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A prospective, multicentre first-in-man study of the polymer-free ultrathin-strut BIOrapid stent (BIOVITESSE)

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KEYWORDS

- coronary artery disease
- drug-eluting stent
- optical coherence tomography
- QCA

Abstract

Background: Polymer-free drug-coated stents aim to avoid the inflammatory potential of durable polymers, thereby improving the long-term safety profile, and allowing a shorter duration of dual antiplatelet therapy.

Aims: The BIOVITESSE study was conducted to assess the safety and clinical performance of the BIOrapid polymer-free coronary stent system coated with a novel highly lipophilic sirolimus derivate.

Methods: BIOVITESSE was a prospective, multicentre, first-in-man study that enrolled subjects with *de novo* coronary lesions in two cohorts of 33 patients each. The primary endpoint of the first cohort was strut coverage at one month as assessed by optical coherence tomography. The primary endpoint of the second cohort was late lumen loss at nine-month follow-up.

Results: Patients were on average 63 years old (range: 42-87) and 12% had diabetes. The 66 patients had 70 lesions with an average lesion length of 12.5±5.4 mm. Predilatation was performed in 91.4% and post-dilatation in 87.1% lesions; device success was obtained in 97.4%. At one month, 95.2±5.6% (95% CI: 93.2-97.2) of struts were covered and at nine months, in-stent late lumen loss was 0.31±0.30 mm (95% CI: 0.20-0.42) and in-segment late lumen loss was 0.20±0.29 mm. Two target lesion failures occurred (3.1%): one at day 1 (to cover an asymptomatic stent edge dissection), and one at day 288 post-procedure for restenosis. No stent thrombosis was reported during the 12-month study duration.

Conclusions: The BIOrapid stent system exhibited an excellent safety profile, high strut coverage at one-month, and moderate angiographic efficacy according to the late lumen loss at nine-month angiographic follow-up.

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Abbreviations

BMS	bare metal stent
DAPT	dual antiplatelet therapy
DCS	drug-coated stent
DES	drug-eluting stent
DFS	drug-filled stent
LLL	late lumen loss
MI	myocardial infarction
OCT	optical coherence tomography
TLF	target lesion failure
TLR	target lesion revascularisation

Introduction

Durable polymer drug-eluting stent (DES) coatings have shown suboptimal biocompatibility and negative effects on vessel healing due to chronic inflammation and local toxicity, potentially leading to proliferative and thrombogenic responses over time. Furthermore, the safety of DES appears to be dependent on relatively long (≥6 months) dual antiplatelet therapy (DAPT), carrying the risk of bleeding[1-3].

To overcome these limitations and to allow a shorter DAPT duration after percutaneous coronary intervention (PCI), polymer-free drug-coated stents (DCS) were introduced to mitigate the disadvantages of a permanent polymer. DCS combine the advantages of drug delivery with the long-term safety profile of a bare metal stent (BMS)[1,2,4,5], because once the drug is delivered to the surrounding tissue only the BMS remains in the vessel. Several different types of DCS have been tested, most of them characterised by a modification of the stent surface through nanopores, micropores or macropores, or microholes which act as drug reservoirs[5-7].

The BIOrapid drug-coated coronary stent system (Biotronik AG, Bülach, Switzerland) is a novel polymer-free spray-coated ultrathin stent with a novel sirolimus derivate that has a higher lipophilicity than sirolimus or other sirolimus derivates used in currently available DES and, as a result, the drug has a higher tissue penetration. The stent backbone is not altered and is the same that is used for the PRO-Kinetic Energy BMS and the Orsiro DES (both Biotronik; strut thickness of 60 µm for stents ≤3.0 mm and 80 µm for >3.0 mm)[8]. The latter has proven to be safe and effective, and non-inferior[8,9] or even superior[10,11] to current DES standards.

Angiographic and histological data from animal studies indicate lower late lumen loss (LLL) and diameter stenosis than the ProKinetic Energy BMS platform, and similar LLL and diameter stenosis to the Orsiro DES, with similar inflammation scores (data on file). The BIOrapid Vascular ImplanT Abluminal PolymerlESs Safety and Efficacy (BIOVITESSE) study intended to assess the safety and performance of this novel device in humans, with early stent strut coverage assessed at one month by optical coherence tomography (OCT), and angiographic late lumen loss at nine months as a surrogate endpoint for efficacy.

Methods

STUDY DESIGN

BIOVITESSE was a prospective, multicentre, first-in-man trial including patients with symptomatic ischaemic heart disease due to discrete *de novo* lesions.

The full list of inclusion and exclusion criteria is provided at the www.ClinicalTrials.gov website (NCT03263858). Main inclusion criteria were age ≥18 and ≤85 years, stable or unstable angina pectoris, documented silent ischaemia or haemodynamically stable non-ST-elevation myocardial infarction, a maximum of 2 single discrete *de novo* lesions in 2 separate native coronary arteries, reference vessel diameter of 3.0-3.8 mm and a target lesion length of up to 22 mm. Main exclusion criteria were left main disease, chronic total occlusion, bifurcation lesions requiring side branch intervention (if side branches >2 mm were involved), or prior treatment with a drug-coated balloon. Sixty-six patients were enrolled in 5 centres in Switzerland (33 in cohort 1 and 33 in cohort 2). After reaching the primary endpoint for cohort 1, an interim report was submitted to SwissMedic and cohort 2 commenced after SwissMedic approval. Clinical follow-up took place at 1, 9, and 12 months.

