or symptoms is also considered clinically-driven. In the absence of QCA data for relevant follow-up angiograms, the clinical need for revascularization is adjudicated using the presence or absence of ischemic signs and symptoms.

Non-clinically driven repeat target lesion revascularizations are those in which the patient undergoes a non-emergent revascularization for a diameter stenosis <50% (by QCA). Non-emergent repeat target lesion revascularization for a diameter stenosis <70% (by QCA) in patients without either a positive functional study or angina are also considered

non-clinically driven defined as any repeat revascularization of the target site whether by PCI or bypass surgery.

TARGET VESSEL REVASCULARIZATION (TVR)
Any target vessel revascularization, death, or MI attributed to the target vessel.

TIMI CLASSIFICATION

TIMI 0	No perfusion.
TIMI 1	Penetration with minimal perfusion. Contrast fails to opacify the entire bed distal to the stenosis for the duration of the cine run.
TIMI 2	Partial perfusion. Contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in the coronary bed distal to the obstruction than in comparable areas not perfused by the dilated vessel.
TIMI 3	Complete perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds.

URGENT TARGET LESION REVASCULARIZATION (UTLR)
Defined as any target lesion revascularization (PCI or CABG) done within 48 hours after hospital admission for symptomatic in-stent restenosis or stent thrombosis associated with new resting ECG changes and/or a rise of biomarkers (CK-MB or troponin) [cutoff according to the Third universal definition[1]]. The event is measured in time relation to the time of hospitalization, not the time post-index procedure.

3.QCA Analysis

QCA analysis was performed at HCor Sao Paolo; Brazil. Instructions for image acquisition were as follows. Selective angiographies of the target vessel/lesion were performed in the two orthogonal projections that best showed the artery of interest, without overlapping of side branches and with less foreshortening. Images were acquired before wiring and after percutaneous intervention, and, at 9-month angiographic follow-up in the same projections as at the index procedure. Analysis of angiographic parameters was performed after an intracoronary bolus injection of nitroglycerine (200 μg) administered through the guiding catheter. Minimal luminal diameter was averaged for two projections. Late luminal loss was calculated from the minimal luminal diameter post procedure and that at follow-up angiography. This parameter was determined in-stent (inside the boundaries of the stent) and in-segment (including 5 mm proximal and 5 mm distal from the stent boundaries). Besides, other angiographic parameters to assess the restenotic process were also analyzed in the angiograms obtained after nitroglycerin infusion. These included acute gain (minimal luminal diameter post-procedure minus that of pre-procedure), reference diameter, percentage diameter stenosis, and its corresponding derivate binary restenosis.

4. Statistical analysis

Categorical summaries included the frequency and percentage of patients who are in each category. Continuous variables were reported as number of values, mean, SD or median and interquartile ranges. For the comparison of baseline categorical variables, statistical differences were by a chi-square test or a Fisher's exact test as appropriate. For continuous baseline variables comparison, the Student t-test was used where appropriate. For non-normal distributed data, non-parametric tests were used (such as Mann-Whitney). Time-to-event variables were investigated using the Cox proportional hazards model. Hazard ratios comparing BF-CoCr and BF-SS stents, associated 95% CIs, and log-rank p-values were obtained from the Cox model. Percentages for each stent group were estimated through the Kaplan-Meier method. In the case clinical outcomes had zero events in any group, rate ratios and 95% CIs were approximated from 2 x 2 contingency tables by adding 0.5 to all cells. Confidence intervals for Kaplan-Meier estimates were based on the log-log transformation. For lesion-based comparison we used generalized linear mixed models to account for multiple lesions per patient. The primary endpoint was tested using the two-sided 95% confidence interval of the difference in LLL between the two arms (BF-CoCr vs. BF-SS) based on the t distribution. If the upper bound of this confidence interval was less than 0.20 mm (the delta for non-inferiority), then we would reject the null hypothesis and declare that the BF-CoCr stent was non-inferior to the BF-SS stent with respect to the primary endpoint. The non-inferiority p-value was computed for the associated t-test.

The statistical hypothesis related to the t-test is defined as:

$$H_0: \mu_{Cocr} - \mu_{ss} \geq 0.20$$

$$H_1: \mu_{Cocr} - \mu_{ss} < 0.20$$

where 0.2 is the non-inferiority margin, μ_{Cocr} is the observed mean late loss in the CoCr group and μ_{SS} is the observed mean late loss in the SS group. The non-inferiority p-value is then computed for the associated t-test corresponding to the hypothesis above. The formula to compute the *T* statistics is given by

$$T = \frac{\mu_{Cocr} - \mu_{ss} - 0.2}{\sqrt{s_p^2\left(\frac{1}{n_{Cocr}} + \frac{1}{n_{SS}}\right)}}$$

where s_p^2 in the denominator is the pooled estimate of the common standard deviations across the two groups. Non-inferiority is claimed if T is smaller than the *T*-critical value from the corresponding t-distribution with $(n_{Cocr} + n_{SS}) - 2$ degrees of freedom.

For the analyses three data sets were defined. Intention To Treat (ITT) set (n=200) was defined as all patients who signed an informed consent and were randomized whether or not they received a study stent. Modified ITT set (n=195) was defined as all patients who received at least one stent and were analysed based on the group they were randomized to, irrespective of whether the patients received the allocated type of study stent. Compared to the ITT population, the modified ITT population does not include patients with zero lesions treated (e.g. randomized into the study in error). The modified ITT analysis set was the main analysis set. Per Protocol set (n=179), was defined as all patients who adhere to the major criteria in the protocol and who did not substantially deviate from the protocol.

5. Ethical considerations

The protocol was prepared in accordance with ISO 14155. In addition, the study is conducted according to the principles of the Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, October 2013. The study was carried out in keeping with applicable local law and regulation. Both the sponsor and the clinical investigator conducted this clinical investigation with strict adherence to the above-mentioned guidelines. The trial was sponsored by Biosensors, which participated in the design of the protocol and in site selection and management but was not involved in data management or analysis. The study was approved by the investigational review board or ethics committee at each participating center, and all patients signed informed consent. The principal investigators had unrestricted data access, prepared the manuscript and vouch for the integrity of the trial, as well as for the fidelity of this report to the trial protocol. The sponsor had a right to a non-binding review of the manuscript but was not otherwise involved in its preparation. The clinical investigation plan is available below.

6. Study Committees

Sponsor:	Biosensors Europe S.A., Rue du Lausanne 29 1110 Morges, Switzerland
Steering Committee	**Manel Sabate**, Hospital Clinic de Barcelona, Barcelona, Spain **Jens Flensted Lassen**, Odense University Hospital, Odense, Denmark **Hans-Peter Stoll,** Biosensors Europe S.A., Rue du Lausanne 29 1110 Morges, Switzerland **Samuel Copt,** Biosensors Europe S.A., Rue du Lausanne 29 1110 Morges, Switzerland **Diana Schuette,** Biosensors Europe S.A., Rue du Lausanne 29 1110 Morges, Switzerland
Contract Research Organization:	**KCRI,** Miechowska 5B/3, 30-055 Kraków, Poland Phone: +48 12 623 19 30 e-mail: mailto:beata.checinska@kcri.org
Corelab	**HCor**, Associaçao Beneficente Siria, R. Desembargador Eliseu Guilherme, 123, Paraíso, 04004-030, Sao Paulo, SP, Brazil
Statistics	**Samuel Copt,** Biosensors Europe S.A., Rue du Lausanne 29 1110 Morges, Switzerland
Clinical Events Committee	**Kristian Thygesen,** Risskov, Denmark **Alaide Chieffo**, Milan, Italy
Data Safety Monitoring Board	**Prof. Michael Haude,** Ratingen, Germany **Prof. Franz Weidinger,** Vienna, Austria **Dr Timothy Kinnaird,** Penarth, United Kingdom **David W. Warne, BSc, MSc, PhD, Cstat,** Swiss Labour Contractors Sarl ('SLC')
Electronic CRF including eCEC system:	**Merge eClinical Inc**

	4205 South Miami Blvd., Bldg. 502, Durham, NC 27703-9141

7. Institutions involved in the trial

Country	Site name	Statistics	Total (N=195)
Spain			
	Dr. Garcia - Hospital Universitario Vall d'Hebron	N (%)	20 (10.3%)
	Dr. Macaya - Hospital Clinico San Carlos	N (%)	15 (7.7%)
	Dr. Moreno - Hospital Universitario La Paz	N (%)	24 (12.3%)
	Dr. Sabaté - Hospital Clínic de Barcelona	N (%)	34 (17.4%)
	Prof. de Prado - Hospital Universitario de León	N (%)	13 (6.7%)
	Prof.Cequier - Hospital Universitario de Bellvitge	N (%)	10 (5.1%)
Denmark			
	Dr. Tilsted - Rigshospitalet. Copenhagen	N (%)	35 (17.9%)
	Prof. Okkels-Jensen - Odense University Hospital	N (%)	44 (22.6%)

8. Description of device, lesion and procedure failures

Device failure

Definition

The attainment of < 20% residual stenosis by visual assessment AND either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, using the assigned device only.

- BF-CoCr:
    - Subject 1 - Lesion 2: Index procedure, 20mm lesion, RVD 2.5mm, de novo, LCX, 1 study stent implanted 2.5mm x 29mm, no CTO, no bifurcation, %stenosis pre-procedure 95%, %stenosis post-procedure 95%
- BF-SS:
    - Subject 3 - Lesion 1: Index procedure, 8mm lesion, RVD 3mm, de novo, LAD, 1 study stent implanted 3mm x 14mm, no CTO, no bifurcation, %stenosis pre-procedure 20%, %stenosis post-procedure 20%

Lesion failure

Definition

The attainment of < 20% residual stenosis by visual estimate AND either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, using any percutaneous method.

- BF-CoCr:
    - Subject 1 - Lesion 2: Index procedure, 20mm lesion, RVD 2.5mm, de novo, LCX, 1 study stent implanted 2.5mm x 29mm, no CTO, no bifurcation, %stenosis pre-procedure 95%, %stenosis post-procedure 95%
    - Subject 1 - Lesion 2: Staged procedure, same subject, same lesion as lesion 1 above. This time no study stent could be implanted, same lesion characteristics as above
    - Subject 2 - Lesion 1: Index procedure, 12mm lesion, RVD 2.5mm, de novo, LAD, no study stent implanted, no CTO, bifurcation, %stenosis pre-procedure 50%, %stenosis post-procedure 50%
- BF-SS:
    - Subject 1 - Lesion 1: Index procedure, 20mm lesion, RVD 2.5mm, de novo, LCX, no study stent implanted 2, CTO, no bifurcation, %stenosis pre-procedure 100%, %stenosis post-procedure 100%
    - Subject 2 - Lesion 1: Index procedure, 10mm lesion, RVD 2mm, de novo, LCX, no study stent implanted, no CTO, no bifurcation, %stenosis pre-procedure 80%, %stenosis post-procedure 20%
    - Subject 3 - Lesion 1: Index procedure, 8mm lesion, RVD 3mm, de novo, LAD, 1 study stent implanted 3mm x 14mm, no CTO, no bifurcation, %stenosis pre-procedure 20%, %stenosis post-procedure 20%

Procedure failure

Definition

The attainment of < 20% residual stenosis by visual estimate AND either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, using any percutaneous method without the occurrence of death, MI, or repeat revascularization of the target vessel during the hospital stay.

- BF-CoCr:
    - The 3 procedure failures are the same as the lesion failures, subject 1 who failed index and staged procedures and subject 2 who failed the index procedure. The reason for failure was always a stenosis post >= 20%.
- BF-SS:
    - 3 procedure failures are the same as the lesion failures. The reason for failure was always a stenosis post >= 20%.
    - One patient stayed ~3 weeks at hospital between index procedure and discharge and experienced a cTVR at day 3)
    - two patients had a MI one day after index procedure while still at hospital

9. In-stent late lumen loss according to relevant clinical variables

We used a mixed linear model to evaluate the impact of adjusting the in-stent LLL analysis for clinically relevant variables. The variables used in the model were diabetes status, lesion length, reference vessel diameter and lesion class (ACC/AHA).

The outcome of the unadjusted analysis is reported in Table 1 below:

Unadjusted analysis - estimates from a mixed linear model with stent group as covariate

	Means	SD	95% CI lower bound	95% CI upper bound	P-value
CoCr	0.3514	0.04778			
SS	0.2891	0.04756			
Diff (CoCr-SS)	0.06230	0.06741	-0.07083	0.1954	0.3568

Adjusted analysis - estimates from a mixed linear model with stent group, diabetes status, lesion length, RVD and lesion class as covariates

	Means	SD	95% CI lower bound	95% CI upper bound	P-value
CoCr	0.3724	0.05426			
SS	0.3106	0.05319			
Diff (CoCr-SS)	0.06187	0.06724	-0.07092	0.1947	0.3589

Adjusting for these variables has little impact on the LLL.

