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First-in-human evaluation of the novel BioMime sirolimus-eluting coronary stent with bioabsorbable polymer for the treatment of single *de novo* lesions located in native coronary vessels - results from the meriT-1 trial

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KEYWORDS

- cobalt-chromium stent
- coronary artery disease
- drug-eluting stent
- quantitative coronary angiography
- sirolimus-eluting stent

Abstract

Aims: We report the initial human evaluation of the novel BioMime™ sirolimus-eluting stent (SES) (Meril Life Sciences Pvt. Ltd., Gujarat, India) with an ultra-thin stent platform (65 µm) and a biodegradable polymer for the treatment of *de novo* coronary lesions.

Methods and results: The meriT-1 trial was a prospective, non-randomised, single-arm, single-centre, first-in-human evaluation of the safety, feasibility and performance of the BioMime SES. Lesion criteria included non-occlusive stenosis ≤19 mm in length located in native coronary vessels. Clinical follow-up (FU) was performed at 1, 8 and 12 months; all patients were assigned for angiographic FU at eight months. A total of 30 patients (30 lesions) were enrolled between March 2009 and February 2010. Mean age was 49.9 years, 30% were diabetics, and 36.7% had previous myocardial infarction (MI). Baseline median [25%, 75% inter-quartile range] lesion length, reference diameter and % diameter stenosis were 15.51 mm [12.74, 20.27], 2.94 mm [2.71, 3.34], and 80.5% [67.0%, 90.7%], respectively. Overall, there was one stent implanted per lesion and procedural success was 100%. At eight-month angiographic FU (26/30), median in-stent late lumen loss was 0.15 mm [0.09, 0.33]; also, there were no cases of binary restenosis within the treated segment. Clinical FU at 12 months (100%) demonstrated absence of MACE (cardiac death, MI and target lesion revascularisation) and stent thrombosis (ST).

Conclusions: The novel BioMime SES demonstrated excellent performance in single coronary lesions including high procedural success and efficacy, as demonstrated by the relatively low late lumen loss (a surrogate of neointimal hyperplasia) at eight-month angiographic FU. Overall, there were no safety concerns in this preliminary evaluation including absence of MACE or ST up to 12 months.

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Introduction

The impact of strut thickness and cell design on neointimal hyperplasia (NIH) with bare metal stents (BMS) has previously been reported, given that metallic platforms with thinner struts and open cell design appeared to benefit from significant reductions in NIH as compared to platforms with thicker struts and closed cell design[1-4]. Drug-eluting stents (DES) have demonstrated marked efficacy in inhibiting NIH and restenosis, and therefore the need for target lesion revascularisation (TLR) compared to BMS[5,6]. However, the implications of strut thickness and cell design on DES have still to be determined as their efficacy relies on the ideal combination of key components including: metallic scaffold, drug carrier and antiproliferative agent, which are critical to achieve adequate drug delivery and release at the target site[7]. Importantly, despite the overall efficacy demonstrated by older-generation DES[5,6], persistent concerns regarding deliverability, effectiveness and especially long-term safety[8,9] have led to the development of new DES systems including low-profile platforms, drug carriers (durable or non-durable) with optimised biocompatibility, and potent antiproliferative drugs[10-15]. Our objective was to report the initial results of a novel DES technology incorporating an ultra-thin platform, a bioabsorbable polymer, and a potent pharmacological agent (sirolimus). It has been considered that such stent design could facilitate deliverability and deployment, especially in complex subsets, without compromising safety and efficacy.

Methods

TRIAL DESIGN AND PATIENT POPULATION

The meriT-1 trial was a prospective, non-randomised, single-arm, first-in-man clinical evaluation of the performance of the novel BioMime™ sirolimus-eluting stent (SES) (Meril Life Sciences Pvt. Ltd., Gujarat, India) in the treatment of non-complex coronary lesions. The objective was to provide preliminary safety, feasibility and efficacy evaluations of this new technology in humans with coronary artery disease treated at a single clinical institution (Lifecare Institute of Medical Sciences and Research, Ahmedabad, Gujarat, India). Key inclusion criteria were: patients >18 years of age; symptoms of stable or unstable angina, or silent ischaemia with a positive functional test for ischaemia; presence of single *de novo* lesion ≤19 mm in length (by visual estimation) located in native coronary vessel with reference diameter (RD) 2.5 to 3.5 mm (by visual estimation); diameter stenosis (DS) ≥50% and <100% (by visual estimation); TIMI flow ≥2; acceptable candidate for coronary bypass surgery; and agreement to undergo all protocol evaluations including angiographic FU. Key exclusion criteria were: acute myocardial infarction (MI) <72 hours; renal insufficiency with baseline serum creatinine >2.0 mg/dL; previous PCI <30 days to index procedure; left ventricular ejection fraction <30%; left main stem; moderate or severe calcium; severe tortuosity or angulation; thrombus; bifurcation with a side branch ≥2.0 mm; aorto-ostial location; total occlusion; in-stent restenosis; any clinical or non-clinical condition leading to non-compliance with dual antiplatelet therapy (DAPT) during study duration; and known illness or any serious clinical condition with life expectancy <2 years.