The study was conducted according to applicable local regulations, the Declaration of Helsinki, ISO14155:2011, and was approved by the sites' ethics committees and competent authorities. All patients provided informed consent. Monitoring included 100% source document verification, an independent angiographic and OCT core laboratory (MedStar Health Research Institute, Washington, D.C., USA) assessed all imaging parameters, an independent clinical events committee adjudicated all adverse events, and an independent data safety monitoring board reviewed all serious adverse events, device and procedure failures and any device-related adverse events. It further permitted the start of the second BIOVITESSE cohort after review of the 30-day outcomes from the first cohort.

STUDY DEVICE AND PROCEDURE

BIOrapid has a thin drug coating of 2-3 µm that consists of BIOTORCIN™ (Biotronik), a highly lipophilic mTOR inhibitor, a derivative of sirolimus, blended with an inert non-polymer excipient. The drug is released over a period of approximately three months **(Supplementary Figure 1)**. Stent sizes available for the study were as follows: diameter 3.0 and 3.5 mm, and length 15, 20, and 26 mm. The rapid-exchange delivery system comes with a polyamide 12 semi-compliant balloon which is the same as used for the PRO-Kinetik Energy BMS and the Orsiro DES (both Biotronik).

Predilatation using a balloon diameter 0.5 mm smaller than the reference vessel diameter and a balloon length equal to or shorter than the target lesion was required. Post-dilatation was optional. Dual antiplatelet therapy was recommended according to the current European Society of Cardiology (ESC) guidelines[3] and standard of care at the study centres.

ENDPOINTS AND DEFINITIONS

The primary endpoint of cohort 1 was strut coverage at one month post-procedure assessed by OCT, the primary endpoint of cohort 2 was in-stent LLL at nine months assessed by quantitative coronary angiography (QCA). Secondary endpoints were device success, defined as final residual diameter stenosis <30% by QCA, using the assigned device only and successful delivery of the stent, appropriate stent deployment, and successful removal of the device. Clinical endpoints were target lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction, and clinically driven target lesion revascularisation (TLR), target vessel failure (TVF), a composite of cardiac death, target vessel myocardial infarction and target vessel revascularisation (TVR), all cause death, myocardial infarction (periprocedural being adjudicated according to the Society of Cardiovascular Angiography and Interventions [SCAI] definition and spontaneous according to the universal and extended historical definitions)[12-14], and stent thrombosis[15]. Angiographic endpoints were in-segment LLL, diameter stenosis and binary restenosis, and OCT endpoints included stent strut data at 1 month (cohort 1) and 9 months (cohort 2) **(Supplementary Appendix 1)**.

STATISTICAL ANALYSIS

This analysis is based on the intention-to-treat population based on the data available. Clinical endpoints are calculated using Kaplan-Meier statistics. Descriptive statistics include the mean and standard deviation and median and interquartile ranges as applicable. For categorical (qualitative) variables, the absolute and relative frequencies are displayed; 95% confidence intervals (CIs) were calculated as applicable. Statistical calculations were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

From September 2017 to March 2018 (cohort 1) and from June 2018 to January 2019 (cohort 2), 66 patients with 70 lesions were enrolled **(Figure 1)**. Patients were 63±11 years on average (range: 42-87 years), 12.1% had diabetes mellitus, and 34.8% previous myocardial infarction **(Table 1)**. Per core laboratory assessment, lesions were 12.5±5.4 mm long and more than half were type B2/C lesions (65.2%) **(Table 2)**.

Nearly all lesions were predilated (91.4%), and post-dilatation was performed in 87.1%. One stent was not deployed because the operator decided to change to another stent size. Device success was obtained in 97.4% **(Table 2)**.

OCT assessment was successfully obtained in 97% of patients of cohort 1 at one month. Stent strut coverage amounted to 95.2±5.6% (95% CI: 93.2-97.2); 1.4±3.0% of struts were uncovered and malapposed. At 9 months, strut coverage of cohort 2 amounted to 98.9±2.1% (95% CI: 98.1-99.6) **(Table 3)**. Angiographic analyses at 9 months were available for 97% of patients of cohort 2 and showed an in-stent late lumen loss of 0.30±0.31 mm (95% CI: 0.20-0.42), median 0.24 (IQR: 0.10-0.44). Approximately 20% of LLL values were above 0.5 mm **(Table 4, Central illustration)**.

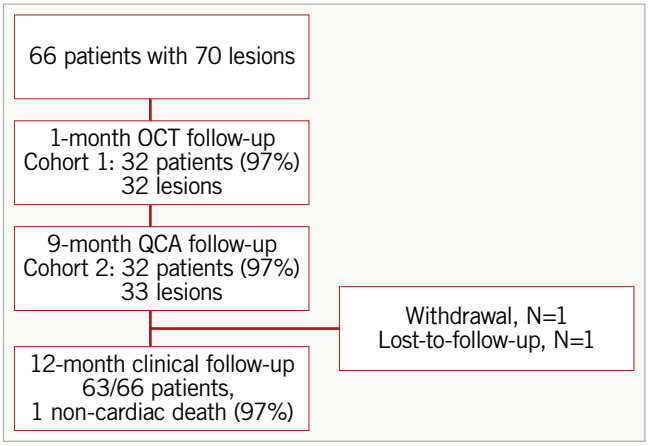

Figure 1. *Study flow chart. One patient excluded due to suboptimal image quality. OCT: optical coherence tomography; QCA: quantitative coronary angiography*

Cardiovascular medication is presented in **Supplementary Table 1**. At 1 month, 90.8% (59/65) of patients were on DAPT, at 9 months 67.2% (43/64) and at 12 months 41.3% (26/63).