10. Supplementary Table 1. Clinical outcomes up to 12 months

Type	BF- CoCr (N=97)	BF- SS (N=98)	Hazard ratio	P-value
All death	2 (2.1)	1 (1.0)	2.02 (0.18:22.28)	0.558
Cardiac death	1 (1.0)	1 (1.0)	1.02 (0.06:16.24)	0.991
Non-cardiac death	1 (1.0)	0 (0)	N/A	.
Myocardial infarction	4 (4.2)	6 (6.3)	0.66 (0.19:2.35)	0.523
TV-MI	3 (3.2)	3 (3.1)	1.00 (0.20:4.96)	0.998
Clinically driven TLR	6 (6.3)	6 (6.2)	1.00 (0.32:3.11)	0.998
Clinically driven TVR	6 (6.2)	7 (7.3)	0.85 (0.28:2.52)	0.765
Definite stent thrombosis	2 (2.1)	0 (0)	N/A	.
Probable stent thrombosis	0 (0)	0 (0)	N/A	.
Possible stent thrombosis	0 (0)	0 (0)	N/A	.
Composite of cardiac death or MI or clinically driven TVR	7 (7.3)	12 (12.5)	0.56 (0.22:1.44)	0.224
Composite of death or MI or any revascularization	11 (11.3%)	14 (14.6)	0.76 (0.35:1.69)	0.506
Target lesion failure (TLF)	7 (7.3)	9 (9.3)	0.77 (0.29:2.06)	0.596

All values expressed as n (%). BF-CoCR: BioFreedom™ cobalt-chromium; BF-SS: BioFreedom™ stainless steel; TV-MI: target vessel myocardial infarction; TLR: target lesion revascularization;: TVR: target vessel revascularization; Target lesion failure is defined as the composite of cardiac death or TV-MI or clinically-driven TLR.

11. Supplementary Table 2. Antithrombotic therapy

Timepoint	Type	BF-CoCr (N=97)	BF-SS (N=98)	Total (N=195)
Discharge	Aspirin	92 (94.8%)	96 (98%)	188 (96.4%)
	Clopidogrel	57 (58.8%)	60 (61.2%)	117 (60%)
	Prasugrel	2 (2.1%)	3 (3.1%)	5 (2.6%)
	Ticlopidine	0 (0%)	0 (0%)	0 (0%)
	Ticagrelor	38 (39.2%)	37 (37.8%)	75 (38.5%)
	Oral anticoagulation	16 (16.5%)	16 (16.3%)	32 (16.4%)
	Dual Anti-Platelet Therapy	92 (94.8%)	93 (94.9%)	185 (94.9%)
1 month	Aspirin	90 (92.8%)	94 (96.9%)	184 (94.8%)
	Clopidogrel	57 (58.8%)	61 (62.9%)	118 (60.8%)
	Prasugrel	2 (2.1%)	3 (3.1%)	5 (2.6%)
	Ticlopidine	0 (0%)	0 (0%)	0 (0%)
	Ticagrelor	37 (38.1%)	35 (36.1%)	72 (37.1%)
	Oral anticoagulation	16 (16.5%)	15 (15.5%)	31 (16%)
	Dual Anti-Platelet Therapy	89 (91.8%)	92 (94.8%)	181 (93.3%)
9 months	Aspirin	82 (86.3%)	91 (94.8%)	173 (90.6%)
	Clopidogrel	38 (40%)	46 (47.9%)	84 (44%)
	Prasugrel	2 (2.1%)	4 (4.2%)	6 (3.1%)
	Ticlopidine	0 (0%)	0 (0%)	0 (0%)
	Ticagrelor	36 (37.9%)	33 (34.4%)	69 (36.1%)
	Oral anticoagulation	17 (17.9%)	16 (16.7%)	33 (17.3%)
	Dual Anti-Platelet Therapy	66 (69.5%)	75 (78.1%)	141 (73.8%)
12 months	Aspirin	81 (85.3%)	89 (92.7%)	170 (89%)
	Clopidogrel	32 (33.7%)	37 (38.5%)	69 (36.1%)
	Prasugrel	2 (2.1%)	4 (4.2%)	6 (3.1%)
	Ticlopidine	0 (0%)	0 (0%)	0 (0%)
	Ticagrelor	27 (28.4%)	27 (28.1%)	54 (28.3%)
	Oral anticoagulation	17 (17.9%)	16 (16.7%)	33 (17.3%)

Timepoint	Type	BF-CoCr (N=97)	BF-SS (N=98)	Total (N=195)
	Dual Anti-Platelet Therapy	51 (53.7%)	62 (64.6%)	113 (59.2%)

12. Supplementary table 3. Antithrombotic regimen according to clinical presentation

		Acute Coronary Syndrome N=80		Chronic Coronary Syndrome N=115	
Timepoint	Type	BioFreedom CoCr	BioFreedom SS	BioFreedom CoCr	BioFreedom SS
Discharge	Aspirin	36 (92.3%)	41 (100%)	56 (96.6%)	55 (96.5%)
	Clopidogrel	11 (28.2%)	13 (31.7%)	46 (79.3%)	47 (82.5%)
	Prasugrel	2 (5.1%)	3 (7.3%)	0 (0%)	0 (0%)
	Ticagrelor	26 (66.7%)	27 (65.9%)	12 (20.7%)	10 (17.5%)
	Oral anticoagulation	6 (15.4%)	5 (12.2%)	10 (17.2%)	11 (19.3%)
	Dual Anti-Platelet Therapy	36 (92.3%)	39 (95.1%)	56 (96.6%)	54 (94.7%)
FU 12 months	Aspirin	33 (86.8%)	39 (95.1%)	48 (84.2%)	50 (90.9%)
	Clopidogrel	9 (23.7%)	10 (24.4%)	23 (40.4%)	27 (49.1%)
	Prasugrel	2 (5.3%)	4 (9.8%)	0 (0%)	0 (0%)
	Ticagrelor	17 (44.7%)	18 (43.9%)	10 (17.5%)	9 (16.4%)
	Oral anticoagulation	6 (15.8%)	5 (12.2%)	11 (19.3%)	11 (20%)
	Dual Anti-Platelet Therapy	23 (60.5%)	30 (73.2%)	28 (49.1%)	32 (58.2%)

13. STUDY PROTOCOL

Evaluation of the efficacy (QCA) and safety of the BioFreedom™ Biolimus A9™ CoCr stent in a randomised trial in patients with CAD

BIOFREEDOM QCA

Clinical Investigation Plan

Protocol number: 17-EU-02

FINAL Version 3.0

Date: 17 May 2018

Biosensors Europe S.A.

Rue du Lausanne 29 - CH-1110 Morges – Switzerland

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Protocol Version	Rev. Date	Classification	Page
Final 3.0	17 May 2018	Confidential	1/2

Protocol number: 17-EU-02

Biosensors Signature Page

SPONSOR - BIOSENSORS Europe S.A.

Name: Dr. Hans Peter-Stoll

_____ _____

Title: Chief Medical Officer Date dd/mmm/yyyy

Name: Samuel Copt

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Title: Associate Director, Biostatistician Date dd/mmm/yyyy

Name: Dervilla Bermingham

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Title: Director, Clinical Research EMEA Date dd/mmm/yyyy

Name: Diana Schuette

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Title: Author and Project Manager, Clinical Research EMEA Date dd/mmm/yyyy

Name: Guylaine Dudley-Casses

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Title: Director, Regulatory Affairs EMEA & LATAM Date
dd/mmm/yyyy

Evaluation of the efficacy (QCA) and safety of the BioFreedom™ Biolimus A9™ CoCr stent in a randomised trial in patients with CAD BIOFREEDOM QCA **Protocol Signature Page**			
Protocol Version	Rev. Date	Classification	Page
3.0	17 May 2018	Confidential	1/1

Protocol number: 17-EU-02

I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and set forth in my agreement with the Sponsor or Sponsor's authorised representative.

Name: Dr Manel Sabate

_____ _____

Signature of Coordinating Investigator Date

Name:

_____ _____

Signature of Principal Investigator Date

REVISION HISTORY

Version	Date	Reason for Change
1.0	06 October 2017	First Version
2.0	31 October 2017	PK sub-study removed Protocol deviations in the definition section corrected

		Section 2 HBR patient exclusion wording removed Section 8.7 reference to single-antiplatelet duration removed
3.0	17 May 2018	Exclusion criteria 2 amended to include intolerance to BA9 analogues Table 1 footnote 4 added Section 8.3 definition of childbearing potential added

PROTOCOL SUMMARY

Title:	Evaluation of the efficacy (QCA) and safety of the BioFreedom™ Biolimus A9™ CoCr stent in a randomised trial in patients with CAD (BioFreedom QCA)
Sponsor:	Biosensors Europe S.A., Morges, Switzerland
Clinicaltrials.gov	NCT03307213
Devices Used:	Study device BioFreedom™ (Cobalt Chromium BA9™ drug-eluting stent; BFCoCr) Control device BioFreedom™ (stainless steel BA9™ drug-eluting stent; BFSS)
Study Population:	"All comer" patients with symptomatic coronary artery disease including chronic stable angina, unstable angina, or silent ischemia, and acute coronary syndromes (STEMI and non-STEMI), who have an indication for percutaneous coronary interventions. Unlike previous studies conducted with the BioFreedom stent, this protocol does not target patients at high bleeding risk.
Enrolment:	200 all-comer patients in approximately 10 sites in up to 2 European countries will be randomized to receive either the BioFreedom™ CoCr stent or the BioFreedom™ SS stent.
Objectives:	The objective of this study is to demonstrate that the BioFreedom™ CoCr Drug Coated Stent (DCS) is non-inferior to the market authorized predicate stent BioFreedom™ SS DCS, with respect to in-stent late lumen loss, and that it has clinical safety characteristics similar to the BioFreedom™ SS DCS. This study will serve as a First-in-human experience for the BioFreedom™ CoCr stent in a population of all-comer patients, who are not at high bleeding risk and can be treated with dual anti-platelet therapy according to current AHA/ACC/ESC/SCAI practice guidelines.
Design:	Prospective, multi-center, single blind (to patient), randomised, comparator trial, designed to randomize 200 all-comer patients at approximately 10 centers in up to 2 European countries. Patients will be randomized 1:1 to receive either a BioFreedom™ CoCr (arm 1) or BioFreedom™ SS stent (arm 2). In-stent late lumen loss (LLL) will be assessed by angiography at 9 months (QCA) and serve as the primary endpoint. All patients will be followed up for 2 years.
Primary Endpoints:	In-stent late lumen loss (LLL) assessed by quantitative coronary angiography (QCA) at 9 months
Secondary Endpoints	At all protocol defined follow-up time points (1, 9, 12 and 24 months) unless otherwise indicated • Cardiac Death

	• Myocardial infarction (according to the Third Universal Definition) • MACE (defined as cardiac death, MI and clinically indicated (ci) target lesion revascularization (TLR)) • All-cause mortality • Clinically driven TLR • Target lesion failure (TLF) (cardiac death, target vessel related MI, ci TLR) • Clinically driven target vessel revascularization (TVR) • Stent Thrombosis per ARC definition • Device success • Procedure success • Lesion success
Inclusion Criteria:	"Real world, all comer" patients 1. Age ≥18 years; 2. Symptomatic coronary artery disease including patients with chronic stable angina, unstable angina, silent ischemia, and acute coronary syndromes including non-ST elevation myocardial infarction and ST-elevation myocardial infarction; 3. Presence of one or more coronary artery stenosis >50% in a native coronary artery or a saphenous bypass graft from 2.50 to 3.5 mm in diameter that can be covered with one or multiple stents (angiographic inclusion); 4. No limitation on the number of treated lesions, and vessels, and lesion length
Exclusion Criteria	1. Individual is pregnant, nursing or planning to be pregnant; 2. Known intolerance to aspirin, clopidogrel, heparin, stainless steel, cobalt chromium, Biolimus A9 ™ or its analogues (e.g. sirolimus, everolimus, zotarolimus) or contrast material 3. Inability to provide informed consent; 4. Currently participating in another trial before reaching primary endpoint; 5. Planned surgery within 6 months of percutaneous coronary intervention (PCI) 6. Patient requires a stent <2.5mm (angiographic exclusion) 7. Patient requires a stent >3.5mm (angiographic exclusion)

	8. Patient requires a non-study stent during the index or staged procedure 9. Use of a drug coated balloon planned at the index or staged procedure	
Sample size considerations:	This study will randomize 200 patients into two arms. Assuming true equivalence of the means between the CoCr and SS Biofreedom™ stents, with a common standard deviation of 0.45 mm and a non-inferiority margin of 0.20 mm, 160 evaluable patients will be needed in order to yield 80% power for non-inferiority using a 1-sided, 2-sample t-test with an alpha of 0.025. Assuming a drop-out rate of 20%, 200 patients will be randomized.	
Antiplatelet Therapy:	DAPT (P2Y12 inhibitor plus aspirin) as recommended by current practice guidelines	
Follow-up:	Clinical follow up: • 9 months (follow-up angiogram) Telephone follow-up: • 1 month (telephone) • 12 months (telephone) • 24 months (telephone)	
Time Course:	Initial Enrolment:	May 2018
	Last patient enrolled:	October 2018
	Last patient 9 month angio:	August 2019
	Final 2-year Follow-up	December 2020
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ICH-GCP or ISO EN 14155 2011 as well as all national legal and regulatory requirements.	

