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The REMEDEE trial: 5-Year results on a novel combined sirolimus-eluting and endothelial progenitor cells capturing stent

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Abstract

Objectives: To evaluate the long-term safety and efficacy of the novel combined sirolimus-eluting endothelial progenitor cell capture Combo stent (OrbusNeich, Fort Lauderdale, FL) at 5 years in the REMEDEE (Randomized study to Evaluate the safety and effectiveness of an abluMinal sirolimus coated bio-Engineered stEnt) trial.

Background: Drug–eluting stents have limited restenosis and reintervention but are complicated by late and very late thrombosis and accelerated neoatherosclerosis. Alternative or adjunctive technologies are needed to address these limitations.

Methods: A total of 183 patients with de novo lesions in native coronary arteries were randomized 2:1 to Combo (n = 124) or Taxus Liberté (n = 59). Primary endpoint was 9 month angiographic in-stent late lumen loss and the secondary endpoint was the occurrence of major adverse events (MACE) through 5-year follow-up.

Results: Compared with Taxus, after 5 years the Combo stent was associated with similar rates of MACE (18.3% vs. 16.9%, p = .89), cardiac death (0.8% vs. 5.1%, p = .07), myocardial infarction (4.1% vs. 3.4%, p = .81), target lesion (9.4% vs. 10.2%, p = .78), and target vessel revascularization (14.4% vs. 11.9%, p = .73). No cases of definite stent thrombosis were reported in the Combo group. The follow-up rate at 5 years was 97.7%.

Conclusion: At 5-year follow-up, the Combo stent remained clinically safe and effective with an overall low rate of MACE comparable to Taxus.

KEYWORDS

drug-eluting stents, percutaneous coronary intervention, progenitor endothelial cells, sirolimus

1 | INTRODUCTION

The effectiveness of drug-eluting stents (DES) to significantly reduce restenosis and the need for repeat revascularization procedures is well documented making them the standard of care for patients presenting with coronary artery stenosis.[1] However, because DES are associated with delayed endothelial healing,[2,3] concerns exist about their long-term safety as evidenced by the occurrence of late and very late stent thrombosis despite prolonged dual antiplatelet therapy (DAPT).[4,5] These concerns have led to the development of newer DES, incorporating thinner struts, directional (abluminal) release of limus analog drugs, and optimized stable or biodegradable polymers with the goal of accelerating neointimal coverage and re-endothelialization of the stented segment, thereby decreasing the incidence of stent thrombosis.

Endothelial progenitor cells (EPC) are circulating bone marrow-derived cells that are mobilized at the site of vessel injury where they differentiate into mature endothelial cells and promote re-endothelialization.[6,7] Indeed, animal studies have demonstrated that stents coated with CD34 antibodies capturing circulatory EPC accelerate re-endothelialization and reduce thrombogenicity.[8–11] In the clinical setting, EPC capturing stents have shown quite acceptable low mid- and long-term rates of major adverse events (MACE),[12–14] but the absence of an antiproliferative drug resulted in higher rates of target lesion revascularization (TLR) in comparison with DES in patients at high risk of restenosis.[15]

The Combo stent design combines the potential of EPC capturing technology with the effectiveness of modern DES and this approach has delivered the envisaged advantages in experimental models.[10,11] Favorable 9-month angiographic and 1 year clinical results of first-in-man REMEDEE (Randomized study to Evaluate the safety and effectiveness of an abluMinal sirolimus coated bio-Engineered stEnt) study provided the first clinical evidence with the Combo stent.[16]

The present report describes the final 5-year clinical outcomes of the randomized multicenter REMEDEE trial in which patients with de novo lesions in native coronary arteries were treated with the Combo stent.

2 | MATERIALS AND METHODS

2.1 | Patient population and study design

REMEDEE [NCT00967902] was a phase III prospective, multicenter, randomized study designed to demonstrate the safety and efficacy of the Combo™ Bio-Engineered Sirolimus-Eluting Stent (OrbusNeich, Fort Lauderdale, FL) in the treatment of symptomatic ischemic heart disease. The study design and methods have been described in detail previously.[16] Briefly, 183 patients ≥18 and ≤80 years of age with a single de novo stenotic lesion located in a native coronary artery ≥2.5–≤3.5 mm in diameter and ≤20 mm in length were randomized 2:1 to Combo (n = 124) or Taxus Liberté (n = 59). The study protocol was approved by the ethics review committee of each participating center, and all patients provided prior written informed consent. The trial was conducted in compliance with the declaration of Helsinki and local regulatory requirements.