Two TLF occurred during the 12-month study duration **(Table 5)**. One proximal edge dissection during the index procedure treated the following day was adjudicated as TLR by the clinical events committee. The second TLR occurred on post-procedure day 288 in a patient with recurrent angina and a 70% restenosis detected during elective nine-month follow-up angiography. No cardiac death, myocardial infarction, or definite, probable or possible stent thrombosis was observed. There was one

Table 1. Baseline characteristics.

		N=66
Age, years		63±11 [60; 66]
Male		53 (80.3%)
Hypertension		44 (66.7%)
Hypercholesterolaemia		51 (77.3%)
Smoking history		44 (66.7%)
Current smoker		22 (33.3%)
Diabetes		8 (12.1%)
Insulin dependent		2 (3.0%)
Renal disease		4 (6.1%)
Previous myocardial infarction		23 (34.8%)
Previous coronary interventions		24 (36.4%)
Congestive heart failure		5 (7.6%)
History of stroke or transient ischaemic attack		1 (1.5%)
History of cancer		5 (7.6%)
Clinical presentation	Stable angina	45 (68.2%)
	Unstable angina	12 (18.2%)
	Documented silent ischaemia	9 (13.6%)
Left ventricular ejection fraction, %	Normal (≥55%)	60 (90.9%)

Continuous data are presented as the means±standard deviation and [95% CI]. Categorical data are given as counts (percentage).

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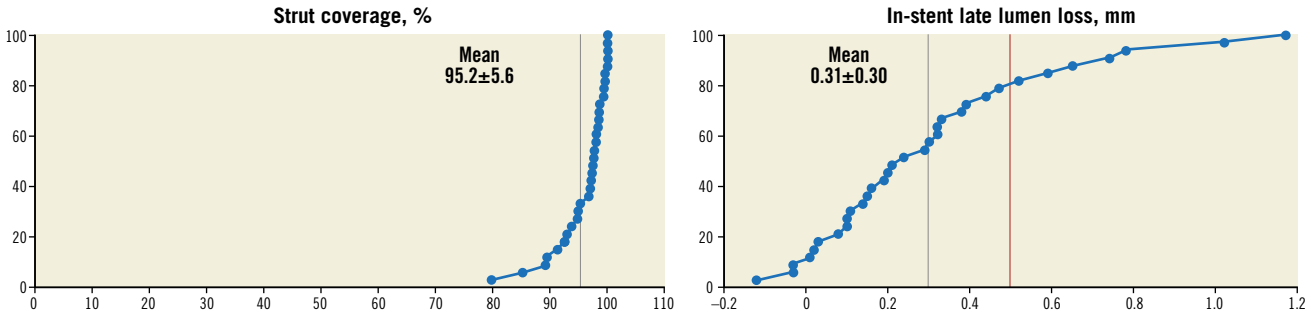
CENTRAL ILLUSTRATION Primary endpoint strut coverage at one month (cohort 1) and in-stent late lumen loss at nine months (cohort 2) by core laboratory assessment.



The black line reflects the mean LLL and the red line the 0.5 mm threshold above which the LLL is considered clinically relevant[29]. Strut coverage is based on patient level. LLL: late lumen loss

Table 2. Procedural characteristics.

		N=66
Lesion localisation, N=65	Left anterior descending	32 (49.2%)
	Left circumflex	17 (26.2%)
	Right coronary artery	16 (24.6%)
ACC/AHA lesion classification	Type A	5 (7.6%)
	Type B1	18 (27.3%)
	Type B2	27 (40.9%)
	Type C	16 (24.2%)
Number of lesions per patient, N=65		1.1±0.1 [1.0; 13]
Reference vessel diameter, mm		2.88±0.40 [2.78; 2.98]
Lesion length, mm		12.5±5.4 [10.7; 13.4]
Diameter stenosis, %		53.0±11.9 [50.0; 55.9]
Severe calcification		1 (1.5%)
Number of stents per lesion, N=70 lesions, 77 stents		1.1±0.4 [1.0; 1.2]
Stent diameter, mm		3.2±0.3
Vascular access	Femoral	5 (7.6%)
	Radial	61 (92.4%)
Predilatation performed, N=70		64 (91.4%)
Post-dilatation performed, 70 lesions, 86 devices		61 (87.1%)
Balloon diameter, mm		3.4±0.4
Max. pressure applied, atm		17.1±5.4
Device success, N=76 devices*		74 (97.4%)
Procedure success*,¶		64 (97.0%)

Continuous data are presented as the means±standard deviation and [95% CI]. Categorical data are given as counts (percentage). Angiographic variables are core laboratory assessed. *Calculated considering the following: one BIOrapid stent that had to be withdrawn because of the wrong sizing was removed from the analyses and for 4 subjects with no analysable post-procedural angiographic assessment, the follow-up angiographic assessment was used instead. ¶Procedural success was defined as final diameter stenosis <30% by QCA, using any percutaneous method, without the in-hospital death, myocardial infarction or repeat revascularisation. QCA: quantitative coronary angiography

non-cardiac death on day 58 due to progredient respiratory failure in the context of a competing pulmonary disease.

Discussion

The use of the novel BIOrapid drug-coated coronary stent system in the BIOVITESSE study resulted in a nearly complete strut coverage (95.2%) at an early time point of 1 month, moderate angiographic efficacy at 9 months, and low clinical event rates with no thrombotic events.

The study was conducted thoroughly, with 100% monitoring, clinical events committee adjudication, core laboratory assessment, and high follow-up compliance.