Table 1. TIME SCHEDULE/DATA COLLECTION

Event	**Screen**	**Index Procedure/ Enrolment (Day 0)**	**If staged[1] Within 6 weeks**	**Post procedure/ discharge[2]**	**1 month (+/-7 days)**	**9 months (+/-7 days)**	**12 months (+/-4 wks)**	**24 months (+/-8 wks)**
Assessment Type	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Phone**	**Clinic**	**Phone**	**Phone**
Consent	X[3]			X[3]				
Inclusion/Exclusion check	X							
Angiographic inclusion/exclusion		X						
Medical History/physical examination	X		(X)			X		
Medication review	X	X	(X)	X	X	X	X	X
Pregnancy status enquiry (if applicable)[4]	X		(X)			X		
12- lead ECG		X	(X)	X		X		
Routine Laboratory Tests incl. CK and/or CK-MB or troponin at time points specified and **in case of a clinical event**	X		(X)	X		X		
Angiography		X	(X)			X		
Stent implantation		X	(X)					
AE/SAE/Device Deficiencies collection	X	X	(X)	X	X	X	X	X
Endpoint collection		X	(X)	X	X	X	X	X

[1]All assessments marked in brackets will only occur for a staged procedure. Blood sampling will be done as per clinical practice

[2]See section 8.7 for more details of post-procedure assessments

[3]STEMI patients will sign a short version of the patient informed consent (PIC) and will then be asked to sign the normal version post-procedure

[4]Women of childbearing potential (defined as 55 years of age or under) will undergo a pregnancy test

Unscheduled visits may also be entered into the eCRF

PRINCIPAL CONTACTS

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1. Background

1.1 Introduction

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality in the Western World, accounting for 1 in every 4 deaths[1] . Since the early days of catheter balloon angioplasty, the field of interventional cardiology has witnessed vast improvement in techniques and an increase in research designed to eliminate some of the limitations associated with coronary angioplasty. Restenosis caused by neointimal hyperplasia is the major limitation after percutaneous coronary intervention (PCI) even with bare metal stent scaffolding. This was addressed by use of drug-eluting stents (DES) that target the central phenomenon of cellular proliferation that causes restenosis. First-generation DES with controlled release of sirolimus or paclitaxel from durable polymers have reduced angiographic and clinical measures of restenosis compared with bare-metal stents.[2-4]

The early enthusiasm for DES was dampened by the alarming reports on potential increases in early and late stent thrombosis, which mandated prolonged dual antiplatelet therapy, leading to a decrease in use, yet stimulated the development of safer and more effective second-generation DES.[6-8] The working hypothesis was that most of the complications with first-generation DES could be attributed to the polymer. Second generation biodegradable polymer drug-eluting stents were subsequently designed to diminish long-term adverse events related to the persistence of durable polymers after completion of drug-release.

Since then we have seen a proliferation of second-generation stents that focus mainly on alloy change, iteration in the stent design (including reductions in strut and polymer thickness), in addition to changes in the durable polymer material, introduction of biodegradable polymers and use of non-polymeric approaches.[9,10, 14]

Limus analogues are more effective than paclitaxel in DES as site-specific agents to reduce neointimal growth and repeat revascularization procedures.[5,11]. These drugs are lipophilic and show uptake in arterial wall tissue. Multiple drug eluting stent trials of first and second generation stents, utilizing sirolimus/limus analogs have demonstrated equivalent safety as measured by rates of death or myocardial infarction and improved efficacy as measured by reduced restenosis and the need for repeat revascularization versus bare metal stents.[15,16] In addition, recent data on second generation DES obtained from both trials and meta-analyses indicate improved safety in second generation vs. first generation DES.[19,20]

In further developing the next generation of stents to address late events, Biosensors hypothesized that polymer-free drug release may reduce late events and developed a newly designed polymer-free Biolimus A9 ™ –coated stent with a stainless steel platform, the BioFreedom™ Drug coated stent (DCS) Coronary Stent System, which received CE-mark in 2013. The BioFreedom™ stent uses the same BA9™ therapeutic agent and dose as the BioMatrix family of stents. In BioFreeedom™, BA9™ is incorporated onto the platform using a novel surface modification of the bare-metal stent without a polymer matrix to house the drug. This enables drug-to-vessel wall tissue transfer from a BioFreedom™ stent to be complete within 28 days of treatment leaving the implant behind as a bare-metal stent. The rapid drug transfer to the vessel wall provides a rationale for an abbreviated dual antiplatelet therapy, which provides an attractive treatment option for patients at high bleeding risk and thus cannot tolerate prolonged DAPT. The LEADERS FREE trial evaluated in patients at high bleeding risk and receiving 1 month DAPT post treatment.[12,13] Therefore, the polymer-free BA9™ coated stent constitutes an ideal next-generation stent that provides the safety profile of a BMS and the anti-restenotic effectiveness of current DES with polymers without their potential risks.

1.2 Study Stent

This study is conducted to investigate the new BioFreedom™ CoCr stent, which is the result of a design iteration of the previous BioFreedom™ SS stent allowing to reduce the strut thickness, which makes the stent more flexible and deliverable.

The investigational device, BioFreedom™ Cobalt-Chromium consists of 1) a cobalt chromium bare metal stent platform which has been modified with a proprietary surface treatment resulting in a selectively micro structured abluminal surface. 2) BA9™ (drug) adhesion to the abluminal surface without the use of a polymer or carrier and 3) a percutaneous transluminal coronary angioplasty catheter (PTCA) called internally as NDS6.

BioFreedom™ Cobalt-Chromium is an iteration of the predicate BioFreedom™ Drug Coated Coronary Stent System ("BioFreedom™"), which is a Stainless Steel Drug Coated Stent with CE-marking and shown to be clinically safe and efficacious, and is the comparator in this trial. The cobalt-chromium (CoCr) stent platform allows an effective reduction of the stent strut thickness while maintaining the radial strength of the stent as the CoCr alloy is stronger and denser than 316L stainless steel. As a result of the thinner CoCr struts, BioFreedom™ CoCr has a smaller crossing profile and should have advantages over the previous BioFreedom™ stainless steel versions in terms of deliverability.

The Cobalt Chromium stent platform alloy is the same as in the CE marked Chroma™ bare metal stent, and in many other commercially available stents used in clinical routine today. The other design elements, which are key to the efficacy and safety of a DES including the BA9™ drug, the drug dose and composition, the absence of polymer and carrier and the release kinetics of the drug were kept identical to those of the previous BioFreedom™ stainless steel stent.

For this study, the BioFreedom™ CoCr stent is available in three stent diameters and six lengths as highlighted in Table 2 below.

Table 2. BioFreedom™ CoCr Specifications

Nominal Expanded Inner Diameter (mm)	Nominal Unexpanded Stent Length (mm)
2.50	9
2.50	14
2.50	19
2.50	24
2.50	29
3.00	9
3.00	14
3.00	19
3.00	24
3.00	36
3.50	9
3.50	14
3.50	19
3.50	24

Nominal Expanded Inner Diameter (mm)	Nominal Unexpanded Stent Length (mm)
3.50	36

Table 3. BioFreedom™ SS Specifications

Nominal Expanded Inner Diameter (mm)	Nominal Unexpanded Stent Length (mm)
2.50	11
2.50	14
2.50	18
2.50	24
2.50	28
3.00	11
3.00	14
3.00	18
3.00	24
3.00	36
3.50	11
3.50	14
3.50	18
3.50	24
3.50	36

1.3 Comparator stent

The BioFreedom ™ DCS Coronary Stent System is the predicate of the study stent. The main difference is that it comprises a 316 L stainless steel bare metal stent platform, and has a different delivery system. The selectively micro-structured surface modification, the Biolimus A9™ (drug) adhesion to the abluminal surface of the stent without the use of a polymer or carrier, and all other components are the same as the study stent.

The BioFreedom™ DCS specifications are found in the IFU.

1.4 Biolimus A9™ (BA9™)

Biolimus A9™ (BA9 ™) is a Biosensors proprietary semi-synthetic sirolimus analog. It is highly lipophilic – about ten times as lipophilic as sirolimus, rapidly absorbed in tissues, and able to reversibly inhibit growth factor-stimulated cell proliferation. Current data suggest that BA9™, on a molecular level, forms a complex with the cytoplasmic proteins that inhibit the cell-cycle between the G0 and G1 phase. The result is an interruption of the cascade governing cell metabolism, growth, and proliferation. Sirolimus is a well-tolerated immunosuppressive agent, with a known and predictable adverse event profile. The adverse event profile of Biolimus A9™ - when released from a coronary stent - was shown to be comparable to that of sirolimus[17].

Due to the lack of the polymer and carrier typically used by other drug-eluting stents, the drug is released from a specifically micro-structured surface and the release is modulated through the superior lipophilicity and other inherent chemical properties of BA9™. The absence of a polymer is the unique design feature of the BioFreedom™ DCS (both the predicate/comparator BF-SST and the investigational BF-CoCr) in comparison with other more traditional drug-eluting stents.

This feature was designed to improve the biocompatibility of the stent as all potential unfavorable tissue interactions with a polymer could be avoided.

1.5 Pre-Clinical Studies with the BioFreedom™ CoCr DCS

The safety of single (non-overlapped) and overlapped pairs of BioFreedom™ CoCr stents were evaluated in a mini swine model for 3, 28, 90 and 180 days with assessment of safety using histomorphometric analysis. Pathologic grading was used to assess injury, inflammation, foreign body reaction, granuloma, presence of fibrin, percentage of uncovered struts and endothelialization. Both the BioFreedom™ CoCr stent and the predicate BioFreedom ™ Stainless Steel (BioFreedom™ SS) stent contain the same BA9™ dosage of 15.6 µg/mm of stent length, which is the same BA9™ dose that is used in the CE-marked and clinically demonstrated BioFreedom™ DCS for the safe and effective treatment of *de novo* coronary artery lesions. In addition to the two active DCS study stents, the Chroma bare-metal CoCr stent was included as the non-active control. The systemic release characteristics of BA9™ in blood as well as in cardiac tissues were evaluated. Blood samples were taken at various times to evaluate residual levels of BA9™. Early and late restenosis rates were included in the assessment.

In summary, the BioFreedom™ CoCr stent showed similar safety and efficacy in histomorphometry as the BioFreedom™ SS DCS in both single and overlapped stent configurations. Hence it can be concluded, that a 15.6 µg/mm dose of BA9™ as delivered from the BioFreedom™ CoCr DCS remains safe at all time points of the study in comparison with the BioFreedom™ SS DCS.

The BA9™ concentration in tissue at 28 days yielded concentrations within the therapeutic window as demonstrated by the histomorphometric results. The BA9™ release profile and uptake into tissue were consistent between the BioFreedom™ CoCr and its predicate, BioFreedom™ SS.

1.6 Related Clinical Studies

The STEALTH PK study was aimed to evaluate the pharmacokinetics of Biolimus A9™ after treatment with the BioMatrix Drug-Eluting Coronary Stent System. There were no cardiac or non-cardiac deaths, myocardial infarctions, target vessel or target lesion revascularizations up to 9 months follow-up. As such, the MACE free survival rate at 9 months was 100%. This study demonstrated that extremely low systemic concentrations of Biolimus A9™ were found post implantation of the BioMatrix Stent in humans. In addition, selected hematology and biochemistry parameters did not show change over time indicating absence of any impact of Biolimus A9™ on distant organs and no signs of toxicity were seen during 9 months follow-up by selected biochemistry parameters.

The STEALTH Fist In Man trial[23-24] demonstrated that extremely low systemic concentrations of Biolimus A9™ were found post implantation of the BioMatrix Stent in humans. In addition, selected hematology and biochemistry parameters did not show change over time indicating absence of any impact of Biolimus A9™ on distant organs and no signs of toxicity were seen during 9 months follow-up by selected biochemistry parameters.

The LEADERS trial is a randomized, single-blinded, non-inferiority trial comparing the safety and efficacy of the Biolimus A9™-eluting stent (BioMatrixFlex™) to the Sirolimus-eluting stent (Cypher®, Cordis, Miami Lakes, FL) in subjects with an indication for PCI (stable or those with acute coronary syndromes, including STEMI) . A total of 1707 patients with 2472 lesions were randomly assigned to either treatment arm. It showed non-inferior safety and effectiveness of biodegradable polymer BA9™ eluting stent (BES), BioMatrix Flex™,

compared with durable polymer sirolimus-eluting stent (SES), Cypher® SELECT™, at 9 months[17], 4 years[20] and 5 years[18].

These clinical trial data demonstrate safety and effectiveness of the BA9™ drug. To date, over 45,000 patients have received Biosensors stents with the same BA9™ drug and dosage in clinical trials and post market registries (evaluating the BioMatrix™ and BioFreedom™ stents). [12, 21, 22]

1.7 BioFreedom ™ DCS Coronary Stent Clinical Experience

The BioFreedom First In man trial, the Ego Biofreedom study, and the landmark LEADERS FREE RCT trials described below were designed to evaluate the predicate and comparator, BioFreedom™ SST:

1.7.1 BIOFREEDOM™ FIM 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 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. [21]

1.7.2 EGO BIOFREEDOM™ STUDY

The EGO BioFreedom™ study was a Physician-Initiated Trial (PIT) conducted in Hong Kong under the lead of Prof. Stephen Lee. It was a prospective single center, single arm study evaluating the healing profile of the BioFreedom™ (BFD) stent using Optical Coherence Tomography (OCT) in patients with ischemic heart disease. A total of 106 patients were enrolled and followed up for 12 months. By serial OCT analysis, the study demonstrated a rapid early healing profile of the BFD stent. Median tissue strut coverage increased from 85.8% at 1 month to 87.0% at 2 months, 88.6% at 3 months, 96.8% at 4 months, and 97.1% at 5 months to complete coverage of 99.6% at 9 months. This study also provides the so far largest cohort of BioFreedom™ patients with systematic angiographic analysis by QCA. Mean in-stent late lumen loss at 9 months was 0.21±0.30mm and demonstrated that the BioFreedom™ stent had an anti-restenotic efficacy similar to other typical DES using polymers. Clinical outcomes of the study were excellent with a total MACE rate at 1 year of 4.0%, including the rate of TLR of 2.0%. There were no stent thromboses observed.