2.2 | Combo™ bio-engineered sirolimus-eluting stent

The dual therapy Combo stent is a 316L stainless steel stent (dual helix design with 100 μm thick strut) with an abluminal coating of a biodegradable polymer matrix formulated with sirolimus (5 μg/mm per stent length) for sustained release, and an additional anti-CD34 antibody coating (3–5 μm thick) on the luminal side. Sirolimus is completely eluted within 30 days, and the polymer carrier is completely degraded within 90 days. The anti-CD34 antibody layer is designed to capture circulatory EPC to accelerate re-endothelialization of the stent. The Combo stent has a crossing profile of 1.06 mm (compatible with a 5F guiding catheter), and is available in diameters of 2.5–4.0 mm and lengths of 9–33 mm.

2.3 | Study procedures

Stents were implanted after balloon predilatation as described.[16] Per protocol, all patients received a 300–600 mg loading dose of clopidogrel 0–24 hr before the procedure and a 300–325 mg loading dose of aspirin at least 2 hr before the procedure. Afterward, all patients received clopidogrel 75 mg/day (or prasugrel 10 mg/day or ticlopidine 250 mg twice daily) for at least 6 months and aspirin (75–162 mg/day) indefinitely.

2.4 | Follow-up

Clinical follow-up was scheduled per protocol at 1, 9, and 12 months and yearly thereafter for 5 years. Quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) follow-ups were also scheduled at 9 months for the primary endpoint of in-stent late lumen loss (LLL).

2.5 | Study endpoints

The primary endpoint was the in-stent LLL of the Combo stent compared to the Taxus stent at 9 months post-procedure. Secondary safety endpoints included all-cause and cardiac mortality, myocardial infarction (MI; Q-wave and non Q-wave), MACE (defined as a composite of death, MI, ischemic TLR, or stent thrombosis). Stent thrombosis was defined per Academic Research Consortium definition of definite and probable stent thrombosis. Secondary efficacy endpoints included clinically driven TLR, clinically driven target vessel revascularization (TVR), target vessel failure (TVF; defined as death, MI, and TVR), and target lesion failure (TLF; defined as death, MI, and TLR). All potential MACE and stent thromboses were reviewed and adjudicated by a clinical events committee. Safety data were reviewed periodically by an independent data monitoring committee.

2.6 | Data management

Data management was performed by Cardiovascular Research Foundation (New York, NY) using the ClinPlus® (Bound Brook, NJ) database. Clinical data quality control was conducted through queries

issued by the contracted monitoring group personnel. Independent monitoring at each clinical site was provided to verify proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse events, and accuracy of data collected on case report forms and device information.

2.7 | Statistical analyses

Statistical analyses were performed by Cardiovascular Research Foundation (New York, NY). All primary and secondary endpoints were evaluated in all subjects enrolled in the study for whom data are available, regardless of whether they received a stent or not (intention-to-treat). Continuous variables were described as mean, median, standard deviation, minimum, maximum and sample size for each treatment group, and two-sided 95% confidence intervals (CIs) of the mean difference between the treatment groups. Two-sample *t* test (for means) and nonparametric Wilcoxon test (for medians) were also performed. Binary variables were described as frequencies, percentages and two-sided 95% CIs of the difference in percentages between treatments using exact methods. Chi-square test or Fisher's exact test were performed as appropriate. For time-to-event data, Kaplan–Meier estimates at the predetermined time points were calculated along with the 95% CIs for the hazard ratio in the estimates and reported with the log-rank test results.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

3 | RESULTS

Between November 19, 2009 and August 30, 2010, a total of 183 patients were randomized to treatment with Combo (*n* = 124) or Taxus (*n* = 59). The CONSORT flow diagram with regard to the inclusion and follow-up rates is presented in Figure 1. Both study groups were well matched for baseline clinical and lesion characteristics (Tables 1 and 2). Follow-up at 5 years was available for 97% (169/173) of patients, with 89.7 and 87.5% of patients in the Combo and Taxus groups still taking aspirin while the compliance to thienopyridine was 16.4 and 12.5%, respectively. Clopidogrel was prescribed for 12 months in approximately 77% of patients (80.2% in Combo and 74.6% in Taxus). The overall usage of antiplatelet medication post PCI is illustrated in Figure 2.