STRUT COVERAGE

Nearly all struts were covered at 1 month (95.2%), comparing well to the stent strut coverage at 1 month of the PRO-Kinetic BMS (93%), which forms the backbone of the BIOrapid stent[16]. In contrast, the Orsiro DES, which uses the same stent backbone, but with a sirolimus-eluting biodegradable polymer cover, exhibits a strut coverage of 80.4% at 1 month[17].

Our study further demonstrated good strut coverage when compared to contemporary stents. At 1-month post-procedure, strut coverage was 88% for the Resolute Integrity™ (Medtronic, Minneapolis, MN, USA)[18], 85% for Ultimaster™ (Terumo Corp., Tokyo, Japan)[19], and 88% for Resolute Onyx™ (Medtronic)[20]. Similar outcomes (91.4% strut coverage) have been reported for the polymer-free drug-filled stent (DFS)[21]. This nearly complete strut coverage may allow to safely stop DAPT early in patients with high bleeding risk or simple lesions with low thrombotic risk. However, complete coverage, as determined by OCT, does not always mean vessel healing, because OCT cannot differentiate between fibrin and true endothelial coverage. Furthermore, the current results were obtained in simple lesions and may not be directly applicable to more complex lesion subsets. A comparison of baseline parameters is provided in **Supplementary Table 2**.

Table 3. Optical coherence tomography core laboratory analysis at baseline and follow-up (paired data).

		Cohort 1, N=32 lesions		Cohort 2, N=33 lesions	
		Post-procedure	1 month	Post-procedure	9 months
Lesion level					
Mean lumen area, mm²		8.6±1.9 [7.9-9.3] 8.4 (6.6-10.3)	8.2±2.0 [7.5-8.9] 7.8 (6.7-9.8)	8.6±1.8 [8.0-9.2] 8.2 (7.4-10.2)	7.2±2.0 [6.5-7.9] 6.9 (5.7-7.9)
Minimal lumen area, mm²		7.1±1.8 [6.5-7.8] 6.8 (5.4-8.7)	6.7±1.8 [6.0-7.3] 6.2 (5.1-8.3)	7.1±1.8 [6.5-7.8] 7.0 (6.0-8.5)	5.5±2.0 [4.8-6.2] 5.4 (4.1-6.8)
Minimal stent area, mm²		7.2±1.8 [6.6-7.9] 6.8 (5.5-8.9)	7.1±1.8 [6.4-7.7] 6.7 (5.7-8.3)	7.3±1.9 [6.7-8.0] 7.1 (6.1-8.8)	7.2±1.8 [6.5-7.8] 6.8 (5.8-8.8)
Mean stent area, mm²		8.6±1.8 [7.9-9.2] 8.4 (6.7-10.5)	8.5±1.8 [7.9-9.2] 8.3 (7.2-10.1)	8.7±1.8 [8.1-9.4] 8.2 (7.6-10.3)	8.7±1.9 [8.0-9.4] 8.1 (7.6-10.6)
Stent volume, mm³		166±50 [148-184] 156 (130-188)	163±58 [142-183] 143 (126-192)	188±65 [165-211] 181 (151-214)	181±54 [162-200] 182 (138-210)
Lumen volume, mm³		166±51 [147-184] 154 (126-196)	156±59 [135-177] 135 (118-196)	186±64 [163-208] 178 (148-213)	148±46 [132-165] 145 (112-180)
Neointimal volume, mm³		NA	10.3±5.8 [8.2-12.4] 9.5 (6.4-12.0)	NA	33.1±16.6 [27.1-38.9] 31.2 (20.4-40.0)
Percent volume obstruction, %		NA	6.6±3.7 [5.3-7.9] 5.5 (4.2-8.1)	NA	18.2±7.1 [15.7-20.8] 19.4 (12.8-23.2)
Covered struts, %		NA	95.2±5.6 [93.2-97.2] 97.6 (94.8-99.3)	NA	98.9±2.1 [98.1-99.6] 99.6 (99.0-100.0)
Malapposition, %		9.3±9.3 [5.9-12.6] 4.1 (2.2-13.8)	1.5±3.4 [0.3-2.8] 0.4 (0-1.2)	6.5±5.0 [4.7-8.3] 4.9 (2.5-7.9)	0.1 ±0.4 [0-0.3] 0.0 (0.0-0.0)
Lesions with	>5% uncovered stent struts	32 (100%)	4 (12.5%)	33 (100%)	2 (6.1%)
	>10% uncovered stent struts	32 (100%)	1 (3.2%)	33 (100%)	0 (0%)
Neointimal thickness, µm		NA	75±23 [67-84] 70 (61-81)	NA	164±57 [144-184] 166 (121-192)
Cross-sectional level					
Number of frames per lesion		N=32 21±6 [19-23] 20 (16-25)	N=32 20±5 [18-22] 19 (16-25)	N=33 23±7 [20-25] 21 (18-27)	N=33 22±6 [20-25] 20 (18-26)
Neointimal area*, mm²		NA	N=608 0.54±0.35 [0.51-0.57] 0.40 (0.30-0.70)	NA	N=709 1.54±0.85 [1.47-1.60] 1.40 (0.90-1.90)
Frames with any malapposition (covered or uncovered), %		N=635 235 (37.0%)	N=606 52 (8.6%)	N=721 230 (31.9%)	N=713 6 (0.8%)
Mean malapposition area, mm² (in cross-sections with malapposition)		N=235 0.39±0.53 [0.32-0.46] 0.20 (0.00-0.60)	N=52 0.71±0.81 [0.48-0.93] 0.30 (0.10-1.00)	N=230 0.20±0.44 [0.14-0.25] 0.00 (0.00-0.20)	N=6 0.28±0.35 [-0.09-0.64] 0.00 (0.00-0.60)
Mean malapposition distance, µm¶ (per malapposed frame/cross-section)		N=235 –58±48 [–64–-52] –48 (–69–-33)	N=52 –1±62 [–18-17] 17 (–10-30)	N=230 –50±41 [–055–-44] –40 (–57–-30)	N=6 48±61 [–15-112] 59 (38-96)
Luminal area, mm²		N=675 8.4±2.1 [8.3-8.6] 8.5 (6.4-10.0)	N=648 8.1±2.2 [8.0-8.3] 7.9 (6.2-9.6)	N=752 8.5±2.1 [8.4-8.7] 8.2 (7.1-10.1)	N=736 7.0±2.2 [6.9-7.2] 6.7 (5.5-8.3)
Stent area, mm²		N=675 8.0±2.7 [7.8-8.2] 8.3 (6.4-9.8)	N=648 7.9±2.9 [7.7-8.1] 8.1 (6.5-9.7)	N=725 8.6±2.1 [8.5-8.8] 8.3 (7.2-10.2)	N=714 8.6±2.1 [8.4-8.7] 8.2 (7.0-9.9)
Strut level					
Number of struts per lesion		N=32 213±62 [191-235] 200 (172-252)	N=32 204±61 [182-227] 200 (154-250)	N=33 227±83 [197-256] 197 (171-271)	N=33 223±82 [194-252] 205 (159-266)
Number of struts per frame		10.7±2.4 [10.5-10.9] 11 (11-12)	10.8±2.3 [10.6-11.0] 11 (11-12)	10.4±2.5 [10.2-10.6] 10 (9-12)	10.3±2.4 [10.1-10.5] 10 (9-12)
Uncovered struts, %		N=6,812 5,006 (73.5%) 75.3% (62.4-82.4)	N=6,542 168 (2.6%) 1.6% (0.2-2.8)	N=7,477 6,069 (81.2%) 83.8% (75.0-86.8)	N=7,344 61 (0.8%) 0.3 (0-0.8)
Malapposed struts, %		N=6,812 660 (9.7%) 4.3% (2.4-13.9)	N=6,542 123 (1.9%) 0.4% (0-0.9)	N=7,477 477 (6.4%) 4.9% (2.5-7.9)	N=7,344 7 (0.1%) 0% (0-0)