1.7.3 LEADERS FREE

The LEADERS FREE study 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.[12] A total of 2,466 patients were enrolled and treated with one month of dual antiplatelet therapy.

Inclusion criteria were designed to create a patient population with high bleeding risk. Patients with coronary artery disease and a clinical indication for PCI were eligible for the study.

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-lesion 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 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 (9.0%) ($P = .01$).

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 <.001). Bleeding was high in both groups, as expected, with 215 BioFreedom ™ patients (18.1%) vs. 225 BMS patients (19.1%) 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 were similar in the two groups, with 24 patients (2.0%) vs. 26 patients (2.2%) experiencing thrombosis through 390 days.

At 2 years of follow-up [13], the composite safety endpoint occurred in 147 patients (12.6%) in the DCS group and in 180 patients (15.3%) in the BMS group (hazard ratio, 0.795; 95% CI, 0.64 to 0.989; p=0.039). Clinically driven TLR occurred in 77 patients (6.8%) in the DCS group and in 136 patients (12%) in the BMS group (hazard ratio, 0.54; 95% CI, 0.409 to 0.715; p<0.0001). 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 the two stent groups were observed with respect to target lesion revascularization by Re-PCI , including urgent TLR, clinically driven TVR (respectively at 24 months, p<0.0001; p=0.0072; p<0.0001) with above mentioned revascularization less likely to occur in the DCS group.

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 1y, and very little increment from 1y to 2y, confirming that the risk for late stent thrombosis associated with the DCS is similar to that of the 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 with high bleeding risk.

2. STUDY PURPOSE and DESIGN RATIONALE

The BioFreedom™ QCA trial is designed to evaluate the safety and efficacy of the Biofreedom™ CoCr DCS coronary stent system compared to the Biofreedom™ stainless steel DCS coronary stent system, in a randomized controlled trial on an all-comers patient population.

This study will serve as a First-in-Man experience for the BioFreedom™ CoCr stent in a population of all-comers patients, who are not at high bleeding risk and can be treated with dual anti-platelet therapy according to current AHA/ACC/ESC/SCAI practice guidelines

The investigational BioFreedom™ CoCr stent is an iteration of the predicate BioFreedom™ Drug Coated Coronary Stent System ("BioFreedom"). The two stents are equivalent, with the exception of the stent platform and the delivery system. The design elements which are key to the efficacy and safety of a DES including the BA9™ drug, the drug dose, the absence of polymer and the release kinetics of the drug were kept identical to those of the previous BioFreedom™ stainless steel stent, thus making the predicate the most suitable choice of comparator for this trial.

The primary objective is to measure non-inferiority of the BioFreedom™ CoCr stent compared to BioFreedom™ DCS as measured by the difference in angiographically measured late lumen loss at 9 months, and the main secondary endpoint is to assess safety as measured by MACE and ST. Two hundred (200) patients will be randomized 1:1 to either stent, allowing for a direct comparison, and will be followed-up to 2 years to measure for late MACE and ST events. The statistical considerations are addressed in section 11. An all-comers patient population is chosen for this trial because these patients are the target indication for drug eluting stents.

3. RISKS AND BENEFITS

3.1 Benefits

The BioFreedom ™ CoCr DCS is a modern, highly deliverable low profile drug coated stent. The major benefit achieved with the design iteration is an improved flexibility, trackability and deliverability of the new stent in comparison with the previous version BioFreedom ™ SS.

Due to the lack of the polymer typically used by other drug-eluting stents, the drug is released from a specifically micro-structured surface, and the release is modulated through the superior lipophilicity and other inherent chemical properties of BA9™. The absence of a polymer is the unique design feature of the BioFreedom ™ DCS, (in both the predicate BioFreedom™ SS and the investigational BioFreedom™ CoCr) in comparison with other more traditional drug-eluting stents. This feature was designed to improve the biocompatibility of the stent as all potential unfavorable tissue interactions with a polymer could be avoided.

The same benefits typical for the predicate device, the BioFreedom™ DCS are also expected from the BioFreedom™ CoCr, based on the established similarities in terms of the technical, clinical, and biological characteristics.

Figure 1 below demonstrates the lipophilicity of the BA9™ vs. drugs used by the currently available drug eluting stents:

FIGURE 1. LIPOPHILICITY OF BA9™ VS. DRUGS USED WITH CURRENTLY MARKETED DES

3.2 Risks – BF-CoCr

The BioFreedom™ CoCr Drug-Coated Coronary Stent system (DCS) is an iteration of the already CE marked predicate device, the BioFreedom™ DCS. The BioFreedom™ CoCr stent is consisting of a cobalt chromium rather than a stainless steel stent platform, while the BA9™ drug is applied in the same dose and released with the same release characteristics than from the predicate stent. The BioFreedom™ CoCr stent is mounted on a monorail stent delivery system with the internal reference NDS6, used to deliver and deploy the stent at the lesion site. The BA9™ drug has been evaluated clinically in the Biosensors clinical studies, including the STEALTH FIM, STEALTH PK, LEADERS, e-BioMatrix Registry, BioFreedom ™ FIM Study and the LEADERS FREE trial. The Biosensors Chroma™ bare metal stent platform uses the same CoCr alloy as the BioFreedom™ CoCr stent, and the same NDS6 stent delivery system, and has been CE-marked since 2013.

Potential risks are those associated with use of the drug BA9™ itself and the cobalt chromium alloy. Of note, this study uses a guideline oriented DAPT regimen and is not designed to assess optimal DAPT duration.

Adverse events that may be associated with the use of the stent in native coronary arteries include but are not limited to:

• Abrupt vessel closure or spasm

• Acute myocardial infarction

• Allergic reaction to anti-coagulation and/ or anti-thrombotic therapy, contrast material, the stent and/ or delivery system materials

• Aneurysm, pseudoaneurysm or arteriovenous fistula

• Arrhythmias, including ventricular fibrillation and ventricular tachycardia

• Bradycardia requiring pharmacologic intervention

• Cardiac tamponade

• Cardiogenic shock

• Death

• Dissection, perforation, or rupture of the artery

• Emboli, distal (air, tissue or thrombotic emboli)

• Emergency coronary artery bypass grafting (CABG) as a result of damage to the stent or injury to the vessel

• Fever

• Hematoma at insertion site

• Haemorrhage requiring transfusion

• Hypotension/ hypertension

• Infection and/ or pain at the insertion site

• Perforation or rupture of the artery

• Peripheral ischemia or peripheral nerve injury

• Stent thrombosis/ occlusion

• Stent migration or stent embolization

• Stroke or transient ischemic attack

• Renal failure

• Restenosis of the stented segment

• Total occlusion of coronary artery

• Unstable angina

Adverse events that may be associated with BA9™ drug coating:

NOTE: BA9™ drug administration is limited to intra-coronary stent delivery. The adverse effects of this drug have not been fully characterized. Although not observed so far with BA9™ stents, side effects experienced with substantially higher BA9™ doses following systemic drug application may include the following:

• Nausea

• Lymphadenopathy

• Mouth ulcers

• Chest Heaviness

• Dizziness

The occurrence of the above listed complications, except for those directly associated with the drug, may lead to repeat catheterization and/or percutaneous coronary intervention, myocardial infarction, stent thrombosis, stroke, emergency bypass surgery, or death.

Appropriate contraindications and warnings are included in the Instructions for Use (IFU).

Additional risks, which are not known at this time, may also exist. Appropriate contraindications and warnings are included in the Instructions for Use (IFU).

The risks associated with the BioFreedom™ SS DCS are listed in the IFU.

Study specific insurance cover for the patients will be provided by the Sponsor.

3.3 Risk-Benefit assessment

The investigational device, intended to be used in this trial, is largely equivalent to the BioFreedom™ Stainless Steel predicate device, which has the same stent-tissue surface contact material and the same BA9™ dose and release characteristics. It is therefore not expected to have a different risk-benefit profile. The predicate BioFreedom™ SS stent has been studied in LEADERS FREE and BioFreedom FIM, and clinical results demonstrated safety and efficacy up to 2 years, and 5 years respectively.

The outcome of the pre-clinical and animal testing on the investigational device did not reveal any new safety signals or residual risks associated with the investigational device.

All individual/cumulative residual risks assessed, within the FMEA approach evaluation, regarding Safety and Efficacy for BioFreedom™ CoCr have been evaluated as a whole and considered to be acceptable as the overall benefits outweigh the risks.

4. STUDY OBJECTIVE

The objective of this study is to demonstrate that the BioFreedom ™ CoCr Drug Coated Stent (DCS) is non-inferior to the market authorized predicate stent BioFreedom ™ SS DCS with respect to in-stent late lumen loss and has similar clinical safety characteristics to the BioFreedom ™ SS DCS.

5. STUDY DESIGN

A prospective, multi-center, open-label, randomised study in patients with coronary artery disease, who are randomly assigned to either the new BioFreedom™ CoCr stent or the CE marked BioFreedom™ SS stent. 200 patients will be randomized at approximately 10 centers in up to 2 European Countries.

6. ENDPOINTS

6.1 Primary Endpoints

Efficacy: In-stent late lumen loss (LLL) assessed by quantitative coronary angiography at 9 months.

6.2 Secondary Endpoints

At all protocol defined follow-up time points (1, 9, 12 and 24 months) unless otherwise indicated

- Cardiac Death
- Myocardial infarction (according to the Third Universal Definition)
- MACE (defined as cardiac death, MI and ci TLR)
- All-cause mortality
- Clinically driven TLR
- TLF (cardiac death, target vessel related MI, ci TLR)
- Clinically driven target vessel revascularization (TVR)
- Stent Thrombosis per ARC definition
- Device success
- Procedure success
- Lesion success

7. STUDY POPULATION

7.1 Number of Patients

Two hundred (200) patients will be randomized to obtain 160 evaluable patients in approximately 10 centres in up to 2 European countries.

7.2 Site Selection

Qualified study centres having adequate numbers of the target patient population and appropriate facilities, time and staff and commitment to conduct the clinical study, will be selected for participation by the study sponsor with assistance from the principal investigator.

7.3 Type of Patients

This trial will enroll "all comer" patients with symptomatic coronary artery disease including chronic stable angina, unstable angina, or silent ischemia, and acute coronary syndromes (STEMI and non-STEMI), who have an indication for percutaneous coronary interventions.

7.4 Inclusion Criteria

"Real world, all comer" patients

5. Age ≥18 years;
6. Symptomatic coronary artery disease including patients with chronic stable angina, unstable angina, silent ischemia, and acute coronary syndromes including non-ST elevation myocardial infarction and ST-elevation myocardial infarction;
7. Presence of one or more coronary artery stenosis >50% in a native coronary artery or a saphenous bypass graft from 2.50 to 3.5 mm in diameter that can be covered with one or multiple stents (angiographic inclusion);
8. No limitation on the number of treated lesions, and vessels, and lesion length

7.5 Exclusion Criteria

10. Individual is pregnant, nursing or planning to be pregnant;
11. Known intolerance to aspirin, clopidogrel, heparin, stainless steel, cobalt chromium, Biolimus A9™ or its analogues (e.g. sirolimus, everolimus, zotarolimus) or contrast material
12. Inability to provide informed consent;
13. Currently participating in another trial before reaching primary endpoint;
14. Planned surgery within 6 months of percutaneous coronary intervention (PCI)
15. Patient requires a stent <2.5mm (angiographic exclusion)
16. Patient requires a stent >3.5mm (angiographic exclusion)
17. Patient requires a non-study stent during the index or staged procedure
18. Use of a drug coated balloon planned at the index or staged procedure

8. STUDY PROCEDURES

8.1 Patient Informed Consent

All patients will be asked to sign a consent form prior to screening and subsequent inclusion into the study and prior to the index procedure. ST-elevation Myocardial Infarct (STEMI) patients will be asked to sign a consent form after verbal explanation of the study by the consenting physician before the procedure. They will then be asked to sign another consent with the full information sheet after the procedure and before they leave the hospital.

A copy of the signed consent form/s will be given to the patient and a copy will be filed in their medical file.

8.2 Patient Pre-Screening

Pre-screening of patients will involve the investigational site checking their patient database for suitable patients in accordance with the inclusion/exclusion criteria.

Once patients are identified, they are consented to potentially be randomised and thus enrolled into the study.

8.3 Screening Assessment

At screening, routine examinations, if performed, will be captured:

- Consent signing
- Physical examination (including height and weight, heart rate and blood pressure)
- Relevant medical history
- Disease Status
- Routine Laboratory Tests including CK and/or CK-MB or troponin prior to the procedure (according to site standard procedure)
- Patients will be asked if they could be pregnant. If yes, they will not be screened further.

The final screening check takes place during the angiography and only once the below criteria are fulfilled can the patient be randomised:

- All study eligibility has been met (inclusion 3 and exclusion 6 ,7, 8 and 9)
- The lesion has been deemed treatable
- The guidewire has crossed the lesion

If the patient has provided informed consent but has failed the final screening for randomisation into the study, he/she will be considered a screen failure and will not be followed up for safety and will be withdrawn by the site from the study.

For the purpose of this study, a woman of childbearing potential is defined as 55 year of age or younger. If a woman is 55 years old or younger, she can only enter the trial if:

a. She has a negative pregnancy test
b. She agrees in writing to not become pregnant during the first 4 weeks after the study stent has been implanted

8.4 Pre-procedure

Beyond the guideline oriented anti-platelet regimen, patients are to be medicated as per institutional procedures. All medications administered are to be captured in the medical notes for subsequent capture in the electronic Case Report Form (eCRF). An electrocardiogram (ECG) will also be performed.