3.1 | Safety outcomes

Five-year cumulative rates of the clinical endpoints are presented in Table 3. Overall, the rates of MACE rates were similar between the Combo (18.3%) and the Taxus (16.9%) groups (p = .89; Figure 3). Seven (5.8%) patients in the Combo group and 3 (5.1%) patients in the Taxus group died (p = .85), with four deaths (one with Combo and three with Taxus, p = .07) adjudicated by the clinical events committee to be cardiac in origin (Figure 4). The only Combo cardiac death occurred at 324 days and was classified as a possible stent thrombosis while the three Taxus

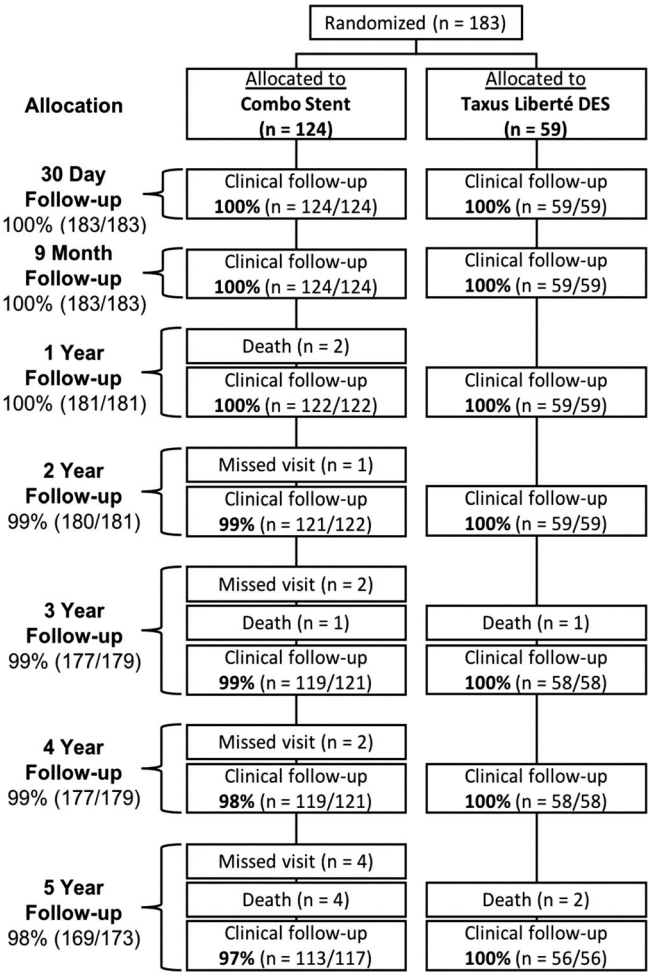


FIGURE 1 CONSORT flow diagram. The flow of patients with regard to the inclusion and follow-up rates. Missed visit means: missed within prespecified time window. All subjects who had missed visits were accounted for outside of the protocol defined time window and any events have been included in the final results

deaths occurred at 946 (possible stent thrombosis), 1,512 (cardiac death), and 1,709 (unknown cause) days post-procedure. The noncardiac deaths occurred in the Combo group at 287, 1090, 1,464, 1,601, 1,711, and 1,748 days post-procedure. Rates of MI were also similar between Combo (4.1%) and Taxus (3.4%) (p = .81), with two late events (one Q-wave and one non Q-wave) in the Combo group that occurred at 2- and 3-year follow-up and one late event (Q-wave) in the Taxus group that occurred at 3 years. Per the Academic Research Consortium definition, no definite stent thrombosis occurred with Combo while one case (categorized as definite) was reported with Taxus (1.8%; p = .15). This thrombotic event with Taxus occurred at 1634 days post-procedure and resulted in a nonfatal target vessel-related non Q-wave MI.

