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The REMEDEE Trial

A Randomized Comparison of a Combination Sirolimus-Eluting Endothelial Progenitor Cell Capture Stent With a Paclitaxel-Eluting Stent

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Objectives This study sought to compare the efficacy and safety results after coronary implantation of a combined sirolimus-eluting CD34 antibody coated Combo stent (OrbusNeich Medical, Ft. Lauderdale, Florida) with the paclitaxel-eluting Taxus Liberté stent (PES) (Boston Scientific, Natick, Massachusetts). This report summarizes the first-in-man randomized, controlled multicenter REMEDEE trial (Randomized study to Evaluate the safety and effectiveness of an abluMinal sirolimus coatED bio-Engineered StEnt) angiographic, intravascular ultrasound, and clinical results up to 12 months.

Background Drug-eluting stents have limited restenosis and reintervention but are complicated by especially late and very late stent thrombosis and accelerated neoatherosclerosis. Alternative or adjunct technologies should address these limitations.

Methods One hundred eighty-three patients with de novo native coronary artery stenoses were randomized 2:1 to Combo stent or PES implantation. The primary endpoint is the angiographic in-stent late lumen loss at 9 months, which was tested for noninferiority between the 2 stent groups. Secondary endpoints include the occurrence of major adverse cardiac events.

Results The Combo stent was found to be noninferior to the PES in 9-month angiographic in-stent late lumen loss with 0.39 ± 0.45 mm versus 0.44 ± 0.56 mm ($p_{noninferiority} = 0.0012$). At 12 months, the occurrence of major adverse cardiac events was 8.9% in the Combo group and 10.2% in the PES group ($p = 0.80$) with no difference in mortality, occurrence of myocardial infarction, or target lesion revascularization. No stent thrombosis was reported in either group.

Conclusions In the REMEDEE trial the Combo stent has shown to be effective by meeting the primary noninferiority angiographic endpoint and safe, with an overall low rate of clinical events in both stent groups, including no stent thrombosis up to 12 months. (J Am Coll Cardiol Intv 2013;6:334–43) © 2013 by the American College of Cardiology Foundation

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Drug-eluting stents (DES) are associated with a significant reduction in neointimal formation compared with bare-metal stents (BMS), resulting in significant reductions in restenosis and reintervention rates. In the inaugural RAVEL trial (A Randomized Study With the Sirolimus Coated Modified BX Velocity Balloon-Expandable Stent in the Treatment of Patients With de Novo Native Coronary Artery Lesions) (1) with the sirolimus-eluting stent (SES), angiographic late lumen loss (LLL) was not measurable by angiography, with an accompanying absence of restenosis. Furthermore, it was observed and cautioned that DES are complex and that the long-term outcomes with these devices would depend on the response to 3 components: the stent, the coating, and the drug. These impressive results have not been as durable as initially hoped, being tempered especially by the ongoing occurrence of late and very late stent thrombosis (ST) (2), despite the prolonged use of dual antiplatelet therapy (DAPT) and additionally the development of in-stent neo-atherosclerosis.

These observations led to the development of second-generation DES that sought to improve the first generation by provision of thinner and absorbable polymer layers, thinner stent struts, alternative drug compounds, and lower doses of drugs. These modifications should produce more biologically compatible stents that would limit the response to stent injury through the healing process. These advancements resulted in lower risks of ST and target lesion revascularization (TLR) (3) rates.

Nevertheless, ST, restenosis, and in-stent neo-atherosclerosis remain an issue with contemporary DES. Therefore, further improvements should address early and predictive healing with neointimal stent strut coverage, allowing a significantly shorter duration of DAPT without losing efficacy with respect to LLL, restenosis, and the need for reintervention.

The immobilization of CD34 antibodies directed toward circulating endothelial progenitor cells (EPCs) applied to intravascular stents has been shown in a human ex vivo shunt model to increase the rate of cellular coverage, the expression of endothelial phenotype markers in the captured cells, and modulation of ST (4). When the CD34 antibody technology was applied to commercially available SES, it was shown to promote vascular healing and endothelialization (5). This has led to the development of a specifically engineered device, the Combo Bioengineered Sirolimus-Eluting Stent (OrbusNeich Medical, Ft. Lauderdale, Florida), which combines sirolimus elution from an abluminal biodegradable polymer matrix along with a covalently bound CD34 antibody layer in a combination device designed for control of neointimal proliferation as well as to promote vessel healing with accelerated stent strut tissue coverage (6) (Fig. 1).

Methods

The REMEDEE (Randomized study to Evaluate the safety and effectiveness of an abluMinal sirolimus coatED bio-Engineered StEnt) trial was undertaken to demonstrate the efficacy and safety of the Combo compared with the commercially available paclitaxel-eluting Taxus Liberté stent (PES) (Boston Scientific, Natick, Massachusetts) in the treatment of single de novo native coronary artery lesions.