8.5 Procedure – Randomization and Stent Implantation

Once the above criteria are met, the patient is called into the interactive web recognition (IWR) system by the study team entering the patient's details and will then be randomised to one of the treatment arms to receive either the BioFreedom™ SS or the BioFreedom™ CoCr stent.

The randomization schedule will be computer generated and stratified by the presence or absence of diabetes mellitus. The investigator will use the stent/stent type allocated by the randomization system to treat the lesion(s). The length of the stent(s) should ensure complete coverage of each lesion from healthy to healthy. If more than one stent per lesion is implanted, at least a 2 mm overlap should be achieved. In case of insufficient stent expansion, the stent will be post-dilated with an appropriately sized balloon.

Use of GP2b3a blockers during the index procedure is left to the discretion of the investigator.

8.5.1 Staged procedures

Treatment of multiple target vessels (within the same procedure) and staged procedure within six week of the initial index procedure (Day 0) are permitted. Staged procedures in the target vessel are NOT permitted. Additionally, any subsequent treatment of a lesion in a non-target vessel that is already present at the time of the index procedure and not treated in the index procedure will be considered as a staged procedure, instead of a repeat PCI.

If multiple stents are required, or a staged procedure is planned, each stent must be chosen from the same randomization group.

The protocol does not limit the use of clinically indicated imaging (Optical Coherence Tomography (OCT)/ Intravascular Ultrasound (IVUS)) or functional test procedures (Fractional Flow Reserve (FFR)/ Instantaneous Free-wave Ratio (iFR)) that represent current clinical practice.

If patients received a non-study stent it is classed as a protocol deviation.

Study stents that are implanted during a staged procedure will not be evaluated by QCA.

For patients undergoing a staged procedure, the follow-up schedule will be calculated from the date of the index procedure. Cardiac markers should be obtained as per institutional standard.

8.6 Antithrombotic Drug Treatment

Dual anti-platelet therapy (DAPT) (P2Y12 inhibitor plus aspirin) as recommended by current practice guidelines.

8.7 Post-Procedural Management

An electrocardiogram (ECG) will be performed prior to discharge. A 12-lead ECG is required to document any suspicious cardiac ischemic episode.

Cardiac troponin (cTn) or creatinine kinase (CK) and/or CK-MB (per institutional standard) will be measured in the case of signs/symptoms of MI and in all cases at least once post procedure with one of the measurements at 18-24 hours post-procedure. If the patient is discharged prior to 18 hours post procedure, cardiac markers will be measured immediately prior to discharge.

If total CK values are utilized and are within normal ranges, CK-MB measurements may not be performed if this is per hospital standards. However, it is encouraged that CK-MB measurements are obtained with every total CK drawn, even if CK values are within normal limits.

Every effort must be made to obtain cardiac enzyme values within the specified time range to help determine presence or absence of MI post-procedure. In the case of multiple measurements prior to discharge, first enzyme measurement and the peak value should be documented on the case report forms.

If any cTn or CK elevation is noted post-procedure, per the Third Universal Definition, cTn or CK and CK-MB measurements should continue to be performed every 6 hours for 24 hours, as per clinical practice starting from when the first elevation is noted. Myocardial infarctions will be adjudicated to the Third universal definition.[1]

Clinical status will be assessed at discharge. All cardiac medications will be recorded. A letter will be sent to the patient's referring physician/general practitioner, explaining his/her participation in the study and a detailed schedule of required study activities and follow up time points.

9. FOLLOW-UP PERIOD (FUP)

Patients will be followed after hospital discharge up to 2 years after the index procedure. These follow-ups consist of telephone contacts or clinic visits to obtain information regarding medication use, hospitalizations, MACEs, all cardiac and procedure related events and serious adverse events at 30 days, 9 and 12 and 24 months. In addition, at 9 months post index procedure, another angiography will be performed for QCA analysis.

A summary of required follow-up procedures is listed in Table 1.

9.1 FUP 30 days Post-Procedure (± 7 days) - Telephone

An assessment of medication intake and any adverse event will be obtained via telephone contact.

9.2 Staged Procedure (if applicable within 6 weeks) – Clinic

Patients will attend clinic to have the following check-ups performed:

- Medication intake
- Adverse events
- 12-lead ECG
- Physical examination
- Angiography and placement of study stent from the same randomization group
- Routine Laboratory Tests incl. CK and/or CK-MB or troponin

9.3 FUP 9 months (± 7 days) Post-Procedure - Clinic

Patients will attend clinic to have the following check-ups performed:

- Medication intake
- Adverse events
- 12-lead ECG
- Physical examination
- Pregnancy status
- Angiography
- Routine Laboratory Tests incl. CK and/or CK-MB or troponin

9.3.1 9-month repeat angiography

A repeat angiogram will be performed 9 months after stent implantation. Although the repeat angiogram should generally be scheduled at the same time as the 9-month clinical visit, a repeat angiogram 3 months prior to or 3 months after the actual 9-month date will be accepted for analysis.

In case an angiogram is performed before the 9-month angiography, the following algorithm will apply:

- Any angiogram performed less than 6 months after the baseline procedure, with no reintervention of a target lesion or a CABG, will be recorded in the CRF as an intercurrent angiography. An angiogram at 9 months will still be required;
- Any angiogram 6 to 9 months after the baseline procedure may be used as the scheduled “9 months” follow-up angiogram. Clinical follow-up at the actual 9-month date is still mandatory; If a target lesion is revascularized at any time between baseline and 9 months, the angiogram will serve as the “9 months” follow-up angiogram for the study. However, if a patient has more than one target lesion and only one is revascularized at, e.g. 3 months post-baseline, the other target lesions will need to be filmed at the scheduled 9 months angiography.

9.4 FUP 12 months (± 4 weeks) Post-Procedure - Telephone

An assessment of medication intake and any adverse event will be obtained via telephone contact.

9.5 FUP 24 months (± 8 weeks) Post-Procedure - Telephone

An assessment of medication intake and any adverse event will be obtained via telephone contact.

9.6 Missed Follow-ups

If the patient cannot be reached for a follow up visit, at least three telephone contacts (or attempts) should be made prior to recording a missed follow-up visit. The patient however remains in the study until the 2-year follow-up. The patient will only be considered as 'Lost to follow-up' if he/she cannot be reached for the final 2-year follow-up.

9.7 Patient Withdrawal

Each patient is free to withdraw from the study at any time and without reason, and without influence on their further medical treatment or relationship to their physicians. Once the patient is withdrawn, they will be followed per institutional standard of care.

Every effort will be made by the investigator to keep the patient in the study; however, should the patient decide to withdraw, the investigator is responsible for reporting the observations thoroughly, and completing the final evaluations and eCRFs. The primary reason for the early withdrawal must be documented on the Study Exit case report form.

Screen Failure Patients

Patients who have signed an informed consent form, but that are screen failures, will be documented as such in the eCRF. Patients will then be treated per the discretion of the Investigator; however, no study material may be used and those patients are told that they have not passed screening and thus won't be enrolled into the study and won't be followed up in accordance with study procedures but as per hospital procedures only.

Withdrawal prior to randomisation and PCI

For patients who were declared eligible for the study but who are discontinued for any reason prior to randomisation or prior to the commencement of any PCI procedure, data until that time period will be collected and the patient will be immediately exited from study. The reason for the early withdrawal must be documented on the Study Exit case report form.

Withdrawal after index procedure

For patients who withdraw their consent after randomisation and after the commencement of PCI and AFTER any study stent was implanted, the patient must be followed up for safety until the end of the study. All data obtained until the date of withdrawal will be kept and entered into the efficacy and safety analysis unless the patient explicitly requests complete deletion of the records, which should be documented by the site.

9.8 Data Collection from Patients Who Receive Non-Study Stents

- If a patient received one or several non-study stents together with a study stent for any reason it is considered to be a major protocol deviation. The patient will be followed only for the intent to treat (ITT) analysis. Patients must continue to be followed per protocol follow-up schedule.
- Patients who receive only non-study stents due to the study stent not implanting properly will be withdrawn from the study follow-up and will not be included in any of the analyses, except for the assessment of device success.

In general, clinical decision making is left to the discretion of the investigator.

9.9 Discontinuation Criteria for the Entire Study

If the Sponsor, Data Safety and Monitoring Board (DSMB), Regulatory Agency, and/or the Principal Investigator discover conditions during the study that indicate the investigation should be terminated for patient safety reasons, an appropriate schedule for termination will be instituted. Final decision to terminate the study lies with the Sponsor.

9.10 Study Termination

If the study is terminated prior to the completion of expected enrolment for any reason, all participating centres will be notified within five working days of this decision. All patients already enrolled/included will continue to be followed for the planned course of study described in this protocol. The study will be terminated following the final follow-up visit of the last enrolled patient. Biosensors reserves the right to terminate the study at any time.

10. SAFETY REPORTING

Safety of the patients participating in this clinical study will be monitored throughout the study using the Adverse Event reporting process to identify real and potential safety issues.

Adverse events / device deficiencies will be reported according to the ISO 14155:2011(E) Clinical Investigation of medical devices for human patients – Good Clinical Practice Guidelines, while recognizing and following other specific laws, regulations, directives, standards and/or guidelines as appropriate as required by the country(ies) in which the study is conducted. The study safety management plan (SMP) will also be adhered to.

Reporting timelines are listed below in Table 3, in general reporting should be immediately but not later than 3 calendar days after investigational site study personnel's awareness of the event in accordance with MEDDEV 2.7/3 rev. 3 from May 2015.

The list of foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation or treatment can be found in the Investigator Brochure and IFU (see also section 3.2 Risks above).

10.1 Definitions of Adverse Events

10.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including an abnormal laboratory finding) in patients, users or other persons whether or not related to the investigational medical device.

Note 1: This includes events related to the investigational medical device (ISO 14155:2011)

Note 2: This includes events related to the procedures involved (ISO 14155:2011)

Note 3: For users or other persons this is restricted to events related to the investigational medical device (ISO 14155:2011)

Note 4: Pre-Existing Medical Conditions: Any medical conditions (including planned surgeries and planned hospitalizations) present at enrolment, which do not worsen in duration, severity or frequency during the study **are not adverse events (AE)**. These pre-existing medical conditions should be adequately documented in the patient's medical history in the eCRF. Medical conditions present at enrolment which worsen after exposure to study treatment will be recorded as an AE on the Adverse Event Form of the eCRF.

At each evaluation, patients should be interviewed in a non-directed manner to elicit potential AEs from the patient. The occurrence of an AE will be based on changes in the patient's physical examination, laboratory results, and/or signs and symptoms at a clinical visit, otherwise based on information given by the patient over the telephone.

10.1.2 Adverse Device Effect (ADE) (ISO 14155:2011 3.1)

Adverse event related to the use of an investigational medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

10.1.3 Serious Adverse Event (SAE) (ISO 14155:2011 3.37)

An adverse event that:

1. led to a death,
2. led to a serious deterioration in the health of the patient that either resulted in:
    a. a life-threatening illness or injury, or
    b. a permanent impairment of a body structure or a body function, or
    c. in-patient or prolonged hospitalization, or
    d. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
3. led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

10.1.4 Serious Adverse Device Effect (SADE) (ISO 14155:2011 3.36):

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

10.1.5 Unanticipated Serious Adverse Device Effect (USADE) (ISO 14155:2011 3.42):

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

10.1.6 Device Deficiency (DD) (ISO 14155:2011 3.15):

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequate labeling.

10.1.7 Device Malfunction (ISO 14155:2011 3.27):

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP.

10.2 Safety Reporting Process

The Principal Investigator (or designee) shall report all adverse events/device deficiencies to the sponsor according to the timelines listed in Table 3. The PI/Sponsor/Clinical Research Organization (CRO) (according to local/national regulations) shall also notify the Ethics

Committee (EC) and Competent Authorities (CA) of all reportable events according to national regulations in acceptable timely conditions, and may also be requested by the ECs and CAs to provide periodic reports. The Investigator shall document all AEs and DDs in the eCRF from the point of inclusion until the patient is exited from the study. The eCRF will be programmed to send AE notifications to the clinical project manager acting as the safety officer, the KCRI safety department and other relevant personnel.

Table 4. Timelines for Reporting Events to the Sponsor/CRO

Class of Event	**Timeline for Reporting**
ADE	Immediately but in any event no later than 3 calendar days
SAE	Immediately but in any event no later than 3 calendar days
SADE	Immediately but in any event no later than 3 calendar days
USADE	Immediately but in any event no later than 3 calendar days
All other AE	In a timely manner, usually within 30 calendar days
Device Deficiency	Immediately but in any event no later than 3 calendar days

The above timelines are based on MEDDEV 2.7/3 rev.3 from May 2015

The Investigator (or designee) will provide the following information, at a minimum, for each adverse event (AE) or device deficiency):

1. Date of the AE
2. Date Investigator (or designee) became aware of AE or DD
3. Description of AE
4. Treatment
5. Resolution
6. Assessment of:

A. Seriousness of the event:

- led to a death,
- led to a serious deterioration in the health of the patient that either resulted in:
    a. a life-threatening illness or injury, or
    b. a permanent impairment of a body structure or a body function, or
    c. in-patient or prolonged hospitalization, or
    d. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

B. Severity (defined below):

a) Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

b) Moderate: minimal, local or noninvasive intervention indicated; limiting

c) Severe: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling

C. Relationship of the event to the investigational device

a) Not related

b) Unlikely

c) Possible

d) Probable

e) Causal relationship

D. Relationship of the event to the index procedure

a) Not related

b) Unlikely

c) Possible

d) Probable

e) Causal relationship

E. Causality (when not related or unlikely related to investigational device/ index procedure)

a) Disease under study

b) Lack of efficacy/worsening of treated condition

c) Medical history

d) Concomitant or previous medication

e) Other (specify)

In accordance with ISO 14155:2011 8.2.5 , the sponsor (or designee) is responsible for the classification of all adverse events and ongoing safety evaluation of the clinical investigation and shall:

1. Review the investigator's assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties

2. Review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties

3. Ensure the reporting to the EC by the principal investigator(s) (if applicable), of all serious adverse events and device deficiencies that led/could have led to a serious adverse device effect, if required by national regulations or by the EC

4. Review and report all reportable events (including device deficiencies) according to national regulations in acceptable timely conditions and shall monitor for increased incidence and severity above that indicated in the Risk Analysis Report. An SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/patients, users or other persons or a new finding to it will be reported immediately but not later than 2 calendar days after awareness by sponsor.