3.2 | Efficacy outcomes

As with safety outcomes, all efficacy endpoints were similar between the Combo and Taxus groups (Table 1). At 5-year follow-up, the rates of clinically driven TLR were similar between Combo (9.4%) and Taxus

TABLE 1 Baseline clinical characteristics

	Combo (n = 124)	Taxus (n = 59)	p value
Age (years)	64.20 ± 9.48	64.05 ± 10.49	.92
Men	89 (71.8%)	42 (71.2%)	.93
Smoking /tobacco usage	71 (57.3%)	28 (47.5%)	.21
Current smoker	26 (21.0%)	10 (16.9%)	
Diabetes mellitus	41 (33.1%)	22 (37.3%)	.57
Insulin dependent	9 (7.3%)	7 (11.9%)	.30
History of hypertension	100 (80.6%)	45 (76.3%)	.50
History of hyperlipidemia	102 (82.3%)	43 (72.9%)	.14
Left ventricular ejection fraction (%)	63.87 ± 11.93 (119)	63.33 ± 11.59 (59)	.77
Premature cardiovascular disease in first degree relative	36 (29.0%)	23 (39.0%)	
Previous congestive heart failure	17 (13.7%)	6 (10.2%)	.50
Previous MI	31 (25.0%)	16 (27.1%)	.76
Previous PCI	29 (23.4%)	12 (20.3%)	.64
Previous CABG	4 (3.2%)	2 (3.4%)	1.00
History of renal insufficiency	8 (6.5%)	1 (1.7%)	.28
Angina status:			
Silent ischemia	13 (10.5%)	6 (10.2%)	.95
Stable angina	91 (73.4%)	43 (72.9%)	.94
CCS I	13 (10.5%)	10 (16.9%)	.22
CCS II	60 (48.4%)	29 (49.2%)	.92
CCS III	15 (12.1%)	4 (6.8%)	.27
CCS IV	3 (2.4%)	0 (0.0%)	.55
Unstable angina	20 (16.1%)	10 (16.9%)	.89
Braunwald I	6 (4.8%)	2 (3.4%)	1.00
Braunwald II	8 (6.5%)	2 (3.4%)	.50
Braunwald III	6 (4.8%)	6 (10.2%)	.21

Note: Data are mean (*SD*) or number (%).
Abbreviations: CABG, coronary bypass surgery; MI, myocardial infarction; PCI, percutaneous coronary intervention.

(10.2%; p = .78; Figure 5). Specifically, five new cases of repeat revascularization occurred between 1- and 5-year follow-up in the Combo group compared to one case (occurring between 2- and 3-year follow-up) in the Taxus group. Of the 17 patients with a TLR, 14 underwent a repeat percutaneous coronary intervention and three underwent coronary artery bypass grafting. TLF rates were similar between Combo (18.3%) and Taxus (16.9%; p = .89; Figure 6). Clinically driven TVR rates were not different between groups at 14.4% for Combo and 11.9% for Taxus (p = .73), similar to the TVF rates (22.4% for Combo and 18.6% for Taxus groups; p = .63).

4 | DISCUSSION

REMEDEE was a phase III prospective, multicenter, randomized trial specifically designed to assess the long-term safety and efficacy of the Combo stent in the treatment of de novo coronary lesions. This study is also the first study evaluating a combined sirolimus-eluting and EPC capture stent to reach 5-year follow-up. The main findings of this final 5-year report are: (a) the cumulative rates of MACE and individual components, repeat revascularization procedures (TLR and TVR), and target lesion and vessel failure were similar between Combo and Taxus, and (b) no definite stent thrombosis occurred with Combo compared to one very late case with Taxus. With low rates of major adverse events, our results collectively suggest the good clinical performance of the Combo stent in the treatment of patients with symptomatic ischemic heart disease.