Data are presented as n (%), means±standard deviation and [95% CI], and median (interquartile ranges Q1-Q3). *Only frames with protrusion were included in N for neotima area. ¶ Data are provided at the frame level in frames with at least one malapposed strut; negative values: area of malapposition exceeds area of strut apposition/coverage in a cross-section; positive values: area of strut apposition/coverage exceeds area of malapposition in the cross-section. NA: not applicable

Table 4. Quantitative coronary analysis at procedure and follow-up (Cohort 2, unpaired data).

		Pre-procedure N=33 lesions	Post-procedure N=34 lesions	9 months N=33 lesions
Lesion length, mm		12.9±5.3 [11.02-14.8]	–	–
Reference vessel diameter, mm	In-stent	2.89±0.42 [2.74-3.04]	2.94±0.38 [2.81-3.07]	2.84±0.37 [2.71-2.97]
	In-segment	2.89±0.42 [2.74-3.04]	2.85±0.41 [2.71-3.00]	2.77±0.39 [2.63-2.91]
Diameter stenosis, %	In-stent	53.9±12.1 [49.6-58.2]	9.9±5.7 [7.9-11.9]	18.2±11.1 [14.2-22.1]
	In-segment	54.0±12.2 [49.6-58.3]	17.4±9.1 [14.3-20.6]	22.1±11.3 [18.1-26.1]
Minimum lumen diameter, mm	In-stent	1.32±0.36 [1.19-1.45]	2.65±0.36 [2.52-2.77]	2.33±0.46 [2.17-2.49]
	In-segment	1.32±0.36 [1.19-1.45]	2.36±0.44[2.21-2.51]	2.16±0.46 [2.00-2.33]
Acute gain, mm	In-stent	NA	1.23±050 [1.16-1.51]	NA
	In-segment		1.05±0.49 [0.88-1.23]	
Late lumen loss, mm	In-stent	NA	NA	0.31±0.30 [0.20-0.42]
	In-segment			0.20±0.29 [0.10-0.30]
Binary restenosis		NA	NA	1 (3.03)

Continuous data are presented as the means±standard deviation and [95% CI]. Categorical data are given as the counts (percentage). NA: not applicable

Table 5. Kaplan-Meier estimates of clinical events.

		30 days	180 days	365 days
Death		0 (0%) [0-0]	1 (1.5%) [0.2-10.3]	1 (1.5%) [0.2-10.3]
Cardiac death		0 (0%) [0-0]	0 (0%) [0-0]	0 (0%) [0-0]
Myocardial infarction*		0 (0%) [0-0]	0 (0%) [0-0]	0 (0%) [0-0]
Target-vessel		0 (0%) [0-0]	0 (0%) [0-0]	0 (0%) [0-0]
TLR, patient-based		1 (1.5%) [0.2-10.3]	1 (1.5%) [0.2-10.3]	2 (3.1%) [0.8-11.8]
Clinically driven		1 (1.5%) [0.2-10.3]	1 (1.5%) [0.2-10.3]	2 (3.1%) [0.8-11.8]
TVR, patient-based		1 (1.5%) [0.2-10.3]	1 (1.5%) [0.2-10.3]	2 (3.1%) [0.8-11.8]
Clinically driven		1 (1.5%) [0.2-10.3]	1 (1.5%) [0.2-10.3]	2 (3.1%) [0.8-11.8]
Stent thrombosis	Definite	0 (0%) [0-0]	0 (0%) [0-0]	0 (0%) [0-0]
	Probable	0 (0%) [0-0]	0 (0%) [0-0]	0 (0%) [0-0]
	Possible	0 (0%) [0-0]	0 (0%) [0-0]	0 (0%) [0-0]
Target lesion failure		1 (1.5%) [0.2-10.3]	1 (1.5%) [0.2-10.3]	2 (3.1%) [0.8-11.8]
Target vessel failure		1 (1.5%) [0.2-10.3]	1 (1.5%) [0.2-10.3]	2 (3.1%) [0.8-11.8]