Study management. The REMEDEE trial was conducted as a first-in-man multinational trial. The study sponsor provided financial support and the Combo stent study devices but otherwise was not directly involved with the study processes. An independent clinical research organization (Cardiovascular Research Foundation, New York, New York) had study responsibility for data collection; safety monitoring; angiographic, intravascular ultrasound, and electrocardiography core lab assessments; adjudication of adverse events by a Clinical Events Committee; data analysis; and independent regional site monitoring. The study was conducted in accordance with the Declaration of Helsinki, and the trial protocol and patient informed consent were reviewed and approved by all sites' institutional ethics committees and the respective local regulatory agencies.

Patient population. Patients eligible to participate in the study were ≥18 and ≤80 years of age, presenting with myocardial ischemia due to a ≥50% stenosed single de novo lesion ≤20 mm in length in a native coronary artery ranging in diameter from ≥2.5 to ≤3.5 mm. Patients had to be acceptable candidates for bypass surgery, should be amenable to long-term DAPT for a minimum of 6 months, and needed to be willing to comply with the specified follow-up evaluations. All patients were informed of the nature of the study, and written informed consent was obtained.

Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
CI = confidence interval
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
DS = diameter stenosis
EPC = endothelial progenitor cell
HAMA = human anti-murine antibody
IQR = interquartile range
IVUS = intravascular ultrasound
LLL = late lumen loss
MI = myocardial infarction
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
QCA = quantitative coronary angiography
SES = sirolimus-eluting stent(s)
ST = stent thrombosis
TLR = target lesion revascularization
VH = virtual histology

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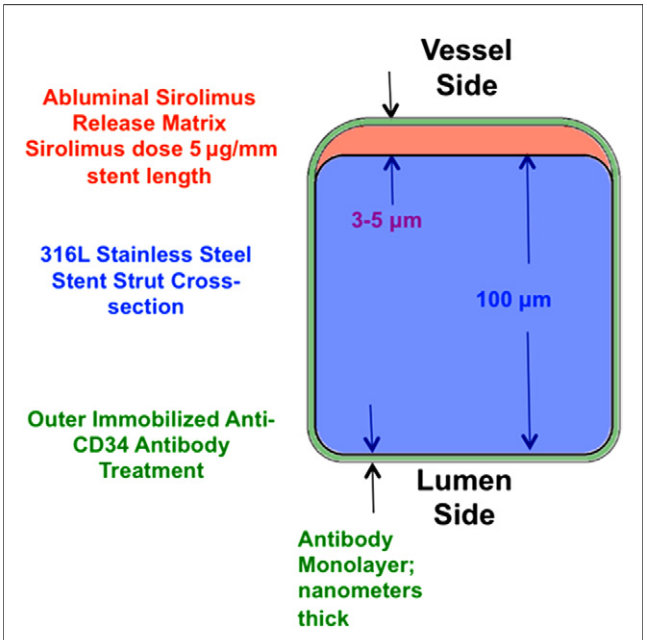

Figure 1. Combo Dual Therapy Stent

Combo stent (OrbusNeich Medical, Ft. Lauderdale, Florida).

Study protocol and randomization. Patients presenting with symptoms of myocardial ischemia were evaluated with the inclusion/exclusion criteria (Online Appendix) for their clinical appropriateness and their angiographic suitability. Baseline angiography of the target vessel was performed in at least 2 orthogonal views according to the angiographic core laboratory guidelines. Pre-dilation of the target lesion was performed per study stent labeling at the discretion of the operator but was mandatory in the setting of calcified lesions. Randomization was assigned with a sealed envelope method in an open-label 2:1 ratio to treatment with a Combo or PES.

Pre-procedural antiplatelet medication included: clopidogrel loading dose of 600 mg administered 0 to 24 h before the procedure or, for those patients already receiving chronic clopidogrel therapy of 75 mg (≥5 days), a loading dose of 300 mg was given; if the subject was allergic to clopidogrel, ticlopidine (500 mg) was administered 6 h before the procedure; all patients received a loading dose of aspirin (300 or 325 mg or dose per standard hospital practice) at least 2 h before the procedure. Subjects received appropriate peri-procedural anticoagulation medications during the stenting procedure according to the local site practice.

Before stent implantation, coronary angiography of the target lesion was recorded in 2 orthogonal views after vasodilation with nitroglycerine. Stents were sized after a stent/artery ratio of 1.1:1. It was recommended that a minimum of 1.5 mm of nondiseased vessel segment on either side of the lesion should be covered by the stent. If necessary, post-dilation of the deployed stents was recommended with a noncompliant shorter balloon within the boundaries of the implanted stent. Bail-out stenting was allowed to treat major flow-limiting dissections, with a study stent of the same type as the randomization stent of the subject in an appropriate size.