The safety and efficacy of EPC capture stents has been demonstrated in diverse patient populations.[12–14,17] Our results are in agreement with these reports but also extend their findings in that patients underwent a longer follow-up period (5 years) suggesting the continued safety and efficacy of the Combo stent. At 5-years, overall rates of MACE and individual components were similar between Combo (18.3%) and Taxus (16.9%). Noteworthy was a trend in a lower rate of cardiac death with Combo (0.8%) compared with Taxus (5.1%; p = .07). Our results compared favorably with those of landmark trials[18,19] and a patient-level pooled analysis of sirolimus-eluting stents.[20]

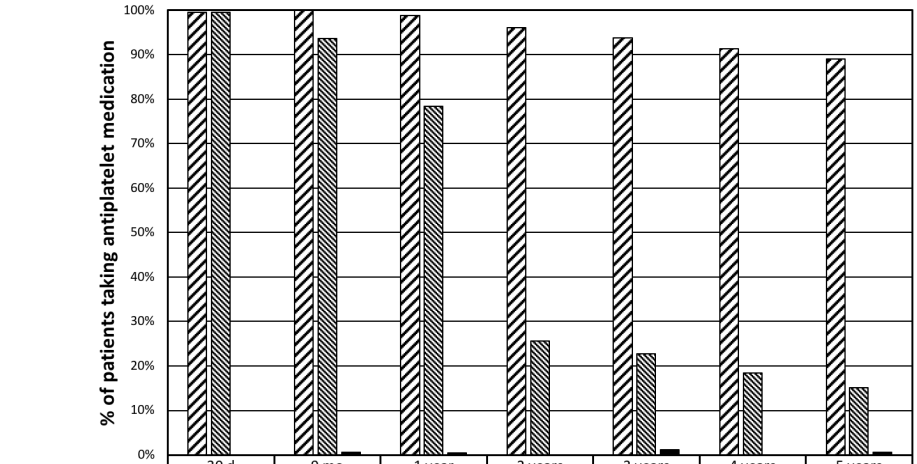
TABLE 2 Baseline lesion characteristics

	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%)	.18
RCA	31 (25.0%)	10 (16.9%)	.22
Circumflex	39 (31.5%)	17 (28.8%)	.72
Lesion location			
Ostial	1 (0.8%)	1 (1.7%)	.54
Proximal	44 (35.5%)	23 (39.0%)	.65
Mid	67 (54.0%)	28 (47.5%)	.41
Distal	12 (9.7%)	7 (11.9%)	.65
Lesion length (mm)			
Mean ± *SD*	13.69 ± 5.07	14.64 ± 4.41	.22
(min, max)	(5.08, 45.57)	(5.25, 24.83)	N/A
Eccentric	4 (3.2%)	8.5% (5/59)	.15
Angulation >45°	12 (9.7%)	4 (6.8%)	.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%)	.19
Moderate	26 (21.0%)	8 (13.6%)	.23
Severe	1 (0.8%)	0 (0.0%)	1.00
TIMI score			
TIMI 0	0 (0.0%)	0.0% (0/59)	N/A
TIMI 1	1 (0.8%)	1 (1.7%)	.54
TIMI 2	5 (4.0%)	2 (3.4%)	1.00
TIMI 3	118 (95.2%)	56 (94.9%)	1.00
Pre-procedure RVD (mm)			
Mean ± *SD*	2.77 ± 0.42	2.85 ± 0.34	.18

Abbreviations: LAD, left anterior descending artery; RCA, right coronary artery; RVD, reference vessel diameter; *SD*, standard deviation; TIMI, thrombolysis in myocardial infarction.

Despite prolonged DAPT, stent thrombosis remains a serious safety concern with DES.[4,5,21,22] In the REMEDEE patient population, 77% received thienopyridine for at least 12 months and 89% were still on aspirin at 5-year follow-up. No patient treated with Combo had a stent thrombosis compared to one very late case with Taxus. It is noteworthy that, compared with pivotal studies in which the rates of stent thrombosis ranged between 2.1 and 3.9%,[18–20] our results suggest the Combo stents were completely covered with dense neointima at 9 months and had 0% definite stent thrombosis in the REMEDEE cohort.[23,24]