5. Report all relevant safety information to the DSMB in a timely manner, per the DSMB Charter

6. Inform all principal investigators in writing of all the serious adverse events at all investigation sites that have been reported to the sponsor on an annual basis at a minimum

7. Ensure that the EC and the regulatory authorities are informed of significant new information about the clinical investigation, and

8. In case of serious adverse device effects and device deficiencies that led/could have led to serious adverse device effects, determine whether corrective or preventive action is required.

10.3 Data Safety Monitoring Board (DSMB)

The DSMB is composed of 3 members (2 physicians from the field of interventional cardiology and 1 biostatistician) who are not participants in the study. Membership will not have primary affiliation with the study sponsor, CRO, Core-lab, the Electronic Data Capture (EDC) supplier or the principal investigator of the study. Members of the DSMB will be determined prior to study enrollment.

The DSMB will review data and determine reporting and stopping rules as specified in the study DSMB charter. The DSMB members will review safety data while maintaining the scientific integrity of the study. The data to be reviewed will consist of adjudicated and non-adjudicated MACE, and secondary endpoints and other Serious Adverse Events and their incidence, in order to identify potential safety issues. Based on the safety data, the DSMB may recommend modifications to the protocol, suspension or termination of the study, and advise the Steering Committee.

Members of the DSMB will meet in person or via telephone conference at the beginning of the study to review the protocol, to determine the meeting schedule, the logistics of reporting the safety data and the stopping rules. Frequency of meetings can change during the study and will be determined by the DSMB and its charter. The DSMB chair will be responsible for approving meeting minutes of all DSMB meetings.

In the event of any reported USADE the DSMB chair will be notified by Biosensors within 24 hours of its knowledge of such an event.

Events to be reviewed by the DSMB will be prepared by the Clinical Study team.

10.4 Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) is made up of 2 interventional cardiologists who are not participants in the study. Study Investigators are not permitted to be CEC members to avoid conflict of interest.

The CEC is responsible for adjudicating all primary and secondary endpoint related events reported during the study following established explicit rules in the CEC charter which outlines the data required and the algorithm followed in order to classify a clinical event.

The CEC will adjudicate events using either the independent review method or the consensus meeting method described in the study CEC charter. CEC findings would be summarized and documented in the CEC reports.

10.5 Reporting to the Authorities

In accordance to the MEDDEV 2.7/3 rev. 3 from May 2015 guidance on SAE reporting under Directive 93/42/EEC and the study SMP, the sponsor or authorized representative will notify the relevant National Competent Authority about:

- any SAE,
- any Device Deficiency that might have led to a SAE if:
    a) suitable action had not been taken or
    b) intervention had not been made or
    c) if circumstances had been less fortunate
- new findings/updates in relation to already reported events.

11. STATISTICAL ANALYSIS

This study is an open-label, prospective, randomized study intended to demonstrate the safety, effectiveness and performance of the Biofreedom™ CoCr by assessment of in stent late loss in patients undergoing angiographic follow-up at 9 months when compared to the SS Biofreedom™ stents

The complete data analysis will be described in the Statistical Analysis Plan (SAP).

11.1 Methods

Sample size derivation

Assuming true equivalence of the means between the CoCr and SS BioFreedom™ stents, with a common standard deviation of 0.45 mm and a non-inferiority margin of 0.20 mm, 160 evaluable patients will be needed in order to yield 80% power for non-inferiority using a 1-sided, 2-sample t-test with alpha of 0.025. Assuming a drop-out rate of 20%, 200 patients will be enrolled.

Randomization and enrollment

Randomization will occur after each patient has signed informed consent and patient eligibility has been confirmed. Subjects will be randomized in a blinded fashion in a 1:1 ratio of BioFreedom™ CoCr stent to BioFreedom™ SS stent. Randomization will be stratified according to diabetic status at time of enrolment. The patient is considered enrolled upon randomization.

Baseline characteristics

Subject demographics, cardiovascular disease histories, other risk factors, pre-procedure target lesion characteristics and procedure characteristics will be summarized descriptively by mean, standard deviation, median , Q1, Q3, min and max.

ITT population

The ITT population consists of all randomised patients whether or not they received a study stent. Patients will be analysed based on the treatment they were randomised to receive. The ITT analysis set will be the main analysis set

Endpoints evaluation

The primary endpoint for the trial is late loss assessed by QCA for patients undergoing angiographic follow-up at 9 months. In-stent Late Loss and other measured angiographic parameters will be reported by providing the observed values, the mean, median standard deviation 1st and 3rd quartiles, minimum and maximum value. Two-sided 95% confidence intervals of the mean will be obtained. A t-test of equal mean will be performed to assess the primary objective of the study to show non-inferiority of between the two study stents. The subsequent test of superiority will be conducted if the non-inferiority hypothesis is met.

Analyses of clinical endpoints will be based on events adjudicated by the Clinical Events Committee. Those data will consist of right-censored clinical event data due to the possibility that a patient is lost to follow-up, withdraws from the study or dies before the clinical endpoint occurs.

Analyses will consider the time to the first event. The comparison between the two stents will be a two-sided superiority test comparing Kaplan-Meier cumulative incidence rate at one year. Hazard ratio will also be provided.

12. QUALITY CONTROL AND ASSURANCE

12.1 Quality Assurance

The study will be conducted in accordance with Good Clinical Practice, following the principles of ISO 14155:2011. Sites will be selected based on previous performance in Biosensors studies, experience running clinical study, having an established clinical study team and having the time and capacity to perform the study.

Sites will be initiated and trained on the clinical study requirements. Assurance of the accuracy and reliability of data will consist of checking the consent forms and consent process, on site and remote monitoring. All required data for this study will be collected into an EDC using electronic case report forms (eCRFs). Appropriate computer edit programs will be run to verify the accuracy of the data. All details are described in the data management plan (DMP).

There will be 100% informed consent verification, and all MACE and secondary endpoint events up to 2 years will be adjudicated by an independent Clinical Events Committee (CEC). Verification of other source documentation will be performed as specified in the monitoring plan.

12.2 Source Data (SD)

Regulations require that investigators maintain information in the study patient's medical records which corroborate data collected on the eCRF. In order to comply with these regulatory requirements, the following information will be maintained in the medical file and made available as required by the sponsor and its monitors and/or regulatory inspectors:

1. Medical history/physical condition of the patient before involvement in the study sufficient to verify protocol entry criteria.
2. Dated and signed notes in the patient's medical record on the day of enrolment into the study that identify: the patient's date of entry into the study, the study sponsor (Biosensors) and a statement that informed consent was obtained.
3. Dated and signed notes for each study patient follow up call.
4. Description of device implantation.
5. Adverse event reporting and follow-up of the adverse events (minimal event description, severity, onset date, duration, relation to study device, outcome and treatment for adverse event).
6. Notes regarding study specified concomitant medications taken during the study (including start and stop dates).
7. Patient's condition upon completion of or withdrawal from the study.

12.3 Selection and Monitoring of Clinical Sites and Operators

In the selection of study investigators, the sponsor requires each investigator to have adequate experience with investigational devices, demonstrate commitment to patient safety and consistency in adherence to the study protocol and its amendments (if applicable).

Monitoring will be conducted by the Sponsor and/or designee. These responsibilities include collecting and tracking data forms and instituting quality control measures for data entry

verification and study compliance. The study will be monitored according to the monitoring plan in order to ensure that applicable regulations are followed.

12.3.1 Initiation and Monitoring of Clinical Sites

Prior to patient enrollment, a study initiation visit (SIV) will be conducted at the investigational site to ensure the following: EC/Competent Authority (CA) approval has been obtained and documented, all essential documentation is in place, the investigators and study personnel are appropriately trained and clearly understand the study and the investigators and study personnel accept the obligations incurred in undertaking this clinical investigation. After the SIV, a site activation checklist will need to be signed off which gives the green light for the device shipment to the site.

Periodic monitoring visits will be made at the study site throughout the clinical study and in accordance with the monitoring plan, to assure that all investigators conduct the study in compliance with the protocol, the Investigators' agreements and all applicable regulations and guidelines. These visits will further assure that the facilities are still acceptable, the EC/CA has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to the Sponsor and the EC/CA, device and device inventory are controlled. The clinical sites will be monitored to ensure the completed eCRFs match the medical records, and resolve any differences.

Each study site will be evaluated for meeting enrolment commitments and for the accurate and timely submission of data forms and films (endpoint reporting).

Biosensors will retain the right to remove either the investigator or the investigational site from the study for issues of non-compliance with the protocol or regulatory requirements.

Significant new information will be reviewed, including unanticipated adverse events and ensure that such information is provided to the appropriate regulatory authorities, the investigators and to all reviewing EC/CA.

12.3.2 Device Accountability

All study stents supplied to sites will be accounted for and managed via the eCRF system and will be accounted for from the time of distribution from the Sponsor until patient implantation or return to the Sponsor. Stent-specific identifiers for each implanted stent will be entered into eCRF system after implantation in order to ensure immediate traceability. All expired and unused stents will be returned to Biosensors distribution center for reconciliation and matched against stents sent for reconciliation. All shipment details and device accountability procedures are outlined in the device management plan.

12.3.3 Core Laboratory

A core laboratory will be used to perform quantitative coronary angiography (QCA) on the 9 month follow-up angiograms and on endpoints requiring a re-PCI. The latter will happen prior to sending the baseline and second angiogram to the CEC members for adjudication of the endpoint.

13. RESPONSIBILITIES

13.1 Investigator Responsibility for Study Conduct

Study investigators will ensure that all work and services they provide will be conducted in compliance with the standards of good clinical and research practice.

The investigators will ensure that the study is conducted in compliance with the CIP and the Investigator's Agreement. The Investigators will be responsible for the day to day conduct of the clinical investigation as well as for the safety and well-being of the patients involved in the study.

The Investigators will have the resources to conduct the clinical investigation properly and obtain from the sponsor information which he judges essential about the device and be familiar with this information.

Access to the eCRF system to be completed for all enrolled patients into the study will be provided to the Investigator. Completion of the eCRFs should be accurate and must record patient's data collected during the study according to ISO 14155:2011 standard and Good Clinical Practices (GCP) recommendations. It is the responsibility of the Investigator to ensure the quality of the data collected and recorded.

The investigators will maintain study records for a minimum of 15 years after study termination or premature termination of the study. The patient's identity shall not be released to third parties without the patient's prior consent. All information and data concerning patients or their participation in this study will be considered confidential. Only authorized personnel will have access to this confidential information. All data used in the analysis and reporting of this evaluation will be without identifiable reference to individual patients.

The site Principal Investigator is responsible for providing the current study protocol to all co-investigators and other staff responsible for study conduct, as well as provide for the training of all co-investigators or other staff involved in the conduct of this research. In addition, investigators will ensure that any source documents that are sent out of the hospital for any reason are anonymized before being sent for adjudication.

13.1.1 Source Documentation Requirements

Regulations require that investigators maintain information in the study patient's medical records which corroborate data collected on the electronic case report forms (eCRF). In order to comply with these regulatory requirements, the following information will be maintained and made available as required by the sponsor and its monitors and/or regulatory inspectors:

1. Medical history/physical condition of the study patient before involvement in the study sufficient to verify protocol entry criteria.

2. Dated and signed notes in the patient's medical record on the day of enrolment into the study that identify: the patient's date of entry into the study, the study sponsor (Biosensors) and a statement that informed consent was obtained.

3. Dated and signed notes for each study patient visit with reference to the eCRFs for further information, if appropriate (for specific results of procedures and exams).

4. Description of device implantation.

5. Notations on abnormal lab results and their resolution.

6. Dated printouts or reports of special assessments, i.e. ECG reports.

7. Adverse event reporting and follow-up of the adverse events (minimal event description, severity, onset date, duration, relation to study device, outcome and treatment for adverse event).

8. Notes regarding study specified concomitant medications taken during the study (including start and stop dates).

9. Study patient's condition upon completion of or withdrawal from the study.

13.2 Reporting

Upon completion of the study, Biosensors and/or designee will draft a final written report. Interim reports will also be drafted, as required, and submitted to the appropriate regulatory agency(ies).