"Device success" was defined as an achievement of a final in-stent residual diameter stenosis (DS) of <50% (by quantitative coronary angiography [QCA]), with the assigned device only and without device malfunction. "Lesion success" was defined as an achievement of a final in-stent residual DS of <50% (by QCA) with any percutaneous method, whereas "procedure success" was quoted as an achievement of a final in-stent DS of <50% (by QCA) with the assigned device and with any adjunctive devices, without the occurrence of cardiac death, Q-wave or non–Q-wave myocardial infarction (MI), or repeat vascularization of the target lesion during the hospital stay.

Post-procedure angiography of the target vessel was performed in the same 2 orthogonal views showing the target lesion, which were repeated during 9-month follow-up angiography.

Six sites were prospectively designated to collect baseline and 9-month intravascular ultrasound (IVUS) with either a 20-MHz imaging catheter (n = 23) (Eagle Eye Gold, Volcano, Rancho Cordova, California) or a mechanical rotating element 40-MHz transducer (n = 43) (Atlantis, Boston Scientific) both by automated pullback at 0.5 mm/s.

Post-procedure, all subjects were treated for at least 6 months up to 12 months with clopidogrel (75 mg/day). Aspirin was prescribed (minimum of 75 mg/day and up to 162 mg/day or dose per local site practice) indefinitely as tolerated per the percutaneous coronary intervention (PCI) treatment guidelines (7,8).

Clinical follow-up. The assessment of safety and effectiveness was evaluated during telephone contacts or office visits at the following time points: in-hospital 30 ± 7 days; 9 months ± 30 days; and 1 year ± 30 days. Continuing clinical follow-up is planned at 2, 3, 4, and 5 years ± 60 days.

Study endpoint definitions. The primary study endpoint was defined as angiographic in-stent LLL at 9 months. Secondary efficacy endpoints included: device, lesion, and procedural success; clinically (ischemia)-driven TLR; clinically (ischemia)-driven target vessel revascularization; clinically (ischemia)-driven target vessel failure; clinically driven-target lesion failure; in-stent, and in-segment angiographic binary restenosis; in-stent and in-segment angiographic minimum lumen diameter; and neointimal hyperplasia volume and percentage in-stent volume obstruction by IVUS and tissue composition of the vessel wall, especially of the intra-stent tissue with backscatter analysis of radiofrequency signals (IVUS-virtual histology [VH]) at 9 months (9,10). Secondary safety endpoints included the occurrence of: all-cause and cardiac mortality; MI; major

adverse cardiac events; and ST. Vascular complications were reported from index procedure through hospital discharge. Each patient was assessed for a human anti-murine antibody (HAMA) response at 30 days and 9 months.

Adjudication of study endpoints. All angiographic, IVUS-based, and clinical (including ST per the Academic Research Consortium [ARC] [11] definitions) endpoints were measured and assessed by the Angiographic Core Laboratory (Cardiovascular Research Foundation, New York) and adjudicated by the Clinical Event Committee, which reported to the Data Safety Monitoring Board.

Statistical analysis. The primary endpoint was an efficacy endpoint of noninferiority in 9-month angiographic in-stent LLL between the Combo and PES. It was assumed that the in-stent LLL at 9 months for the PES would be 0.40 and 0.30 mm for Combo with similar SDs of 0.53 mm (12). A noninferiority margin of 0.20 mm was chosen. With a statistical power of 90%, an α-error of 0.05, a 2:1 randomization, and an anticipated loss to follow-up of 20%, a sample size determination found that 120 patients should be randomized to the Combo and 60 to the TAXUS arm.

An intention-to-treat analysis was performed for the primary endpoint with the noninferiority t test. Per study protocol, if the test for noninferiority was successful, then a test for superiority was to be performed. All angiographic secondary endpoints were evaluated in the full analysis set with descriptive statistics. All clinical secondary endpoints were evaluated in the intention-to-treat population without pre-defined hypothesis testing. The secondary endpoints were summarized with the mean, median, SD, minimum, maximum, and sample size for each treatment group, including 2-sided 95% confidence intervals (CIs) of the mean difference between the treatment groups for continuous variables; frequencies, percentages, and 2-sided exact 95% CIs for binary endpoints; or time-to-event Kaplan-Meier analysis, as appropriate, for clinical endpoints. A p value of <0.05 was considered statistically significant.

Results

Between November 2009 and August 2010, a total of 183 patients were enrolled at 17 investigative sites in Australia, Europe, Brazil, and Asia-Pacific, with 124 in the Combo group and 59 in the PES group.

Baseline characteristics. The baseline key demographic data, medical history, pre-procedural cardiac status, and baseline lesion characteristics were well-matched between the study groups (Tables 1 and 2). A relatively high proportion of the subjects (33.1% and 37.3%, respectively) were diabetic. No significant differences were seen in any of these baseline parameters between the treatment groups.

Procedural results. The baseline device and procedural characteristics are summarized in Table 3. The procedure success was 96.8% in the Combo group and 98.3% in the PES group (p = 1.00). There were no significant differences in any of these procedural parameters between the treatment groups.