The main benefit of DES is the reduction of in-stent restenosis. At the 9-month QCA evaluation,[16] Combo was found to be non-inferior to Taxus with respect to in-stent LLL. At 5-year follow-up TLR, was low (9.4%) and similar to Taxus (10.2%) suggesting the sustained efficacy of Combo in reducing restenosis in comparison with bare metal stents. TLR results in the REMEDEE patient population (4.8% at 1 year, 5.7% at 2 years) compare well with 1 and 2 year results of the REMEDEE Registry (N = 1,000), with a TLR rate of 4.4% at 1 and 5.9% at 2 years.[25,26] Moreover, as the majority of TLRs occurred within the first 12 months after the index procedure, the long-term benefit at 5 years is supporting no or very little late catch-up. Indeed, the 9-month IVUS evaluation suggests a more favorable development of neointimal hyperplasia.[23] This may partly be due to the pro-healing benefits of the immobilized anti-CD34 antibody and the reduced magnitude of inflammation with the rapid disappearance of the biodegradable polymer. In addition to these beneficial effects, no case of late acquired malapposition was observed with Combo and although the small



	30 d	9 mo	1 year	2 years	3 years	4 years	5 years
Aspirin	99.5%	100.0%	98.8%	96.1%	93.8%	91.4%	89.0%
Clopidogrel	99.5%	93.7%	78.4%	25.6%	22.7%	18.4%	15.1%
Other P2Y12 inhibitor	0.0%	0.6%	0.5%	0.0%	1.1%	0.0%	0.6%

FIGURE 2 Overall antiplatelet usage over time. The percentage of all patients (Combo and Taxus groups combined) taking aspirin, clopidogrel, or other P2Y12 inhibitor during 5 years of follow-up. There was no significant difference in medication usage between the groups

TABLE 3 Kaplan–Meier estimates of adjudicated clinical endpoints at 5-year follow-up

	Combo (*n* = 124)	Taxus (*n*= 59)	Hazard ratio [95% CI]	*p* value
Safety outcomes				
All-cause mortality (%)	5.8 (7)	5.1 (3)	1.14 [0.29, 4.40]	.85
Cardiac death	0.8 (1)	5.1 (3)	0.16 [0.02, 1.57]	.07
MI (%)	4.1 (5)	3.4 (2)	1.22 [0.24, 6.29]	.81
Q-wave	0.8 (1)	1.7 (1)	0.49 [0.03, 7.86]	.61
Non Q-wave	3.3 (4)	1.7 (1)	1.93 [0.22, 17.28]	.55
MACE (%)	18.3 (22)	16.9 (10)	1.05 [0.50, 2.22]	.89
Stent thrombosis (%)	0.0 (0)	1.8 (1)	N/A	.15
Efficacy outcome				
TLR (%)	9.4 (11)	10.2 (6)	0.87 [0.32, 2.34]	.78
TVR (%)	14.4 (17)	11.9 (7)	1.16 [0.48, 2.81]	.73
TLF (%)	18.3 (22)	16.9 (10)	1.05 [0.50, 2.22]	.89
TVF (%)	22.4 (25)	18.6 (11)	1.19 [0.59, 2.40]	.63

Abbreviations: CI, confidence interval; MACE, major adverse cardiac events; MI, myocardial infarction; N/A, not available; TLF, target lesion failure; TVF, target vessel failure; TLR, target lesion revascularization; TVR, target vessel revascularization.

number of patients who underwent IVUS evaluation precludes any definitive conclusions, there is no evidence that Combo had an adverse impact on long-term remodeling. It is noteworthy that more than 98% of the Combo struts were covered with endothelial cells by 9 months and, across the ostium of side branches, more Combo struts were covered than Taxus. This is in agreement with animal studies demonstrating the greater re-endothelialization of EPC stents,[8–11] and that the combination of anti-CD34 antibodies with sirolimus results in a faster and greater degree of endothelialization than sirolimus alone.[10] Meanwhile, data from the REMEDEE OCT study and longitudinal (2 month out to 2 years) OCT observations from the EGO-COMBO study confirm a robust coverage of the Combo stent of 87% at 2 months, 93% at 3 months and increasing toward 100% at 9 months[24,27] with a mature neointima without signs of neoatherosclerosis. These observational results suggest the use of the Combo stent could possibly allow a shorter DAPT duration. Recently, the REDUCE trial in patients with acute coronary syndrome receiving the COMBO stent with 3-month or 12-month DAPT showed a non-inferiority in clinical outcomes between the two DAPT durations. Furthermore, a low late stent thrombosis risk was documented for the COMBO stent in the REMEDEE Registry (*N* = 1,000), where only a single case of very late stent thrombosis occurred between 1 and 2 years post index.