Data are presented as events (Kaplan-Meier estimates). *SCAI/universal or extend. hist. def. SCAI: Society for Cardiovascular Angiography and Intervention; TLR: target lesion revascularisation; TVR: target vessel revascularisation

ANGIOGRAPHIC EFFICACY

An improvement in in-stent LLL (0.31±0.30 mm, median 0.24) compared with the PRO-Kinetic BMS backbone (0.88±0.58 mm at 6 months in the MULTIBENE study)[22] could be observed, showing a drug effect. However, LLL was higher than for the Orsiro DES (0.10±0.32 mm and 0.05±0.02 mm 9-month LLL in the BIOLFLOW-II and -VI studies)[23,24] and other contemporary DES such as the XIENCE DES (Abbott) (0.11±0.29 mm and 0.07±0.02 mm LLL in the BIOLFLOW-II and -IV studies), similar to the Ultimaster DES (0.26±0.35 mm)[23-25], and higher than postulated in the systemic review from the ESC-European Association of Percutaneous Cardiovascular Interventions (EAPCI) task force (LLL of 0.18 mm [IQR: 0.13-0.25] for new DES and 0.16 mm [IQR 0.13-0.22] for new FDA-approved DES)[26].

The LLL results were, however, similar to other polymer-free DES. The BioFreedom US trial reported an LLL of 0.32±0.53 mm (median 0.19)[7], the BioFreedom first-in-man trial reported LLL medians of 0.17 (IQR 0.12-0.35) and 0.19 (IQR 0.07-0.58) for the high- and low-dose formulation[27]. For the Medtronic polymer-free DFS, an LLL of 0.26±0.28 mm was reported[21], and for the COBRA Polyzene-F NanoCoated stent (NCS; CeloNova BioSciences, Inc., TX, USA) an LLL of 0.84±0.48 mm[28].

Whether the current high stent strut coverage and moderate late lumen loss represents a sweet spot between high degree of early safety and sufficient angiographic potency remains to be demonstrated in larger clinical trials. A recent patient-level meta-analysis considers LLL values of ≤0.5 as clinically negligible and suggests the cut-off value of 0.5 mm as an objective performance criterion[26,29].

Whether the applied drug concentration of novel sirolimus-derivate on the BIOrapid stent system should be increased can be speculated, e.g., the nominal active drug dose on the BIOrapid stent was around eight times lower than on the BioFreedom stent[27] and approximately three times lower than on the Orsiro stent (data on file) for similar stent sizes. Likewise, the BioFreedom stent showed a large variance in 9-month LLL in the low-dose formulation with an interquartile range of 0.07 to 0.58 mm and inferior 12-month TLR rate in the low-dose application (6.7% versus 1.7%), leading to a discontinuation of the low-dose DCS in that study. Notably, this effect weakened over time, with a 5-year TLR rate of 10.8% in the low-dose application versus 13.4%[27].

It can also be assumed that the total dispersion of the drug through the stent over a period of approximately 3 months was not sufficient to prevent further hyperplasia between 3 months and 9 months after the procedure.

CLINICAL OUTCOMES

Clinical outcomes were promising with the absence of ischaemic thrombotic events such as stent thrombosis or target vessel myocardial infarction. Further, only one restenosis-associated TLR occurred. However, this is a first-in-man trial with relatively simple lesions and TLR rates could increase in more complex lesions considering the moderate LLL observed.

Limitations

This first-in-man trial has several limitations. The device has been studied in a selected patient population with relatively simple coronary lesions. Moreover, around two thirds of patients were still on DAPT at 9-month follow-up. The study is not randomised and can only be compared against historical controls. The small patient number prevents a thorough analysis of the root cause(s) for the higher than expected LLL. Considering the fact that this is the first assessment of a novel sirolimus derivate administered in a low dose, in hindsight, a higher dose should have been tested simultaneously, as done for the BioFreedom DCS[27].

Conclusions

In this first-in-man trial evaluating the novel polymer-free abluminally drug-coated BIOrapid stent system, it was shown that, up to 12 months, the system is safe and clinically effective in treating *de novo* coronary artery lesions, with only one restenosis-associated TLR (1.5%) and no thrombotic events. Near complete stent strut coverage was achieved at one month with 95.2% of struts covered. Late lumen loss confirms the antirestenotic efficacy of the novel sirolimus derivate as compared to LLL for the same platform without the drug. However, results suggest a lower efficacy for this iteration than observed with modern thin-strut DES.

Impact on daily practice

This is the first trial of the polymer-free BIOrapid stent system and the first human exposure to a low-dose highly lipophilic sirolimus derivate coated on a vascular implant. The BIOVITESSE study demonstrates that the device is safe and effective, but with regard to late lumen loss it was not competitive with contemporary drug-eluting stents, particularly considering that impaired outcomes may be expected in more complex patients and lesions. Given the promising clinical outcomes and high strut coverage at one month, it might be worthwhile to assess a device iteration with a higher drug dose.