Table 1. Baseline Clinical Characteristics

	Combo (n = 124)	TAXUS (n = 59)	p Value
Age (yrs)	64.20 ± 9.48	64.05 ± 10.49	0.92
Men	89 (71.8%)	42 (71.2%)	0.93
Smoking/tobacco usage	71 (57.3%)	28 (47.5%)	0.21
Current smoker	26 (21.0%)	10 (16.9%)	0.52
Diabetes mellitus	41 (33.1%)	22 (37.3%)	0.57
Insulin-dependent	9 (7.3%)	7 (11.9%)	0.30
History of hypertension	100 (80.6%)	45 (76.3%)	0.50
History of hyperlipidemia	102 (82.3%)	43 (72.9%)	0.14
Left ventricular ejection fraction (%)	63.87 ± 11.93 (119)	63.33 ± 11.59 (59)	0.77
Premature cardiovascular disease in 1st-degree relative	36 (29.0%)	23 (39.0%)	
Previous congestive heart failure	17 (13.7%)	6 (10.2%)	0.50
Previous MI	31 (25.0%)	16 (27.1%)	0.76
Previous PCI	29 (23.4%)	12 (20.3%)	0.64
Previous CABG	4 (3.2%)	2 (3.4%)	1.00
History of renal insufficiency	8 (6.5%)	1 (1.7%)	0.28
Angina status			
Silent ischemia	13 (10.5%)	6 (10.2%)	0.95
Stable angina	91 (73.4%)	43 (72.9%)	0.94
CCS I	13 (10.5%)	10 (16.9%)	0.22
CCS II	60 (48.4%)	29 (49.2%)	0.92
CCS III	15 (12.1%)	4 (6.8%)	0.27
CCS IV	3 (2.4%)	0 (0.0%)	0.55
Unstable angina	20 (16.1%)	10 (16.9%)	0.89
Braunwald I	6 (4.8%)	2 (3.4%)	1.00
Braunwald II	8 (6.5%)	2 (3.4%)	0.50
Braunwald III	6 (4.8%)	6 (10.2%)	0.21

Values are mean ± SD or n (%). Combo stent (OrbusNeich Medical, Ft. Lauderdale, Florida); Taxus Liberté stent (PES) (Boston Scientific, Natick, Massachusetts).

CABG = coronary bypass surgery; CCS = Canadian Cardiovascular Society; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Primary endpoint. In the Combo group, in-stent LLL was 0.39 ± 0.45 mm, which was noninferior to the in-stent LLL of 0.44 ± 0.56 mm in the PES group ($p_{noninferiority}$ = 0.0012). This difference in in-stent LLL of 0.05 mm in favor of the Combo stent was not statistically significant ($p_{superiority}$ = 0.5514). The distribution of in-stent LLL in the PES group showed a bimodal appearance resulting in a larger SD, compared with the Combo group (Fig. 2). With regard to the non-normal nature of the in-stent LLL distributions, the nonparametric Mann–Whitney test of the medians was performed with the same margin of 0.20 mm as before. The result of this test confirmed that the 9-month in-stent late loss with the Combo stent is noninferior to the

Table 2. Baseline Lesion Characteristics

	Combo (n = 124)	TAXUS (n = 59)	p Value
Target lesion type, de novo	124 (100.0%)	59 (100.0%)	N/A
Target lesion vessel			
LAD	54 (43.5%)	32 (54.2%)	0.18
RCA	31 (25.0%)	10 (16.9%)	0.22
Circumflex	39 (31.5%)	17 (28.8%)	0.72
Lesion location			
Ostial	1 (0.8%)	1 (1.7%)	0.54
Proximal	44 (35.5%)	23 (39.0%)	0.65
Mid	67 (54.0%)	28 (47.5%)	0.41
Distal	12 (9.7%)	7 (11.9%)	0.65
Lesion length (mm)	13.69 ± 5.07	14.64 ± 4.41	0.22
(min, max)	(5.08, 45.57)	(5.25, 24.83)	N/A
Eccentric	4 (3.2%)	5 (8.5%)	0.15
Angulation >45°	12 (9.7%)	4 (6.8%)	0.52
Thrombus	0 (0.0%)	0 (0.0%)	N/A
Tortuosity			
None	119 (96.0%)	57 (96.6%)	1.00
Moderate	4 (3.2%)	2 (3.4%)	1.00
Severe	1 (0.8%)	0 (0.0%)	1.00
Calcification			
None or mild	97 (78.2%)	51 (86.4%)	0.19
Moderate	26 (21.0%)	8 (13.6%)	0.23
Severe	1 (0.8%)	0 (0.0%)	1.00
TIMI score			
TIMI 0	0 (0.0%)	0 (0.0%)	N/A
TIMI 1	1 (0.8%)	1 (1.7%)	0.54
TIMI 2	5 (4.0%)	2 (3.4%)	1.00
TIMI 3	118 (95.2%)	56 (94.9%)	1.00
ACC/AHA lesion class			
A	14 (11.3%)	12 (20.3%)	0.10
B1	28 (22.6%)	11 (18.6%)	0.54
B2	70 (56.5%)	30 (50.8%)	0.48
C	12 (9.7%)	6 (10.2%)	0.92
Pre-procedure RVD (mm)	2.77 ± 0.42	2.85 ± 0.34	0.18

Values are n (%) or mean ± SD.