The study complied with the Declaration of Helsinki regarding investigation in humans, and was approved by the local ethics committee at the participating institution. All patients provided written informed consent prior to enrolment. The meriT-1 trial was registered at the National Institute of Medical Statistics, Indian Council of Medical Research (Clinical Trials Registry - India [CTRI]) at www.ctri.nic.in/Clinicaltrials: REFCTRI-2009000496, and at the United States National Institute of Health at www.clinicaltrials.gov: NCT01507519.

STUDY DEVICE

The BioMime SES is built on the CE mark-approved Nexgen™ L605 cobalt-chromium stent platform (Meril Life Sciences Pvt. Ltd., Gujarat, India), which combines ultra-thin struts (65 µm) with a unique hybrid cell design comprising a mix of open and closed cells in order to provide optimal radial strength (recoil <3%) without compromising flexibility **(Figure 1A)**. Additional stent specifications include: 6, 8 and 10 crown configurations; Y-connectors and S-links ensuring absence of longitudinal stent compression (or foreshortening); and metal-to-artery ratio ranging from 14% to 16%. The delivery system includes a 0.014" guidewire-compatible semi-compliant rapid exchange balloon catheter made of nylon material with a PTFE-

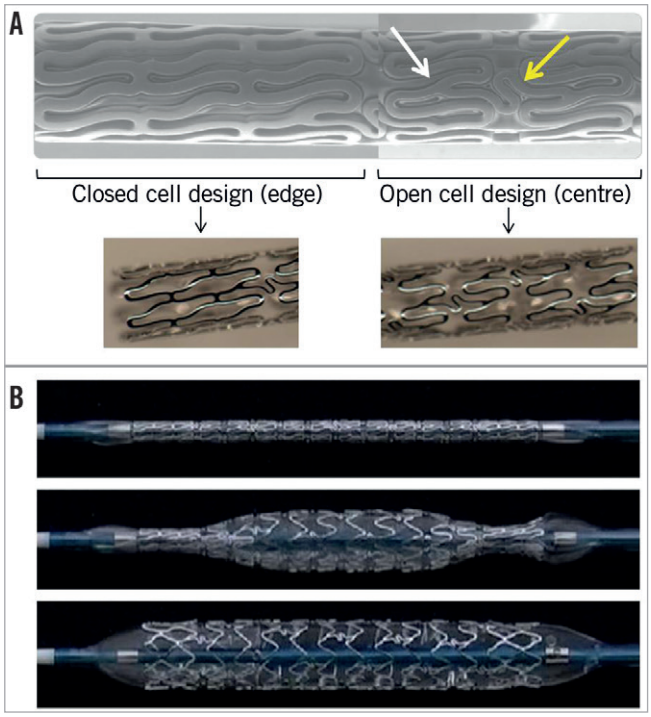

Figure 1. *A) Illustration of the BioMime SES design demonstrating its hybrid configuration including closed cell at edges and open cell in the middle (centre). Image on top shows crimped device (SEM image with 50x magnification) with Y-connectors (white arrow) and S-links (yellow arrow). B) Illustration of mediated stent expansion feature: crimped stent (top image); partial expansion starting in the centre portion (image in the middle) followed by full expansion extending to proximal and distal ends or edges (image at bottom). SEM: scanning electron microscope.*

(polytetrafluoroethylene) coated stainless steel hypotube shaft, which includes two radiopaque markers underneath the balloon that are used to delimit its working length. The balloon is designed with abrupt shoulders and minimal overhang (once crimped) to minimise balloon-related edge injury; also, it allows mediated stent expansion from middle (centre) to edges during deployment **(Figure 1B)**.

The drug-carrier component of the BioMime device consists of a proprietary co-polymer combination (BioPoly™) of biocompatible and bioabsorbable polymers: PLLA (poly-L-lactic acid) and PLGA (poly-lactic-co-glycolic acid). Overall, this co-polymer formulation provides uniformly thin coating (2 µm) which degrades in approximately 60 days after implantation (data on file at Meril Life Sciences Pvt. Ltd., Gujarat, India). The properties and mechanisms of action of sirolimus, the pharmacological agent used in BioMime, have previously been detailed elsewhere[16]. In brief, sirolimus exhibits potent immunosuppressive and anti-inflammatory properties, as well as potent suppression of vascular smooth muscle cell proliferation due to cell cycle arrest at the G_1-S interface. For the BioMime DES system, sirolimus is coated in a dosage of 1.25 µg per mm^2 of stent surface area, given that the total drug dose for a 3.0×19 mm stent would be approximately 121 µg.