14. PUBLICATION POLICY and STEERING COMMITTEE

14.1 Publication policy

Biosensors acknowledges that the Institution and/or Investigator may have a legitimate interest to publish relevant parts of the Study Information. If the Institution and/or Investigator wants to publish such study information in appropriate scientific journals or other professional publications or present such information at scientific conferences/symposia, they may do so patient to the following conditions: (a) only if the publication is consistent with the rules and conventions governing clinical studies and regulatory submissions in all relevant jurisdictions, and only if drafts of the material have been reviewed by Biosensors and the Steering Committee; (b) Institutional data, sub-analysis or any other experience in the study may not be published until the multi-center collective results of primary endpoints at 1 year follow-up, as a whole, are published. The results of the study will have no bearing on the submission of the manuscript for publication. This publication of the primary endpoints will be submitted to a peer-reviewed journal within six (6) months of the outcome of all of the primary measures being met (i.e. within six months of all patients having completed one-year follow-up.) In the event that the study is terminated early, manuscript submission will occur within 90 days of study termination; (c) the Investigator and/or the Institution shall deliver the material intended for publication to Biosensors at least sixty (60) days prior to the first intended submission for publication. Biosensors will review and respond with its comments, if any, within (30) days of receipt of such copy. If Biosensors believes that any proposed publication contains any Confidential Information of Biosensors, then Biosensors shall so notify the Institution and the Investigator, and the Institution and Investigator shall delete such Confidential Information. In no event will any Confidential Information of Biosensors be released in any manuscript or public release concerning Study data or results without Biosensors' prior written approval. If Biosensors believes that any proposed publication contains any information relating to patentable items, the disclosure of such proposed publication to any third party shall be delayed for an additional sixty (60) days to permit the filing of a patent application. Should Biosensors request such a delay, then upon the written request of the Institution and Investigator, Biosensors shall use its best efforts consistent with reasonable business and scientific practice to do all things which it believes would expedite the filing of such patent application. Biosensors retains the right of final review prior to publication. In all publications, credit shall be given to Biosensors for its sponsorship of the Study and the supply of the Device under the Study. Any deviation of the publication policy by the Institution and/or the Investigator will be considered as a material breach of the Clinical Study Agreement and Biosensors reserves the right to terminate the Agreement accordingly and reserves any remedy that may be allowed by law.

14.2 Steering Committee

The Steering Committee (SC) membership will include, but not limited to, the coordinating investigator, principal investigator (PI) from each country, Biosensors medical director, Biosensors bio-statistician and the Biosensors Clinical Project Manager. The role of the SC is to provide overall supervision of the study. The SC plus a representative of the Biosensor regulatory, clinical and quality assurance departments will review and input into the study protocol and any protocol amendments and provide advice to the investigators on all aspects of the study. The SC will be responsible for the management of the study. This committee will meet periodically by teleconference (TC) or in person to monitor the progress of the study, including patient enrollment, clinical site progress and protocol compliance. This committee will be responsible

for reviewing the final results, determining the methods of presentation and publication, and the selection of secondary projects and publications.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Role of the Study Sponsor

As the study sponsor, Biosensors has the overall responsibility for the conduct of the study, including assurance that the study meets and is conducted within the regulatory requirements specified by the reviewing regulatory authority. This study will be conducted according to the International Conference of Harmonization (ICH) and GCP, appropriate country medical device laws and in accordance with ISO 14155: 2011 and the Declaration of Helsinki.

In this study, Biosensors will have certain direct responsibilities and will delegate other responsibilities to other designees. Biosensors and/or designee will ensure adherence to the sponsor general duties, selection of investigators, monitoring, supplemental applications, maintaining records, and submitting reports.

15.2 Patient Confidentiality

Patient confidentiality will be maintained throughout the clinical study. No personal data will be collected in the EDC and patients are identified by a unique patient identification code (site ID – patient ID). If data are missing, the study site can get in touch with patients using their code list as a link.

Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidential and that the patient's privacy is guaranteed. Patient data should only be accessible to authorized personnel at the site and to the Sponsor's representatives.

15.3 Selection of Investigators

Qualified investigators and their sites will be selected based on previous performance in Biosensors studies, experience running clinical studies, having an established clinical study team and having the time and capacity to perform the study. Sites must have a signed study agreement in place prior to being provided the information necessary to conduct the study.

15.4 Training Requirements

Investigators and relevant staff will be trained on the following elements prior to enrollment of the first patient at a site:

- Clinical Investigational Plan (CIP)
- Electronic data capturing system
- Informed consent procedure
- Study documentation and administration
- Investigator and sponsor responsibilities
- Role of the EC and regulatory authority
- Adverse Event reporting procedures
- Protocol deviation reporting procedures
- Monitoring requirements and expectations
- Applicable regulatory requirements

Training will be done on an individual basis during a site visit before the first enrollment at each participating center. Additional training may be provided as needed. A training log will be used to document that training has been done. This will be filed in the site binder. When a new member

joins the study site staff, the investigator/delegate or Clinical Research Organization (CRO) will provide the appropriate training prior to their performing any study related activity.

15.5 Study Management

The Sponsor of the study, Biosensors, designates responsibility for the overall study management to the CRO called KCRI. The general duties of the CRO consist of submitting the application to appropriate regulatory authorities, obtaining regulatory and EC approvals, selecting investigators together with the Sponsor, ensuring proper clinical site monitoring and ensuring that the investigator has obtained proper informed consent from the patients.

15.5.1 Device Supply

The Biosensors study manager or designated representative is responsible for supplying the device materials before study start at each center in accordance with the device management plan.

15.5.2 Supplemental Applications

Biosensors and/or designee, will submit changes in the protocol to the appropriate regulatory authorities and investigators to obtain EC/CA re-approval.

15.5.3 Maintaining Records

Biosensors and/or designee will maintain copies of correspondence, data, shipment of devices, adverse device effects and other records related to the clinical study. Biosensors or its designees will maintain records related to the signed Investigator Agreements.

15.5.4 Submitting Reports

Biosensors and/or designee will submit reports required by the reviewing regulatory authority. This includes unanticipated serious adverse device effects, withdrawal of EC or regulatory approval, current investigators list, annual progress reports, recall information and final reports.

15.5.5 Site Record Retention Policy

The core laboratory as well as clinical sites will maintain study records until the sponsor notifies them and the reviewing regulatory authorities are notified that research is completed/terminated under the clinical investigation in compliance with national law. All study data will be archived for a minimum of 15 years after study termination or premature termination of the study.

15.5.6 Informed Consent

All patients must provide written informed consent in accordance with local regulations. Biosensors in collaboration with KCRI will create, review and approve a master consent form prior to submission to the EC. The site must provide KCRI with a copy of the study site's EC approval letter and the approved consent document should a change from the master have been made. Approvals for the continuation of the study must be kept current and notification forwarded to KCRI.

15.6.7 Protocol Deviations

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the patient requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator).

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee should contact Biosensors or KCRI at the earliest possible time by telephone. All deviations will be reported in the eCRF and reviewed by the clinical study manager on a regular basis as outlined below.

The patient must continue to be followed up for safety as described in section 10. The decision regarding the patient's continuation in the study lies with the investigator. The EC will be informed of all protocol changes by the investigator in accordance with the EC established procedure.

All deviations must be reported to the clinical project manager, regardless of whether medically justifiable, pre-approved, when possible, by Biosensors, or taken to protect the patient in an emergency. In addition, the investigator is required to adhere to the EC procedures for reporting deviations.

Deviations include, but are not limited to the following list:

- Failure to obtain informed consent prior to conducting study specific activities
- Inclusion/exclusion criteria not met
- Non-study stents are implanted at the index or staged procedure
- Study stent implanted not in accordance with the randomization procedure
- Incorrect version of the PIC used
- Patient could not be reached for a follow-up visit or follow-up visit was outside window
- Adverse Events not reported by investigators in the required timeframe as specified in the protocol
- Source data permanently lost

Site compliance with regard to deviations will be reviewed and analysed by the clinical study manager on a regular basis and corrective and preventative actions will be put in place accordingly. In addition, all deviations from the protocol will be documented in the final report.

15.6.8 Protocol Amendments

Biosensors will inform the investigator about any relevant changes in the protocol. They will be documented as an amendment to the protocol which will be signed by each investigator. No changes can be implemented by the investigator before a fully approved amendment is available. If applicable, due to the nature of the amendment, and in accordance with local regulations, EC and CA notification and/or approval is also required before the amendment is implemented. Only amendments that are required for patient safety may be implemented prior to EC approval.

16. REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and stroke statistics—2012 update: a report from the AHA. Circulation. 2012 Jan 3;125(1):188-97.
2. Pendyala L, Jabara R, Robinson K, Chronos N. Passive and active polymer coatings for intracoronary stents: novel devices to promote arterial healing. J Interv Cardiol. 2009 Feb;22(1):37-48. Review.
3. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–1323.
4. Stone GW, Ellis SG, Cannon L, et al. Comparison of a polymer based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: A randomized controlled trial. JAMA 2005;294:1215–1223
5. Schomig A, Dibra A, Windecker S, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. J Am Coll Cardiol 2007; 50: 1373–80.
6. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004; 364: 1519–21.
7. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007; 369: 667–78.
8. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008; 52: 333–42.
9. Stone GW, Midei M, Newman W, et al, for the SPIRIT III Investigators. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease. JAMA 2008; 299: 1903–13.
10. Pinto TL, Waksman R. Overview of the 2007 Food and Drug Administration Circulatory System Devices Panel Meeting on the Endeavor zotarolimuseluting coronary stent. Circulation 2007; 117: 1603–08.
11. Grube E, Buellesfeld L. BioMatrix biolimus A9-eluting coronary stent: a next generation drug-eluting stent for coronary artery disease. Expert Rev Med Devices 2006; 3: 731–41.
12. 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;373:2038-47.

13. Garot P, Morice MC, Garot P, Morice MC, Tresukosol D, et al. Two-Year Outcomes of High Bleeding Risk Patients after Polymer-Free Drug-Coated Stents. JACC 2017 Jan 17;69(2):162-171

14. Cook S, Ladich E, Nakazawa G, et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. Circulation 2009;120:391-9.

15. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773-80.

16. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221-31.

17. 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;372:1163-73.

18. Serruys PW; Farooq V; Kalesa 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 Limus Eluted From A Durable Versus ERodabale Stent Coating (LEADERS) randomised, non-inferiority trial. JACC, Volume 62, Issue 3, 2013, pp. 181-190

19. Baber U, Mehran R, Sharma SK, et al. Impact of the everolimus-eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials. J Am Coll Cardiol 2011;58:1569-77.

20. 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;378:1940-8

21. Costa R, 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 VOL. 9, NO. 1, 2016

22. Räber L, Kelbæk H, Ostoijc M, et al; COMFORTABLE AMI Trial Investigators. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on

cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. JAMA. 2012 Aug 22;308(8):777-87

23. STEALTH FIM: Greenhalgh J, Hockenhull J, Rao N, Dundar Y, Dickson RC, Bagust A. Drug-eluting stents versus bare metal stents for angina or acute coronary syndromes. Cochrane Database Syst Rev. 2010 May 12;(5):CD004587.
24. STEALTH FIM: Grube E, Hauptmann Ke et al, Six-month results of a randomized study to evaluate safety and efficacy of a Biolimus A9™ eluting stent with a biodegradable polymer coating. EuroIntervention - Volume 1 - Number 1 - May 2005 - page 53 to 57
25. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47
26. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. European heart journal 2012;33:2551-67.
27. Mabin TA, Holmes DR, Jr., Smith HC, et al. Intracoronary thrombus: role in coronary occlusion complicating percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1985;5:198-202.
28. Capone GT, Meyer BB, Wolf NM, Meister SG. Incidence of intracoronary thrombi in patients with active unstable angina pectoris. Circulation 1984;70 (suppl II):II-415.
29. Ellis SG, Vandormael MG, Cowley MJ, et al. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease. Implications for patient selection. Multivessel Angioplasty Prognosis Study Group. Circulation 1990;82:1193-202

APPENDIX I. DEFINITIONS

ABRUPT CLOSURE

Abrupt Closure. Defined as the occurrence of new (during the index procedure) severely reduced flow (TIMI grade 0-2) within the target vessel that persisted and required rescue by stenting or other treatment, or resulted in myocardial infarction or death. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus, or severe spasm. Abrupt closure does not connote "no reflow" (due to microvascular flow limitation), in which the epicardial artery is patent but had reduced flow. Abrupt closure also does not connote transient closure with reduced flow in which the index treatment application does reverse the closure.

Threatened Abrupt Closure. Defined as a grade B dissection and ≥ 50% diameter stenosis or any dissection of grade C or higher.

BINARY ANGIOGRAPHIC RESTENOSIS

Defined as >50% in-stent diameter stenosis at the follow-up angiogram. If an in-stent measurement is not available, the in-lesion diameter will be used.

BLEEDING COMPLICATIONS (AS PER BARC DEFINTIONS)

Bleeding Academic Research Consortium Definition for bleeding[25]

Type 0 no bleeding

Type 1 bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2 any overt, actionable sign of hemorrhage (e.g. More bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4 or 5 but does meet at least one of the following criteria:

4) requiring nonsurgical, medical intervention by a healthcare professional,
5) leading to hospitalization or increased level of care, or
6) prompting evaluation.

Type 3a

- overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin a drop is related to bleed
- any transfusion with overt bleeding

Type 3b

- overt bleeding plus hemoglobin drop≥ 5 g/dl (provided hemoglobin drop is related to bleed)
- cardiac tamponade
- bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
- bleeding requiring intravenous vasoactive agents

Type 3c

- intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
- subcategories confirmed by autopsy or imaging or lumbar puncture
- intraocular bleed compromising vision

Type 4

- perioperative intracranial bleeding within 48 h
- reoperation after closure of sternotomy for the purpose of controlling bleeding

CABG related	• transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period • chest tube output ≥2L within a 24-h period
Type 5	• fatal bleeding
Type 5a	• probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b	• definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood =1g/dL hemoglobin).