ACC = American College of Cardiology; AHA = American Heart Association; LAD = left anterior descending artery; RCA = right coronary artery; RVD = reference vessel diameter; TIMI = Thrombolysis In Myocardial Infarction.

TAXUS Liberté stent (Combo: median = 0.29 mm, interquartile range [IQR: 0.485 mm; TAXUS: median = 0.29 mm, IQR: 0.445 mm; 95% CI for the difference between the medians: −0.120 to 0.120, $p_{noninferiority} = 0.002$).

Secondary angiographic and IVUS endpoints. At the 9-month angiographic follow-up, all results of the angiographic and IVUS measurements were comparable between the groups (Table 4). The 9-month angiographic group consisted of 109 from the Combo group and 52 from the PES group. The Combo stent showed a numerically lower occurrence of angiographic binary restenosis and a trend toward a reduced in-segment LLL in comparison with the PES. In addition to the 2-sample *t* test of the in-segment LLL (Table 3), the nonparametric Mann–Whitney test of the medians of the in-segment LLL was performed with the following result: Combo: median = 0.16 mm, IQR: 0.445 mm; TAXUS: median = 0.31 mm, IQR: 0.680 mm; 95% CI for the difference between the medians: −0.291 to 0.045, $p_{superiority} = 0.127$.

Baseline IVUS was performed in a subgroup of 66 patients (45 Combo and 21 Taxus). The IVUS follow-up at 9 months consisted of 35 from the Combo group and 17 from the PES group. IVUS revealed a numerically lower neointimal hyperplasia volume of 21.5 ± 21.7 mm^3 versus 25.9 ± 18.7 mm^3 (p = 0.4955) for Combo compared with PES. The in-stent volume obstruction was 15.24 ± 14.22% versus 14.59 ± 8.38% (p = 0.8432). IVUS-VH comparison of Combo with PES found a significantly less necrotic core area at maximum site on neointimal hyperplasia of 0.25 mm^2 versus 0.46 mm^2 (p = 0.04) and a less confluent necrotic core of 10% versus 80% (p = 0.02), as illustrated in Figure 3.

Secondary clinical endpoints. The adjudicated clinical endpoints and associated Kaplan-Meier estimates for event rates at 30 days and 12 months are summarized in Table 5. Very low event rates were reported in all categories for both groups, with no significant differences in any of the categories. Two deaths were reported in the Combo group. One patient first received a nonstudy device in the right coronary artery (nontarget vessel) and then a Combo in the left circumflex coronary artery during the index procedure. This patient underwent 9-month follow-up angiography, revealing both stents patent. The site coordinator learned the patient had died on day 324 post-index PCI while scheduling the 1-year follow-up. The site reported that the patient was receiving DAPT at the time of death. The critical event committee has adjudicated this as a cardiac death. The other patient developed a sub-arachnoidal hemorrhage while taking DAPT, leading to a fatal outcome. This case was adjudicated by the Clinical Events Committee as a noncardiac death. All incidences of MI in both groups were cases of peri-procedural non–Q-wave MI associated with the index procedure. No ARC definite or probable ST occurred in either group during the 12-month follow-up period.

HAMA plasma level response. At baseline, 4 subjects were found to have a detectable level of HAMA, but coincidentally none of these were randomized to the Combo arm—all were in the PES cohort. At both 30 day and 9-month follow-up, none of the subjects receiving the Combo device showed a detectable level, whereas 3 of the subjects receiving the PES had detectable levels of HAMA at both follow-up time points.

Discussion

Angiographic results. In the REMEDEE trial, the Combo stent was found to be noninferior to the PES with respect to 9-month angiographic in-stent LLL and thereby met its primary endpoint. The observed in-stent LLL of 0.39 mm