PRECLINICAL STUDIES

The pharmacokinetics of the BioMime SES were assessed in a study using a rabbit iliac model performed at the CV Path Institute, Inc., Gaithersburg, MD, USA. In this analysis, 20 stents were implanted in bilateral iliac arteries in 10 animals, and results demonstrated that around 58% of the drug was released in the first three days, with an additional 30% of drug released by 14 days; at 28 days, nearly all the drug was released (data on file at Meril Life Sciences Pvt. Ltd., Gujarat, India) **(Figure 2)**. Furthermore, the histopathologic and histomorphometric evaluations comparing the BioMime SES vs. a control polymer-coated only stent vs. the Cypher™ SES (Cordis Corporation, Miami Lakes, FL, USA) in a porcine model were performed using a previously described methodology[17,18]. Overall, there were 48 stents implanted (BioMime 26; control polymeric 13; Cypher 9) in 27 animals. At 28 days, mean % diameter stenosis (DS) and neointimal thickness were: 19.4% vs. 25.8% vs. 20.6% (p=not significant [NS]), and 0.20 mm vs. 0.31 mm vs. 0.48 mm (p=NS), respectively; at 90 days, results were: 14.2% vs. 26.6% vs. 52.9% (p<0.05), and 0.22 mm vs. 0.42 mm vs. 0.92 mm (p=NS); for BioMime vs. control polymeric vs. Cypher, respectively. Regarding inflammation and injury scores, both BioMime and control polymeric devices showed positive and comparable results including low scores at 28 days (0.22 vs. 0.00, 0.09 vs. 0.23) and at 90 days (0.00 vs. 0.33, 0.17 vs. 0.44), respectively. Also, Cypher showed a higher deposit of fibrinogen at seven days, higher fibrin and necrosis scores at 28 days, and higher inflammation score at 90 days as compared to BioMime and control polymeric, given that such features were virtually absent in both BioMime and control polymeric. Lastly, mean endothelialisation scores with BioMime at days 7, 28 and 90 were 2.94, 3.0 and 2.96, respectively, suggesting near complete strut coverage at early FU (study performed at the Division of Animal Pathology, Division of Cardiology, University of Turin, Turin, Italy; data on file at Meril Life Sciences Pvt. Ltd., Gujarat, India).

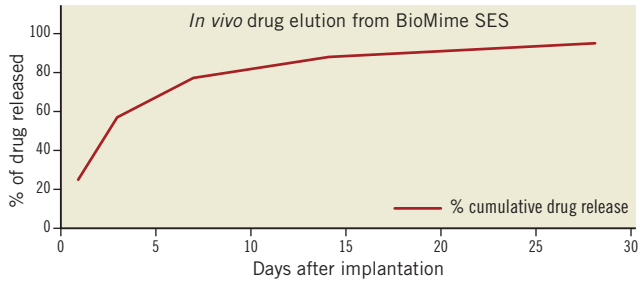

Figure 2. *Drug release kinetics of the BioMime SES system.*

PROCEDURE

PCI procedure was performed according to current standard guidelines[19]. Pre-treatment of the target lesion with any devices other than a regular balloon catheter used in angioplasty was not allowed, but direct stenting was allowed. For this study, the BioMime SES device was available in the following range of sizes: 13, 16, 19 and 24 mm in length for diameters of 2.5, 3.0 and 3.5 mm. Multi-stenting and multivessel procedures were not allowed; however, in case of a bail-out situation, a second study stent could be placed either proximally or distally overlapping with the primary stent. A routine 12-lead electrocardiogram was obtained before procedure, immediately post procedure, and 24 hours later. Blood sample laboratory analysis included CK and CK-MB before procedure (<24 hours), <24 hours after procedure, and daily thereafter until hospital discharge.

During procedure, intravenous heparin (70-100 units/Kg) was administered after sheath insertion to maintain an activated clotting time >250 seconds (or >200 seconds if glycoprotein IIb/IIIa inhibitors were used, at the operator's discretion). Regarding DAPT, aspirin 100-325 mg was given >24 hours prior to procedure if not already taken; for thienopyridine (clopidogrel), a loading dose of 300 mg was given >24 hours prior to procedure (or 600 mg at least two hours prior to procedure) if not already taken (75 mg daily). After the procedure, all patients received aspirin (100-325 mg) daily indefinitely and clopidogrel 75 mg was prescribed daily for at least six months.