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Conflict of interest statement

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Supplementary data

Supplementary Appendix 1. BIOVITESSE - Polymer-free drug-coated stent with ultrathin struts: 12-month outcomes of a prospective, multicentre FIM study.

Supplementary Table 1. Cardiovascular medication.

Supplementary Table 2. Baseline parameters, one-month strut coverage and nine-month late lumen loss of BIOrapid compared to current drug-eluting stents.

Supplementary Figure 1. BIOrapid residual drug concentration in porcine implants.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00537

Supplementary data

Supplementary Appendix 1. BIOVITESSE – Polymer-free drug-coated stent with ultrathin struts: 12-month outcomes of a prospective, multicentre FIM study.

BIOrapid pharmacokinetics

Measurement of BIOTORCIN™ (Biotronik, AG, Bülach, Switzerland) levels up to three months after implantation in hybrid farm pigs were performed to determine:-

• The BIOTORCIN blood concentrations.

• Uptake of BIOTORCIN into the treated vessel tissue and its persistence

in the coronary vessel tissue over a period of 90 days.

Two hundred blood samples were analysed. Within five minutes after implantation, a maximum blood concentration of 0.126 ng/mL of BIOTORCIN was reached. Thereafter, the BIOTORCIN blood levels decreased until four hours after implantation when BIOTORCIN blood levels fell below the limit of quantitation.

Notably, the maximum blood levels after BIOrapid stent (Biotronik) implantation are lower at all measurement times than levels observed during immunosuppressant therapy (4-20 ng/mL).

BIOTORCIN was detected in porcine tissue at scheduled times up to 90 days after implantation of BIOrapid stents. The median drug content values for BIOrapid stents (3.0 x 13 mm) at two dose levels are provided in **Supplementary Figure 1** below. The high-dose stents were coated with a drug dose of 2.10 µg/mm² and the low-dose stents with 1.05 µg/mm². The drug dose used for BIOrapid clinical study stents was 1.70 µg/mm².

Angiographic core laboratory methods

An independent core laboratory (MedStar Cardiovascular Research Network, Washington DC, USA) performed all quantitative coronary angiography (QCA) and optical coherence

tomography (OCT) analyses. Angiograms were recorded in two orthogonal views after intracoronary injection of nitroglycerine (200 μg), with matching projections taken before and after the procedure and at follow-up. QCA analysis was carried out using a validated offline software, CASS 7.5 (Pie Medical Imaging BV, Maastricht, the Netherands).

Optical coherence tomography methods

Optical coherence tomography of the stented segment was performed with the frequency domain Dragonfly™ DUO (LightLab, St. Jude Medical/Abbott, Abbott Park, IL, USA) with a non-occlusive imaging technique following the administration of nitroglycerine. Quantitative OCT analysis was performed using a validated offline software (QIVUS; MEDIS, Leiden, the Netherlands).

Luminal and stent cross-section contouring were done at contiguous 1 mm intervals at the stent location and references. All struts within the 1 mm interval cross-sections were numbered and classified (covered, apposed, malapposed). Lumen and stent areas were determined by semi-automatic algorithms in each analysed cross-section. Neointimal hyperplasia (NIH)/tissue protrusions areas were derived from the areas between the stent and lumen contours in the cross-sections with stent area >lumen area. Incomplete apposition and malapposition areas and distances were determined by taking into consideration the device thickness and strut to lumen distances. Stent strut parameters were also determined based on the strut distances from the lumen; negative values <the device thickness=uncovered, negative values >the device thickness=malapposed, positive values ≥0.02 mm=covered (to account for the resolution of OCT technology). Percentage NIH (% area obstruction) and % volume obstruction were calculated by dividing neointima hyperplasia area/volume by the scaffold area/volume respectively multiplied by 100.

Supplementary Table 1. Cardiovascular medication.

	1 month N=65	**9 months N=64**	**12 months N=63**
Subject on DAPT*	59 (90.8%)	43 (67.2%)	26 (41.3%)
- ASA+clopidogrel	31 (47.7%)	30 (46.9%)	30 (47.6%)
- ASA+ticagrelor	26 (40.0%)	26 (40.6%)	25 (39.7%)
- ASA+prasugrel	7 (10.8%)	7 (10.9%	7 (11.1%)
- ASA+ticlopidine	1 (1.5%)	1 (1.6%)	1 (1.6%)
Statins	N=56 51 (91.1%)	N=55 48 (87.3%)	N=54 47 (88.9%)

Categorical data are given as the counts (percentage). *without interruption/change.
ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy

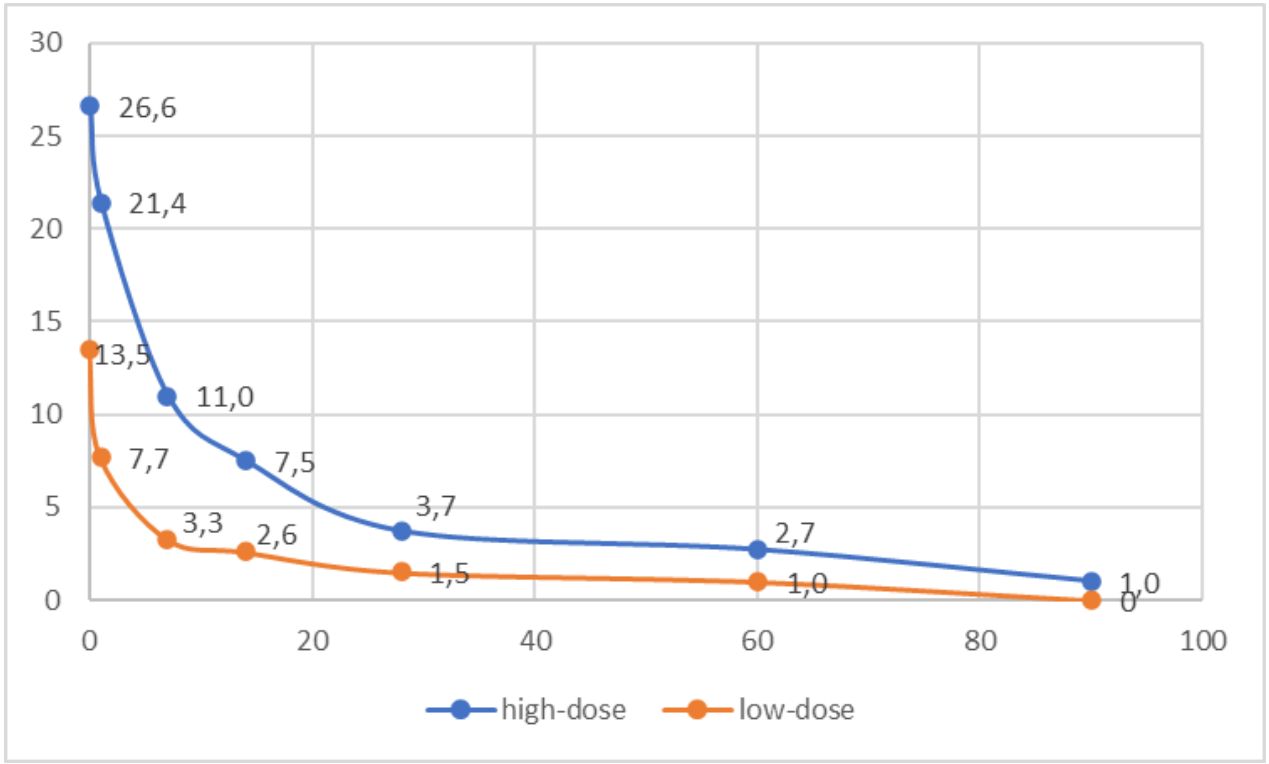
Supplementary Table 2. Baseline parameters, one-month strut coverage and nine-month late lumen loss of BIOrapid compared to current drug-eluting stents.

	BIOrapid	**BioFreedom [7,27]**	**Polymer-free DFS [21]**	**Orsiro [17,23,24]**	**Ultimaster [19,25]**	**Resolute Onyx [20]**	**XIENCE [23,24,25]**	**COBRA [28]**
Stent-type	PF	PF	PF	BP	BP	DP	DP	DP Nano-coated
Drug	BIOTORCIN	Biolimus A9	Sirolimus	Sirolimus	Sirolimus	Zotarolimus	Everolimus	Drug-free polymer PzF
Drug dose	1.7 µg/mm²	15.6 and LD: 7.8 µg/mm stent length	~1.1 µg/mm²	1.4 µg/mm²	3.9 µg/mm stent length	~1.6 µg/mm²	100 µg/cm²	NA
Baseline parameter								
Diabetes	12.1%	31.9% 28.3% 29.0% LD	30.0%	28.2% 27.3% 50%	23.3% 31.9%	26%	28.6% 26.4% 30.9%	33.7%
Stable angina	68.2%	 81.7% 75.8% LD	56.0%	-[4,5,6]	56.7% 49%	-	 46%	54.7%
ACC/AHA classification					-			-
Type A	7.6%	16.1%	-		4.4%	6%	3.9%	
Type B1	27.3%	38.3%	-		13.6%	27%	15.2%	
Type B2	40.9%	23.5%	-		48.3%	40%	53.0%	
Type C	24.2%	22.2%	-	77.5%	33.7%	27%	27.9%	
Type B2/C lesions	65.1%	 44.1% 44.4 LD%	76.8%		72.0%	67%	78.9% 80.9%	
RVD, mm	2.88±0.40	2.67±0.55 2.8*	2.70±0.43	2.78±0.49 2.86±0.64	2.62±0.55	-	2.75±0.49 2.86±0.56 2.66±0.55	2.74±0.48
Lesion length, mm	12.5±5.4	10.8±4.7	12.9±5.2	13.4±6.8	-	-	13.7±5.6	12.8±6.5

		10.6* 11.3 LD*		14.7±7.1	16.9±9.7		14.9±6.9 15.9±8.7	
Diameter stenosis, %	53.0±11.9	65.99±13.5 76.0%* 77.2%*,	63.8±9.5	66.7±14.3 62.0±12.6	67.4±12.2	-	65.3±14.5 62.0±14.5 67.4±13.4	64.95±11.4
Follow-up								
1-month strut coverage, %	95.2±5.6	-	91.4%*	80.4%	85.1±12.7	88%		-
9-month in-stent LLL, mm	0.30±0.31	0.32±0.53 0.17*,# 0.19 LD*,#	0.26±0.28	0.10±0.32 0.05±0.21	0.26±0.35	-	0.11±0.29 0.07±0.22 0.18±0.31	0.84±0.48

Data are displayed as mean±SD or %. * median. # @12 months.

BP: biodegradable polymer; DB: durable polymer; DFS: drug-filled stent; LLL: late lumen loss; NA: not applicable; PF: polymer free; Pzf: poly-bis(trifluoroethoxy)phosphazene; RVD: reference vessel diameter



Supplementary Figure 1. BIOrapid residual drug concentration in porcine implants.

3.0 x 13 mm stents, median values [days]