Table 3. Procedural Results

	Combo (n = 124)	TAXUS (n = 59)	Difference (95% CI)	p Value
Site reported				
Device success	123 (99.2%)	59 (100.0%)	1.01 (0.99 to 1.02)	1.00
Lesion success	124 (100.0%)	59 (100.0%)	N/A	N/A
Procedure success (protocol defined)	120 (96.8%)	58 (98.3%)	1.02 (0.97 to 1.06)	1.00
Procedure success (ARC)	114 (91.9%)	56 (94.9%)	1.03 (0.95 to 1.12)	0.55
Number of lesions treated/patient	1.10 ± 0.31	1.15 ± 0.36	−0.05 (−0.15 to 0.05)	0.36
Number of study stents deployed/patient	1.06 ± 0.33	1.03 ± 0.18	0.03 (−0.06 to 0.12)	0.42
Total length of implanted study stents (mm)	19.45 ± 6.91	20.07 ± 5.23	−0.62 (−2.62 to 1.39)	0.50
Maximum diameter of implanted study stents (mm)	3.02 ± 0.36	3.03 ± 0.30	−0.01 (−0.11 to 0.10)	0.92
QCA				
Number of stents implanted/lesion	1.07 ± 0.32	1.03 ± 0.18	0.04 (−0.05 to 0.13)	0.30
Final % DS				
In-stent	4.61 ± 7.40	4.65 ± 6.46	−0.03 (−2.25 to 2.19)	0.98
In-segment % DS	17.13 ± 7.11	17.40 ± 7.50	−0.27 (−2.53 to 1.99)	0.81
Acute gain (mm)				
In-stent	1.84 ± 0.42	1.87 ± 0.33	−0.03 (−0.15 to 0.10)	0.66
In-segment	1.50 ± 0.43	1.51 ± 0.36	−0.01 (−0.14 to 0.12)	0.89
Final TIMI score				
TIMI 3	124 (100.0%)	59 (100.0%)	0.00 (−1.3 to 1.3)	N/A

Values are n (%) or mean ± SD.

ARC = Academic Research Consortium; CI = confidence interval; DS = diameter stenosis; QCA = quantitative coronary angiography; TIMI = Thrombolysis In Myocardial Infarction.

for the Combo stent was greater than that reported for conventional SES, where Cypher (Cordis, Miami Lakes, Florida) LLL values have been reported up to 0.24 mm, including diabetic patients (13–15). These angiographic results are in line with the expected capture of circulating EPCs by the CD34 antibody, creating a fast and complete layer of cells leading to the covering of the stent struts. Experimental data have shown that the abluminal release of sirolimus by the Combo stent results in a similar effective dosage in the stented arterial wall, as with the omnidirectional release by the SES, yet with a drastically reduced release to the circulation (6).

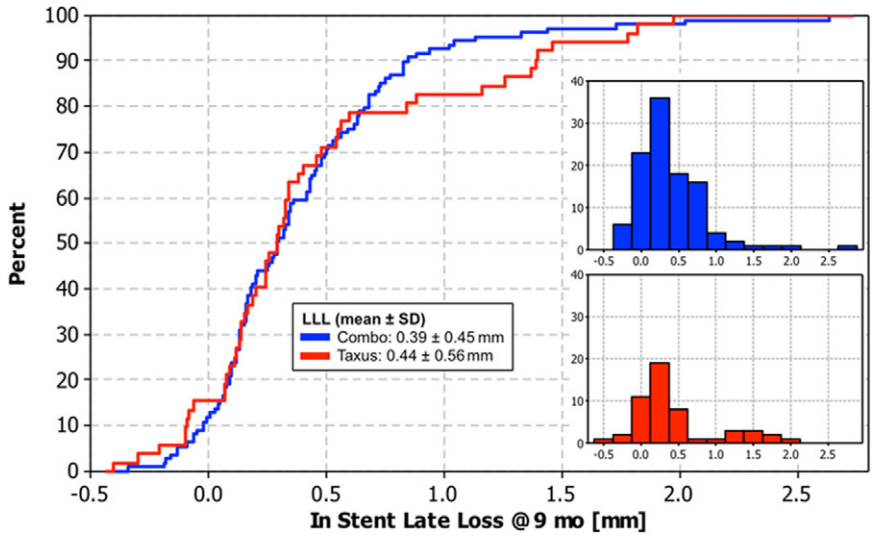

Figure 2. Cumulative Frequency Distribution and Histograms of Angiographic In-Stent LLL

LLL = late lumen loss.

Table 4. Angiographic Results

	Combo (n = 109)	TAXUS (n = 52)	Difference (95% CI)	Superiority p Value
Angiographic binary restenosis (%)				
In-stent	6 (5.5%)	5 (9.6%)	−4.1% (−14.7 to 6.5)	0.34
In-segment	9 (8.3%)	7 (13.5%)	−5.2% (−17.3 to 6.9)	0.30
MLD (mm), post-procedure				
In-stent	2.69 ± 0.40	2.76 ± 0.31	−0.06 (−0.18 to 0.05)	0.24
In-segment	2.35 ± 0.42	2.40 ± 0.36	−0.05 (−0.17 to 0.08)	0.46
MLD (mm), 9-month follow-up				
In-stent	2.31 ± 0.58	2.30 ± 0.56	0.02 (−0.17 to 0.21)	0.86
In-segment	2.09 ± 0.56	1.97 ± 0.57	0.12 (−0.06 to 0.31)	0.19
In-stent LLL (mm)	0.39 ± 0.45	0.44 ± 0.56	−0.5 (−0.21 to 0.11)	0.0012
			(Noninferiority p value)	
In-segment LLL (mm)	0.27 ± 0.46	0.41 ± 0.54	−0.14 (−0.30 to 0.02)	0.08

Values are n (%) or mean ± SD. Full analysis set: intent-to-treat patients with qualifying 9-month angiographic follow-up included in the analyses. Late loss estimated by angiographic core laboratory for patients with available 9-month qualifying angiogram.