ENDPOINTS AND CLINICAL FOLLOW-UP

The primary safety endpoint was the rate of major adverse cardiac events (MACE) at 30 days after procedure. The primary efficacy endpoint was in-stent late lumen loss (LLL) at angiographic FU at eight months. Secondary endpoints were MACE at all study time points up to 24 months and binary restenosis at eight-month angiographic FU. Other predefined endpoints included stent thrombosis (ST) up to 24 months and other quantitative coronary angiography (QCA) parameters at post-procedure and eight-month angiographic FU. MACE was defined as the composite endpoint of cardiac death, MI and ischaemia-driven TLR. Target vessel revascularisation (TVR) included any new revascularisation to the target vessel including TLR. By protocol, all deaths were considered cardiac unless a non-cardiac

cause could be clearly established by either clinical assessment or pathological study. MI was classified according to its type (Q-wave or non-Q-wave), and occurrence (periprocedural, spontaneous or post-CABG), following standard definitions as previously reported. ST was classified according to the definitions of the Academic Research Consortium[20]. Angiographic success was defined as residual stenosis <20% plus final TIMI flow 3 after PCI with the study device. Procedural success was defined as angiographic success plus absence of MACE during index hospitalisation.

Clinical FU was scheduled at 1, 8, 12 and 24 months. All patients were assigned for angiographic FU at eight months. Baseline, procedural and clinical FU data were collected by dedicated clinical research associates; data monitoring was performed physically at the participating clinical site. Data management was performed by an independent clinical research organisation (Integrity Health Services, Mumbai, India). In the current analysis, we report the procedural results, eight-month angiographic FU and 12-month clinical FU.

ANGIOGRAPHIC ANALYSIS

After intracoronary administration of nitroglycerine, serial angiographic studies were obtained in two orthogonal matching views pre- and post-procedure, and at eight-month FU. Angiographic analyses were performed off-line according to standard methodology for DES[13] by experienced operators at an independent angiographic core laboratory (Cardiovascular Research Center, São Paulo, Brazil), with a validated 2-D software for QCA analysis (QAngio XA version 7.2; Medis, Leiden, The Netherlands). The minimum lumen diameter (MLD) and the mean reference diameter (RD), obtained from averaging 5 mm segments proximal and distal to the target lesion location, were used to calculate the diameter stenosis (DS=[1–MLD/RD]x100). Acute gain was the change in MLD from baseline to post-stent implantation; late lumen loss (LLL) was the change in MLD from the post-stent implantation angiogram to FU. Overall, QCA measurements were reported as "in-stent" within the stented segment, and "in-segment", spanning the stented segment plus the 5 mm proximal and distal peri-stent areas.

STATISTICAL ANALYSIS

Categorical data were presented as frequencies (percentages of the total). Data sets with continuous variables were tested for normal distribution with the Shapiro-Wilk normality test. In case of normal distribution, data were presented as mean values±standard deviation (SD); when non-normal distribution was evidenced data were presented as median values with interquartile range [25%, 75%].

Results

A total of 30 patients were enrolled between March 2009 and February 2010. Mean age was 49.9 years, 30% were diabetics (non-insulin-dependent only), and 36.7% (11/30) had previous MI (eight of 11 asymptomatic post-recent MI <30 days) **(Table 1)**. LAD was the most prevalent target vessel, and the majority of lesions had moderate complexity **(Table 2)**. Procedural outcomes are depicted in **Table 3**. Radial access was used in approximately 1/3 of cases; the majority of lesions were predilated (90%); there was only one stent implanted per lesion; and angiographic success was 100%. In addition, there were no adverse events during index hospitalisation (procedural success 100%).

Baseline and final QCA are presented in **Table 4**. Median lesion length, RD and % DS pre-procedure were 15.51 mm, 2.94 mm, and

Table 1. Baseline clinical demographics.

Variable	N=30
Age (years)	49.9±7.7
Female gender (%)	17.7 (5/30)
Diabetes mellitus (%)	30.0 (9/30)
Hypertension (%)	56.7 (17/30)
Dyslipidaemia (%)	30.0 (9/30)
Smoking (current) (%)	23.3 (7/30)
Prior MI (≥30 days) (%)	10.0 (3/30)
Prior PCI (%)	3.3 (1/30)
Prior CABG (%)	3.3 (1/30)
Renal insufficiency* (%)	3.3 (1/30)
Clinical presentation (%)	
Silent ischaemia	30.0 (9/30)
Stable angina	13.3 (4/30)
Unstable angina	30.0 (9/30)
Recent MI (<30 days)¶	26.7 (8/30)

*Defined as baseline serum creatinine >2.0 mg/dL. ¶Asymptomatic post-recent MI. ACS: acute coronary syndrome; CABG: coronary artery bypass graft surgery; MI: myocardial infarction; PCI: percutaneous coronary intervention

Table 2. Angiographic data.