CLINICALLY DRIVEN

Stenosis >70% (by QCA), or stenosis >50% + ischemic symptoms, or stenosis >50% + positive Fractional Flow Reserve (FFR) measurement

DEATH

Death is divided into 2 categories:

- Cardiac death is defined as death due to any of the following:
- Acute myocardial infarction.
- Cardiac perforation/pericardial tamponade.
- Arrhythmia or conduction abnormality.
- Stroke within 30 days of the procedure or stroke suspected of being related to the procedure.
- Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery.
- Any death in which a cardiac cause cannot be excluded.

Non-cardiac death is defined as a death not due to cardiac causes (as defined above).

DEVICE SUCCESS

The attainment of < 20% residual stenosis by visual assessment AND either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, using the assigned device only.

DISSECTION, NHLBI (National Heart, Lung, and Blood Institute) CLASSIFICATION

Type A	Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.
Type B	Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles.
Type C	Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material.

Type D Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow.

Type E Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen.

Type F Filling defect accompanied by total coronary occlusion.

DISTAL EMBOLIZATION

Defined as a new abrupt cut off of contrast column or filling defect distal to the treated lesion.

EMERGENT BYPASS SURGERY

Defined as coronary bypass surgery performed on an urgent or emergent basis for severe vessel **dissection or closure, or treatment failure resulting in new ischemia.**

LESION CLASS (AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION CLASS)

Type A Lesions: Minimally complex, discrete (length <10 mm), concentric, readily accessible, non-angulated segment (<45°), smooth contour, little or no calcification, less than totally occlusive, not ostial in location, no major side branch involvement, and an absence of thrombus.

Type B Lesions: Moderately complex, tubular (length 10 to 20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (>45°, <90°), irregular contour, moderate or heavy calcification, total occlusions <3 months old, ostial in location, bifurcation lesions requiring double guidewires, and some thrombus present.

Type B1: One adverse characteristic

Type B2: Two or more adverse characteristics

Type C Lesions: Severely complex, diffuse (length >2 cm), excessive tortuosity of proximal segment, extremely angulated segments >90°, total occlusions >3 months old and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions.

LESION SUCCESS

The attainment of < 20% residual stenosis by visual estimate AND either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, using any percutaneous method.

MYOCARDIAL INFARCTION

Criteria for acute myocardial infarction[26]

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
- Symptoms of ischaemia.

- New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
- Development of pathological Q waves in the ECG.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Table 5. Classification of myocardial infarction

Type 1: Spontaneous myocardial infarction
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.
Type 2: Secondary myocardial infarction
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.
Type 3: Myocardial infarction related to sudden cardiac death
Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)
Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (≤99thpercentile URL) or a

rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
Type 4b: Myocardial infarction related to stent thrombosis
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.
Type 4c: Myocardial infarction related to restenosis
Myocardial infarction associated with restenosis is arbitrarily defined as ≥50% stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of cTn values >99th percentile URL and no other significant obstructive CAD of greater severity following: (i) initially successful stent deployment or (ii) dilatation of a coronary artery stenosis with balloon angioplasty (<50%).
Type 5: Myocardial infarction related to coronary artery bypass graft surgery (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a prior MI.

NO REFLOW

Defined as a sustained or transient reduction in antegrade flow that is not associated with an obstructive lesion at the treatment site.

PERCUTANEOUS CORONARY INTERVENTION (PCI) PROCEDURE

A PCI procedure will be considered to have commenced at the time the guidewire crosses the first lesion to be treated.

PERFORATION

Perforations will be classified as follows:

Angiographic perforation: perforation detected by the clinical site or the core laboratory at any point during the procedure.

Clinical perforation: perforation requiring additional treatment (including efforts to seal the perforation or pericardial drainage), or resulting in significant pericardial effusion, abrupt closure, myocardial infarction, or death.

Pericardial hemorrhage/tamponade: perforation resulting in cardiac tamponade.

PROCEDURE SUCCESS

The attainment of < 20% residual stenosis by visual estimate AND either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, using any percutaneous method without the occurrence of death, MI, or repeat revascularization of the target vessel during the hospital stay.

PROTOCOL DEVIATION

An incident where the investigator or site personnel did not conduct the study according to the investigational plan, protocol or the investigator agreement.

Major deviation:

Any deviation from patient inclusion and exclusion criteria or patient informed consent procedures.

- Failure to obtain informed consent prior to conducting study specific activities
- Inclusion/exclusion criteria not met
- Non-study stents are implanted at the index or staged procedure
- Study stent implanted not in accordance with the randomization procedure
- Incorrect version of the PIC used
- Adverse Events not reported by investigators in the required timeframe as specified in the protocol
- Source data permanently lost

Minor deviation:

Deviation from a protocol requirement such as incomplete/inadequate patient testing procedures, follow-ups performed outside specified time windows, etc.

REFERENCE VESSEL DIAMETER (RVD)

Defined as the average diameter of normal segments within 10 mm proximal and distal to the target lesion from 2 orthogonal views by visual estimate.

STENT THROMBOSIS (ARC definition)

Stent Thrombosis should be reported as a cumulative value over time and at the various individual time points as specified below. ***Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the Cath lab.***

Type	Timing
Acute stent thrombosis (*):	0 – 24 hours post stent implantation
Subacute stent thrombosis (*):	> 24 hours – 30 days post stent implantation
Late stent thrombosis (**):	> 30 days – 1 year post stent implantation
Very late stent thrombosis (**):	> 1 year post stent implantation

(*) Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 – 30 days) will be used in the remainder of this document.

(**) including ‘primary’ as well as ‘secondary’ late stent thrombosis; ‘secondary’ late stent thrombosis is a stent thrombosis after a target segment revascularization.

We recognize three categories of evidence in defining stent thrombosis.

Definite stent thrombosis:	
Definite stent thrombosis is considered to have occurred by either a. angiographic or b. pathologic confirmation.	
c. Angiographic confirmation of stent thrombosis:	Thrombolysis In Myocardial Infarction (TIMI) flow is: c) TIMI flow grade 0 with occlusion originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of a thrombus (*). d) TIMI flow grade 1, 2, or 3 with occlusion originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of a thrombus (*). **AND** at least one of the following criteria has been fulfilled within a 48-hours-time window: 14. New acute onset of ischemic symptoms at rest (typical chest pain with duration >20 minutes) 15. New ischemic ECG changes suggestive of acute ischemia 16. Typical rise and fall in cardiac biomarkers (refer to definition non-procedural related MI).
Comment: the incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion). (*) Intracoronary thrombus[27-29] **Non-occlusive thrombus:** Intracoronary thrombus is defined as a (spheric, ovoid or irregular) non-calcified filling defect or lucency surrounded by contrast material (on three sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream. **Occlusive thrombus:** A TIMI 0 or TIMI 1 intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originating from the side branch).	
d. Pathologic confirmation of stent thrombosis	Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.
Probable stent thrombosis:	
Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases: **Any unexplained death within the first 30 days.** Irrespective of the time after the index procedure any MI, which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.	

Possible stent thrombosis:
Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow-up.

STROKE
Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.

TARGET SITE
Defined as the stented site plus 5mm on either side of the stent margins.

TARGET LESION (TL)
The target lesion is the treated lesion starting 5 mm proximal of the stented lesion and to end 5 mm distal of the stented lesion.

TARGET VESSEL (TV)
The TV is defined as the index coronary artery which was in physical contact with any component (guiding catheter, guide wire, balloon catheter, etc.) of the angioplasty hardware during the initial procedure.

TARGET LESION FAILURE (TLF)
Cardiac death, target-vessel myocardial infarction, or ischemia-driven target-lesion revascularization.

TARGET LESION REVASCULARIZATION (TLR)
Defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel.

Clinically-driven revascularizations are those in which the patient has a positive functional study, ischemic ECG changes at rest in a distribution consistent with the target vessel, or ischemic symptoms. Revascularization of a target lesion with an in-lesion diameter stenosis ≥70% (by QCA) in the absence of the above-mentioned ischemic signs or symptoms is also considered clinically-driven. In the absence of QCA data for relevant follow-up angiograms, the clinical need for revascularization is adjudicated using the presence or absence of ischemic signs and symptoms.

Non-clinically driven repeat target lesion revascularizations are those in which the patient undergoes a non-emergent revascularization for a diameter stenosis <50% (by QCA). Non-emergent repeat target lesion revascularization for a diameter stenosis <70% (by QCA) in patients without either a positive functional study or angina are also considered non-clinically driven defined as any repeat revascularization of the target site whether by PCI or bypass surgery.

TARGET VESSEL REVASCULARIZATION (TVR)
Any target vessel revascularization, death, or MI attributed to the target vessel.

TIMI CLASSIFICATION

TIMI 0	No perfusion.
TIMI 1	Penetration with minimal perfusion. Contrast fails to opacify the entire bed distal to the stenosis for the duration of the cine run.

TIMI 2	Partial perfusion. Contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in the coronary bed distal to the obstruction than in comparable areas not perfused by the dilated vessel.
TIMI 3	Complete perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds.

URGENT TARGET LESION REVASCULARIZATION (UTLR)

Defined as any target lesion revascularization (PCI or CABG) done within 48 hours after hospital admission for symptomatic in-stent restenosis or stent thrombosis associated with new resting ECG changes and/or a rise of biomarkers (CK-MB or troponin) [cutoff according to the Third universal definition[1]]. The event is measured in time relation to the time of hospitalization, not the time post-index procedure

APPENDIX II. DECLARATION OF HELSINKI

World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Patients

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, SomersetWest, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly,Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human patients, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human patients to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience
are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human patients.

6. The primary purpose of medical research involving human patients is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions(methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is patient to ethical standards that promote and ensure respect for all human patients and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research patients.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research patients. The responsibility for the protection of research patients must always rest with the physician or other health care professionals and never with the research patients, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human patients in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research patients set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human patients must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research patients.

15. Appropriate compensation and treatment for patients who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human patients may only be conducted if the importance of the objective outweighs the risks and burdens to the research patients.

17. All medical research involving human patients must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison

with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human patients unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result
from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human patients must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human patients must be clearly described and justified in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for patients and information regarding provisions for treating and/or compensating patients who are harmed as a consequence of participation in the research study. In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research patients set forth in this Declaration. The committee must have the right to monitor ongoing studies.

The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research patients and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as patients in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human patients capable of giving informed consent, each potential patient must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential patient must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential patients as well as to the methods used to deliver the information. After ensuring that the potential patient has understood the information, the physician or another appropriately qualified individual must then seek the potential patient's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed. All medical research patients should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential patient is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research patient who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential patient, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research patient who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential patient's dissent should be respected.

30. Research involving patients who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving patients with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the patient or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to with draw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be

impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an interventionAnd the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be patient to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial
in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human patients must be registered in a publicly accessible database before recruitment of the first patient.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human patients and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available.
Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX III. LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Association
ARC	Academic Research Consortium
ASADE	Anticipated Serious Adverse Device Effect
BARC	Bleeding Academic Research Consortium
BMS	Bare Metal Stent
BA9™	Biolimus A9™
CA	Competent Authority
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CEC	Clinical Events Committee
CK	Creatinine Kinase
CoCr	Cobalt Chromium
CRO	Clinical Research Organization
CIP	Clinical Investigation Plan
cTn	Cardiac Troponin
DAPT	Dual Anti-Platelet Therapy
DCS	Drug Coated Stent
DD	Device Deficiency
DES	Drug Eluting Stents
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESC/EACTS	European Society of Cardiology /European Association for Cardio-Thoracic Surgery
FFR	Fractional Flow Reserve
FUP	Follow up
GCP	Good Clinical Practices
Hgb	Hemoglobin
ICH	International Conference of Harmonization
ID	Identification
IFU	Instructions for Use
iFR	Instantaneous Free-wave Ratio
ITT	Intent to Treat
IVUS	Intravascular Ultrasound
LBBB	Left Bundle Branch Block
LLS	Late Lumen Loss
MACE	Major Adverse Cardiac Events
MI	Myocardial Infarction

NHLBI	National Heart, Lung, and Blood Institute
NOAC	New Oral Anticoagulant
N-STEMI	Non-ST-Elevation Myocardial Infarct
NSTE-ACS	Non-ST Elevation Acute Coronary Syndrome
OCT	Optical Coherence Tomography
PD	Protocol Deviations
PCI	Percutaneous coronary intervention
PIC	Patient informed consent
PLT	Platelet Count
PTCA	Percutaneous Transluminal Coronary Angioplasty
QCA	Quantitative Coronary Angiography
RVD	Reference Vessel Diameter
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SCAI	Society for Cardiac Angiography and Interventions
SD	Source Data
STEMI	ST-elevation myocardial infarct
ST	Stent thrombosis
TC	Teleconference
TL	Target Lesion
TLF	Target Lesion Failure
TIMI	Thrombolysis In Myocardial Infarction
TLR	Target lesion Revascularization
TV	Target Vessel
TVR	Target Vessel Revascularization
URL	Upper Reference Limit
USADE	Unanticipated Serious Adverse Device Effect
UTLR	Urgent Target Lesion Revascularization

Supplementary Appendix 11. CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	Supplem Appendix
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6,7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA

Sample size	7a	How sample size was determined	8,9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	8
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8,9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8,9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	11
	14b	Why the trial ended or was stopped	NA

Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	25,26
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	25,26
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	28
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	28
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	NA
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13,16
Other information			
Registration	23	Registration number and name of trial registry	5
Protocol	24	Where the full trial protocol can be accessed, if available	Supplem Appendix
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.