CI = confidence interval; DS = diameter stenosis; LLL = late lumen loss; MLD = minimal lumen diameter.

Angiographic LLL has been used as a surrogate for DES efficacy in preventing angiographic restenosis and the need for repeat TLR (16,17). A pooled analysis of 11 randomized DES trials enrolling 8,726 patients confirmed that LLL is indeed a suitable surrogate for 12-month TLR rates in comparing DES with BMS (18). However, given the logistic curvilinear relationship between LLL and TLR and the relatively flat curve at LLL values below 0.5 to 0.6 mm, it seems very unlikely that improvements in LLL translate into sizable differences in TLR, considering the statistical power calculation of this trial. Interestingly, the observed differences in corresponding rates of angiographic restenosis at 9 months of 5.5% for the Combo stent compared with 9.6% for PES and an incidence of TLR at 12 months of 4.9% for the Combo stent compared with 8.5% for PES did not gain statistical significance but were unexpected, given the similarity in in-stent LLL. The numerically lower LLL of the Combo stent seems to be leveraged in a disproportionally lower TLR rate with Combo in comparison with PES. This cannot be explained by the difference between the averages alone but more likely is the result of the bimodal nature of the LLL distribution in the PES arm. This bimodal nature indicates a diminished antiproliferative response to the stent in a particular patient subgroup and has been reported before for PES and SES (19).

Furthermore, it has been suggested that in-segment LLL rather than in-stent LLL might be a better predictor for clinical events with DES, because edge stenosis at the stent margins have been found to lead to more TLRs with DES

Figure 3. Gray-Scale and VH IVUS at Baseline and 9-Month Follow-Up

IVUS = intravascular ultrasound; VH = virtual histology.

Table 5. Secondary Effectiveness and Safety Endpoints

Safety and Effectiveness Measures	Combo (n = 124)	TAXUS (n = 59)	Difference or Hazard Ratio (95% CI)	p Value
Acute success				
Device success	123 (99.2%)	59 (100.0%)	1.01 (0.99–1.02)	1.00
Lesion success	124 (100.0%)	59 (100.0%)	N/A	N/A
Procedure success (protocol defined)	120 (96.8%)	58 (98.3%)	1.02 (0.97–1.06)	1.00
Procedure success (ARC)	114 (91.9%)	56 (94.9%)	1.03 (0.95–1.12)	0.55
Vascular complications	3 (2.4%)	2 (3.4%)	0.71 (0.12–4.16)	0.66
Measures at 30 days				
Death	0 (0.0%)	0 (0.0%)	N/A	N/A
Cardiac death	0 (0.0%)	0 (0.0%)	N/A	N/A
MI (protocol defined)	3 (2.4%)	1 (1.7%)	1.44 (0.15–13.83)	0.75
Q-wave	0 (0.0%)	0 (0.0%)	N/A	N/A
Non–Q-wave	3 (2.4%)	1 (1.7%)	1.44 (0.15–13.83)	0.75
MACE (protocol defined)	3 (2.4%)	1 (1.7%)	1.44 (0.15–13.83)	0.75
ARC stent thrombosis (definite or probable)	0 (0.0%)	0 (0.0%)	N/A	N/A
Clinically driven TLR	0 (0.0%)	0 (0.0%)	N/A	N/A
Clinically driven TVR	0 (0.0%)	0 (0.0%)	N/A	N/A
Clinically driven TVF (protocol defined)	3 (2.4%)	1 (1.7%)	1.44 (0.15–13.83)	0.75
Clinically driven TLF (protocol defined)	3 (2.4%)	1 (1.7%)	1.44 (0.15–13.83)	0.75
Measures at 12 months				
Death	2 (1.6%)	0 (0.0%)	N/A	0.33
Cardiac death	1 (0.8%)	0 (0.0%)	N/A	0.49
MI (protocol defined)	3 (2.4%)	1 (1.7%)	1.44 (0.15–13.83)	0.75
Q-wave	0 (0.0%)	0 (0.0%)	N/A	N/A
Non–Q-wave	3 (2.4%)	1 (1.7%)	1.44 (0.15–13.83)	0.75
MACE (protocol defined)	11 (8.9%)	6 (10.2%)	0.88 (0.32–2.37)	0.80
ARC stent thrombosis (definite or probable)	0 (0.0%)	0 (0.0%)	N/A	N/A
Clinically driven TLR	6 (4.9%)	5 (8.5%)	0.57 (0.17–1.88)	0.35
Clinically driven TVR	8 (6.5%)	6 (10.2%)	0.64 (0.22–1.85)	0.41
Clinically driven TVF (protocol defined)	13 (10.5%)	7 (11.9%)	0.90 (0.36–2.24)	0.81
Clinically driven TLF (protocol defined)	11 (8.9%)	6 (10.2%)	0.88 (0.32–2.37)	0.80