Variable		N=30
Target coronary vessel (%)	LAD	40.0 (12/30)
	LCx	23.3 (7/30)
	RCA	36.7 (11/30)
Lesion location (%)	ostial	3.3 (1/30)
	proximal	40.0 (12/30)
	mid	50.0 (15/30)
	distal	6.7 (2/30)
Angulation >45 degrees (%)		3.3 (1/30)
Calcium (moderate/severe) (%)		16.7 (5/30)
Eccentric (%)		80.0 (24/30)
Lesion type (ACC/AHA) (%)	A	0.0 (0/30)
	B1	23.3 (7/30)
	B2	50.0 (15/30)
	C	26.7 (8/30)
Baseline TIMI flow (%)	grade 0/1	0.0 (0/30)
	grade 2	6.7 (2/30)
	grade 3	93.3 (28/30)
LVEF (%)		47.1±9.2*

*Variable available in 24 of 30 patients. ACC: American College of Cardiology; AHA: American Heart Association; LAD: left anterior descending; LCx: left circumflex; LVEF: left ventricular ejection fraction; RCA: right coronary artery; TIMI: Thrombolysis In Myocardial Infarction

Table 3. Procedure.

Variable	N=30
Radial access (%)	30.0 (9/30)
Glycoprotein IIb/IIIa inhibitor use (%)	13.3 (4/30)
Predilatation (%)	90.0 (27/30)
Study stent implanted (%)	100.0 (30/30)
Additional stent implanted (%)	0.0 (0/30)
Nominal stent extension (mm)	19.67±4.22
Nominal stent diameter (mm)	3.10±0.36
Deployment pressure (atm.)	14.5±1.7
Balloon post-dilatation (%)	53.3 (16/30)
Final TIMI flow grade 3 (%)	100.0 (30/30)
TIMI: Thrombolysis In Myocardial Infarction	

80.5%, respectively. Post procedure, median in-stent % DS was <10%. Angiographic FU was available in 86.7% of patients (26/30), since four (asymptomatic) patients refused angiographic re-evaluation. Median in-stent LLL (primary endpoint) was 0.15 mm; also, there were no cases of binary restenosis reported as well as no exaggerated NIH at the edges outside the stent **(Table 5)**. **Figure 3** illustrates the cumulative distribution curve for MLD.

Clinical FU up to 12 months was completed in all patients, and there was neither MACE nor ST (ARC) reported.

Table 4. Baseline and final QCA analysis.

Variable	N=30
Baseline (pre-procedure)	
Lesion length (mm)	15.51 [12.74, 20.27]
<10 mm (%)	13.3 (4/30)
10-20 mm (%)	60.0 (18/30)
>20 mm (%)	26.7 (8/30)
Reference diameter (mm)	2.94 [2.71, 3.34]
MLD (mm)	0.57 [0.30, 0.94]
% DS	80.5 [67.0, 90.7]
Final (post-procedure)	
Reference diameter (mm)	2.98 [2.89, 3.36]
In-stent	
MLD (mm)	2.84 [2.69, 3.07]
% DS	6.2 [3.3, 8.6]
acute gain (mm)	2.18 [1.72, 2.69]
In-segment	
MLD (mm)	2.56 [2.22, 2.91]
% DS	15.0 [11.1, 20.0]
acute gain (mm)	1.78 [1.58, 2.36]
Proximal edge	
MLD (mm)	2.84 [2.60, 3.16]
% DS	5.2 [1.7, 12.7]
Distal edge	
MLD (mm)	2.56 [2.15, 2.88]
% DS	10.2 [5.2, 14.4]
Balloon-artery ratio	1.11 [1.07, 1.14]
DS: diameter stenosis; MLD: minimum lumen diameter	

Table 5. QCA results at 8-month follow-up.

Variable	N=26
Reference diameter (mm)	2.97 [2.81, 3.28]
In-stent	
MLD (mm)	2.68 [2.32, 2.83]
% DS	10.9 [7.3, 15.6]
late lumen loss (mm)	0.15 [0.09, 0.33]
late lumen loss index	0.07 [0.04, 0.12]
binary restenosis (%)	0.0 (0/26)
In-segment	
MLD (mm)	2.29 [2.06, 2.60]
% DS	21.2 [16.4, 26.3]
late lumen loss (mm)	0.17 [0.07, 0.35]
late lumen loss index	0.07 [0.04, 0.18]
binary restenosis (%)	0.0 (0/26)
Proximal edge	
MLD (mm)	2.51 [2.33, 3.10]
% DS	10.4 [5.5, 18.3]
late lumen loss (mm)	0.18 [0.09, 0.33]
binary restenosis (%)	0.0 (0/26)
Distal edge	
MLD (mm)	2.49 [2.17, 2.76]
% DS	10.0 [8.1, 19.5]
late lumen loss (mm)	0.09 [0.05, 0.24]
binary restenosis (%)	0.0 (0/26)
DS: diameter stenosis; MLD: minimum lumen diameter	

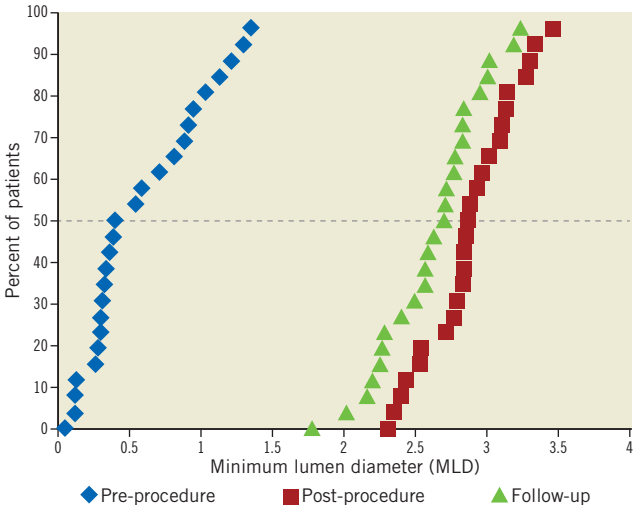

Figure 3. *Cumulative frequency distribution curve for MLD at baseline, final (in-stent) and FU (in-stent) for patients with serial angiographic analysis (n=26).*

Discussion

In the current analysis, the novel BioMime SES with ultra-thin struts demonstrated favourable outcomes in single *de novo* coronary lesions including: a) high angiographic and procedural success (100%) in lesions with moderate complexity (mainly type B); b) relatively low in-stent LLL (0.15 mm) at mid-term angiographic FU (87%); and c) absence of MACE or ST up to 12 months. Interestingly, a relatively young population (~50 years) with a relatively high prevalence of diabetes (30%) was present, representing the high prevalence of coronary artery disease found in adults in India[21]. Also, most type C lesions had a baseline lesion length measured marginally over 20 mm by independent QCA analysis, despite visual estimation according to inclusion criteria (≤19 mm), as assessed by operators during the index procedure.

The impact of stent design on outcomes has been already reported. In the ISAR-STEREO trial, 651 patients from daily practice were randomly assigned for PCI with stents with similar design but different strut thickness: thin-strut group (ACS Multi-Link 50 µm) versus thick-strut group (ACS Multi-Link RX Duet 140 µm) (both devices manufactured by Guidant, Santa Clara, CA, USA). At six-month angiographic FU (77%), QCA parameters favoured the thin-strut group (LLL 0.94 vs. 1.17 mm, p=0.001; restenosis 15 vs. 25.8%, p=0.003). Correspondingly, ischaemia-driven TLR at one year was also lower in the thin-strut group (8.6 vs. 13.8%, p=0.03)[3]. In the subsequent ISAR-STEREO-2 trial, 611 patients were randomly assigned for PCI with stents with different design and strut thickness. In this study, the thin-strut group was treated with ACS RX Multi-Link (interconnected ring design, 50 µm) versus the thick-strut group with Bx VELOCITY® (closed cell design, 140 µm) (Cordis Corporation, Miami, FL, USA). At six-month angiographic FU (78%), there was significantly lower LLL (0.93 vs. 1.19 mm, p<0.001) and restenosis (17.9 vs. 31.4%, p<0.001) with thin struts with open cell design versus thick struts with closed cell design. At one year, TVR due to restenosis was found in 12.3% in the thin-strut group versus 21.9% in the thick-strut group (p=0.002)[4]. In general, thicker struts appear to induce more NIH with uncoated stents[1-4]; hence, a similar behaviour would be intuitively anticipated with coated devices. However, such linear correlation has not been clearly demonstrated with DES, as a potent antiproliferative local drug effect may counterbalance or even annul the negative impact of strut thickness on NIH. A randomised study by Pache et al comparing Cypher™ SES (Bx VELOCITY platform) versus thin-strut (76 µm) uncoated BeStent™ 2 (Medtronic, Santa Rosa, CA, USA) in 500 patients showed marked reductions in LLL (0.14 vs. 0.94 mm, p<0.001) and restenosis (8.3 vs. 25.5%, p<0.001) with SES versus thin-strut BMS, respectively; also, a significant reduction in TVR was observed with SES (7.2 vs. 18.8%, p<0.001)[22]. Notwithstanding this, deliverability issues (especially in complex anatomies) as well as stent fracture leading to PCI failure have been seen with older (first) generation DES including Cypher SES[23,24]. Therefore, most newer-generation DES systems developed to date have incorporated low-profile cobalt-chromium platforms with open cell designs in order to reduce strut thickness, enhance flexibility and deliverability, and improve outcomes[10,12,14,15,25]. On another topic, the degree of vascular injury caused during PCI procedure may also impact on outcomes. A study by Costa et al (n=1,557) demonstrated that longitudinal and axial injury within the treated segment during stent implant (all Cypher SES) was a common finding (66.5%) and associated with MI (p=0.03) and TVR (p=0.04) up to one year[26]. The novel BioMime device has one of the smallest strut thicknesses (65 µm) compared to other approved DES systems. In addition, it incorporates a balloon-expandable cobalt-chromium alloy with hybrid design and mediated expansion properties in order to enhance flexibility and avoid vascular injury **(Figure 1B)**. In meriT-1, median balloon-artery ratio was 1.11 and in-stent LLL at eight months was 0.15 mm with neither exaggerated NIH at the edges nor restenosis reported. Such outcomes are comparable to first-in-man evaluations of the most effective DES systems tested to date[11,12,27].