Values are n (%) or mean ± SD. Kaplan-Meier estimates for the rates at the indicated time point are displayed for time-to-event variables. Hazard ratios and 2-sided 95% CIs for time-to-event variables were obtained from Cox regression models with treatment as main effect. Differences in proportions and 2-sided 95% CIs for binary variables were calculated with exact methods.

MACE = major adverse cardiac events (composite of death, MI [Q-wave or non–Q-wave], emergent CABG, or target lesion revascularization [TLR] by repeat percutaneous transluminal coronary angioplasty, or CABG); TLF = target lesion failure; TVF = target vessel failure; TVR = target vessel revascularization; other abbreviations as in Tables 1 and 3.

than with BMS (18). In the REMEDEE trial, the Combo stent showed a strong trend toward a reduced in-segment LLL compared with the PES.

Recent data have shown that LLL after DES stent implantation is increasing over time, resulting in a continuous increase of TLRs and ST between 1 and 5 years after stenting, seemingly driven by aggressive in-stent neo-atherosclerosis. The time course of TLR and ST rates with several DES platforms have clearly shown that an initial low LLL and TLR rate at 1 year is not predictive of long-term durability (20–23). In fact, the stent with an initially higher TLR (and in-stent LLL) demonstrates more stable long-term clinical outcome. It seems that in the long run patients benefit more from an adequately healed stent than from an initially lower LLL. Long-term follow-up to 5 years in the REMEDEE trial will provide information as to whether the CD34 antibody-mediated capturing of EPCs combined with the antiproliferative effect of abluminal sirolimus elution produces durable clinical results.

IVUS results. Neointimal hyperplasia volume and percentage in-stent volume obstruction measured by gray-scale IVUS showed similar results for the Combo stent and PES. The observation of neo-atherosclerosis in DES has raised questions on the nature of long-term healing and the parameters that influence it (24). Even though neo-atherosclerosis was also observed in BMS, it seems that its progress is more gradual and that the tissue is denser and contains less confluent necrotic core than with DES. In the REMEDEE study, IVUS and VH–IVUS results revealed a

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BMS-like composition and morphology of the neointimal tissue, showing less confluent necrotic core in the Combo stent in comparison with PES (10). Despite the small number of patients with VH–IVUS evaluation this observation was statistically significant, and these observations of the Combo stent are consistent with the anticipated prohealing effect of the immobilized CD34 antibody together with the time-limited inflammatory aspect of the biodegradable polymer, which is resorbed 90 days after implantation, leaving only a BMS after that time (25).

Clinical results. The REMEDEE trial was not powered to differentiate for clinical endpoints, and very few clinical events were reported in either group, so it was not surprising that differences in death, MI, TLR, and their composites between both groups did not reach statistical significance. No ARC definite or probable ST was reported for either device. Long-term follow-up to 5 years will provide results on very late ST. The absence of a positive HAMA response after Combo stent implantation suggests that sensitization by the CD34 antibody is unlikely.

Study limitations. The PES was selected as a control, because at the time of the study design initiation it represented a well-accepted first-generation DES that has been used in other first-in-man studies as a comparator and because its in-stent LLL value was expected to be in the same range as with Combo, allowing an assessment of the primary endpoint with a smaller number of patients.

The REMEDEE trial was powered only for noninferiority of in-stent LLL. Other comparisons between the 2 arms should be interpreted as hypothesis-generating observations warranting further clinical studies, both with clinical endpoints and with suitable surrogate endpoints to demonstrate the healing effect of the stent. Additionally, the study population was limited to uncomplicated patients with stable angina, undergoing elective PCI.

Conclusions

The first-in-man REMEDEE trial with the Combo stent met the primary objective and found the COMBO stent to be noninferior to the PES in angiographic in-stent LLL at 9 months. In-stent and in-segment late loss and binary restenosis rates for the Combo were accordingly low and comparable to the PES. There was an overall low rate of clinical events observed in both groups, including no ARC definite or probable ST. The Combo stent was shown to be effective and safe throughout the first year in the REMEDEE trial. Future studies will have to document long-term safety and efficacy, allowing the attempt for a reduced duration of DAPT.

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Key Words: DES ■ EPC capture stent ■ healing ■ stent.

APPENDIX

For a detailed listing of the inclusion and exclusion criteria from the study protocol, please see the online version of this paper.