Furthermore, biocompatible polymers appear to be vital constituents of DES since their absence has been related to DES failure due to poor drug delivery and uncontrolled release kinetics[28]. Durable polymers have been used in first and second-generation DES systems[5,6,10,12,14]; however, their presence (mainly first-generation DES) has been associated with marked local inflammatory response over time that could lead to intense tissue proliferation or delayed healing and extensive vessel enlargement[29]. Even though the genesis of ST has been well recognised as multifactorial[30], we may speculate that the drug carrier's everlasting presence may play a role. Moreover, previous studies comparing second-generation DES with biodegradable polymer vs. first-generation DES with durable polymer demonstrated significant reduction in very late ST with DES with biodegradable polymer[31]. Nonetheless, whether such technology (bioabsorbable polymeric drug carrier) can influence DAPT duration is still unknown and needs further evaluation. For BioMime, a bioabsorbable polymer is used, but the impact of this technology in late outcomes has yet to be determined.

Limitations

In the current analysis, there were no safety concerns up to 12 months, but the relatively low number of patients precludes any definite conclusions regarding safety beyond the perspective of a preliminary single-centre feasibility study. Angiographic results at eight-month FU (87%) suggested high efficacy of the BioMime SES in inhibiting NIH, but serial IVUS analysis was not available.

Conclusions

The novel BioMime SES demonstrated good performance in single coronary lesions including high procedural success and efficacy, as demonstrated by the relatively low late lumen loss (a surrogate of neointimal hyperplasia) at eight-month angiographic FU. Overall, there were no safety concerns in this preliminary evaluation including absence of MACE or ST up to 12 months.

Conflict of interest statement

R. A. Costa has received a research grant from Meril Life Sciences. S. Bhatt is a full-time employee of Meril Life Sciences. The other authors have no conflicts of interest to declare.

References

1. De Jaegere PP, De Feyter PJ, Van der Giessen WJ, Serruys PW. Intracoronary stents: a review of the experience with five different devices in clinical use. *J Interv Cardiol.* 1994;7:117-28.

2. Kastrati A, Dirschinger J, Boekstegers P, Elezi S, Schuhlen H, Pache J, Steinbeck G, Schmitt C, Ulm K, Neumann FJ, Schomig A. Influence of stent design on 1-year outcome after coronary stent placement: a randomized comparison of five stent types in 1,147 unselected patients. *Catheter Cardiovasc Interv.* 2000;50:290-7.

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

4. Pache J, Kastrati A, Mehilli J, Schuhlen H, Dotzer F, Hausleiter J, Fleckenstein M, Neumann FJ, Sattelberger U, Schmitt C, Muller M, Dirschinger J, Schomig A. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO-2) trial. *J Am Coll Cardiol.* 2003;41:1283-8.

5. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med.* 2003;349:1315-23.

6. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med.* 2004;350:221-31.

7. Sousa JE, Serruys PW, Costa MA. New frontiers in cardiology: drug-eluting stents: Part I. *Circulation.* 2003;107:2274-9.

8. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Juni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW. 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.

9. Feres F, Costa JR Jr, Abizaid A. Very late thrombosis after drug-eluting stents. *Catheter Cardiovasc Interv.* 2006;68:83-8.

10. Meredith IT, Ormiston J, Whitbourn R, Kay IP, Muller D, Bonan R, Popma JJ, Cutlip DE, Fitzgerald P, Prpic R, Kuntz RE. First-in-human study of the Endeavor ABT-578-eluting phosphorylcholine-encapsulated stent system in de novo native coronary artery lesions: Endeavor I Trial. *EuroIntervention.* 2005;1:157-64.

11. Costa RA, Lansky AJ, Mintz GS, Mehran R, Tsuchiya Y, Negoita M, Gilutz Y, Nikolsky E, Fahy M, Pop R, Cristea E, Carlier S, Dangas G, Stone GW, Leon MB, Muller R, Techen G, Grube E. Angiographic results of the first human experience with everolimus-eluting stents for the treatment of coronary lesions (the FUTURE I trial). *Am J Cardiol.* 2005;95:113-6.

12. Serruys PW, Ong AT, Piek JJ, Neumann FJ, van der Giessen WJ, Wiemer M, Zeiher A, Grube E, Haase J, Thuesen L, Hamm C, Otto-Terlouw PC. A randomized comparison of a durable polymer Everolimus-eluting stent with a bare metal coronary stent: The SPIRIT first trial. *EuroIntervention.* 2005;1:58-65.

13. Costa RA, Lansky AJ, Abizaid A, Mueller R, Tsuchiya Y, Mori K, Cristea E, Leon MB, Sousa JE, Schmidt T, Hauptmann KE, Grube E. Angiographic results of the first human experience with the Biolimus A9 drug-eluting stent for de novo coronary lesions. *Am J Cardiol.* 2006;98:443-6.

14. Meredith IT, Worthley S, Whitbourn R, Walters D, Popma J, Cutlip D, Fitzgerald P. The next-generation Endeavor Resolute stent: 4-month clinical and angiographic results from the Endeavor Resolute first-in-man trial. *EuroIntervention.* 2007;3:50-3.

15. Costa JR Jr, Abizaid A, Feres F, Costa R, Seixas AC, Maia F, Tanajura LF, Staico R, Siqueira D, Meredith L, Bhat V, Yan J, Ormiston J, Sousa AG, Fitzgerald P, Sousa JE. EXCELLA First-in-Man (FIM) study: safety and efficacy of novolimus-eluting stent in de novo coronary lesions. *EuroIntervention.* 2008;4:53-8.

16. Marx SO, Marks AR. Bench to bedside: the development of rapamycin and its application to stent restenosis. *Circulation.* 2001;104:852-5.

17. Schwartz RS, Edelman ER, Carter A, Chronos N, Rogers C, Robinson KA, Waksman R, Weinberger J, Wilensky RL, Jensen DN, Zuckerman BD, Virmani R. Drug-eluting stents in preclinical studies: recommended evaluation from a consensus group. *Circulation.* 2002;106:1867-73.

18. Kornowski R, Hong MK, Tio FO, Bramwell O, Wu H, Leon MB. In-stent restenosis: contributions of inflammatory responses and arterial injury to neointimal hyperplasia. *J Am Coll Cardiol.* 1998;31:224-30.

19. King SB 3rd, Smith SC Jr, Hirshfeld JW Jr, Jacobs AK, Morrison DA, Williams DO, Feldman TE, Kern MJ, O'Neill WW, Schaff HV, Whitlow PL, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Page RL, Riegel B, Tarkington LG, Yancy CW. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee. *Circulation.* 2008;117:261-95.

20. 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. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.

21. Ashavaid TF, Ponde CK, Shah S, Jawanjal M. Cardiovascular disease in India. *Clin Lab Med.* 2012;32:217-30.

22. Pache J, Dibra A, Mehilli J, Dirschinger J, Schomig A, Kastrati A. Drug-eluting stents compared with thin-strut bare stents for the reduction of restenosis: a prospective, randomized trial. *Eur Heart J.* 2005;26:1262-8.

23. Ako J, Bonneau HN, Honda Y, Fitzgerald PJ. Design criteria for the ideal drug-eluting stent. *Am J Cardiol.* 2007;100:3M-9M.

24. Canan T, Lee MS. Drug-eluting stent fracture: incidence, contributing factors, and clinical implications. *Catheter Cardiovasc Interv.* 2010;75:237-45.

25. Moreno R, Jimenez-Valero S, Sanchez-Recalde A, Galeote G, Calvo L, Martin-Reyes R, Sabate M, Plaza I, Macaya C, Lopez-Sendon JL. Periprocedural (30-day) risk of myocardial infarction after drug-eluting coronary stent implantation: a meta-analysis comparing cobalt-chromium and stainless steel drug-eluting coronary stents. *EuroIntervention.* 2011;6:1003-10.

26. Costa MA, Angiolillo DJ, Tannenbaum M, Driesman M, Chu A, Patterson J, Kuehl W, Battaglia J, Dabbons S, Shamoon F, Flieshman B, Niederman A, Bass TA. Impact of stent deployment procedural factors on long-term effectiveness and safety of sirolimus-eluting stents (final results of the multicenter prospective STLLR trial). *Am J Cardiol.* 2008;101:1704-11.

27. Sousa JE, Costa MA, Abizaid A, Abizaid AS, Feres F, Pinto IM, Seixas AC, Staico R, Mattos LA, Sousa AG, Falotico R, Jaeger J, Popma JJ, Serruys PW. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation.* 2001;103:192-5.

28. Lansky AJ, Costa RA, Mintz GS, Tsuchiya Y, Midei M, Cox DA, O'Shaughnessy C, Applegate RA, Cannon LA, Mooney M, Farah A, Tannenbaum MA, Yakubov S, Kereiakes DJ, Wong SC, Kaplan B, Cristea E, Stone GW, Leon MB, Knopf WD, O'Neill WW. Non-polymer-based paclitaxel-coated coronary stents for the treatment of patients with de novo coronary lesions: angiographic follow-up of the DELIVER clinical trial. *Circulation.* 2004;109:1948-54.

29. 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.

30. Steinberg DH, Satler LF. Drug-eluting stent thrombosis. *Minerva Cardioangiol.* 2008;56:127-37.

31. Stefanini GG, Kalesan B, Serruys PW, Heg D, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, van Es GA, Meier B, Windecker S, Juni P. 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.