The study results have to be seen in the context of the evolution of stent technology, in particular in decreasing strut thickness. A recent meta-analysis has shown that ultra-thin strut DES (<70 μm) are associated with lower target-lesion failure rates.[28] It can be speculated that an anti CD-34 antibody layer on an ultra-thin strut DES could result in even faster endothelial strut coverage.

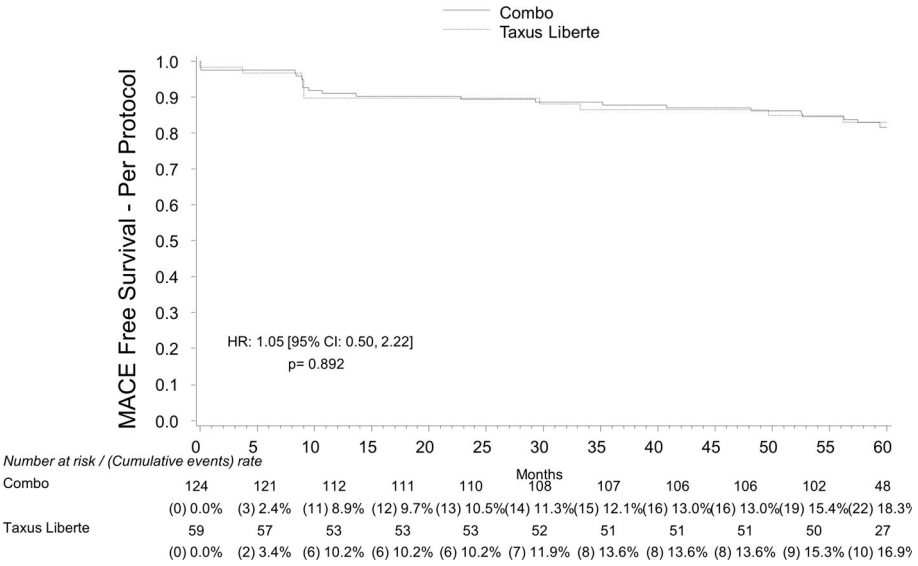


FIGURE 3 Kaplan–Meier plot of major averse cardiac events-free survival. Kaplan–Meier estimates of 5-year cumulative rates of major adverse cardiac events

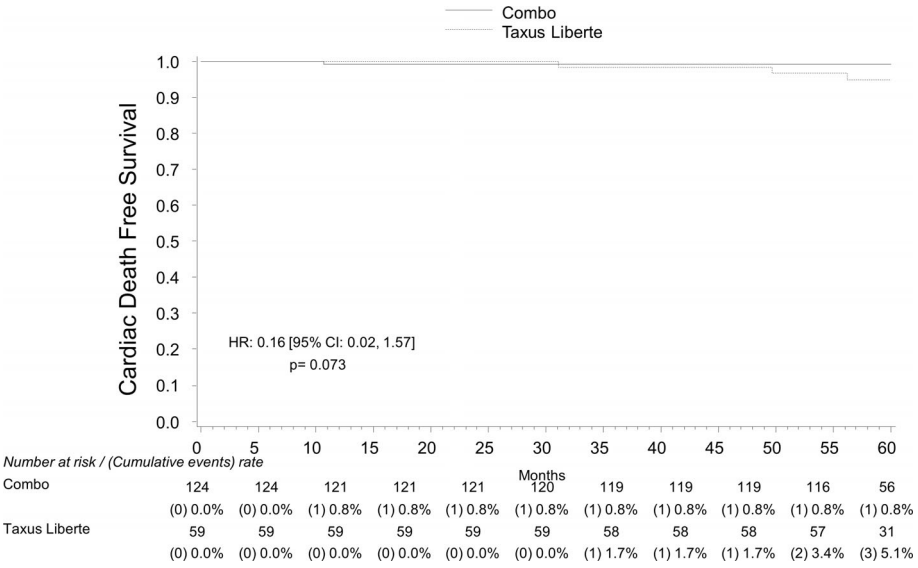


FIGURE 4 Kaplan–Meier plot of cardiac death-free survival. Kaplan–Meier estimates of 5-year cumulative rates of cardiac death

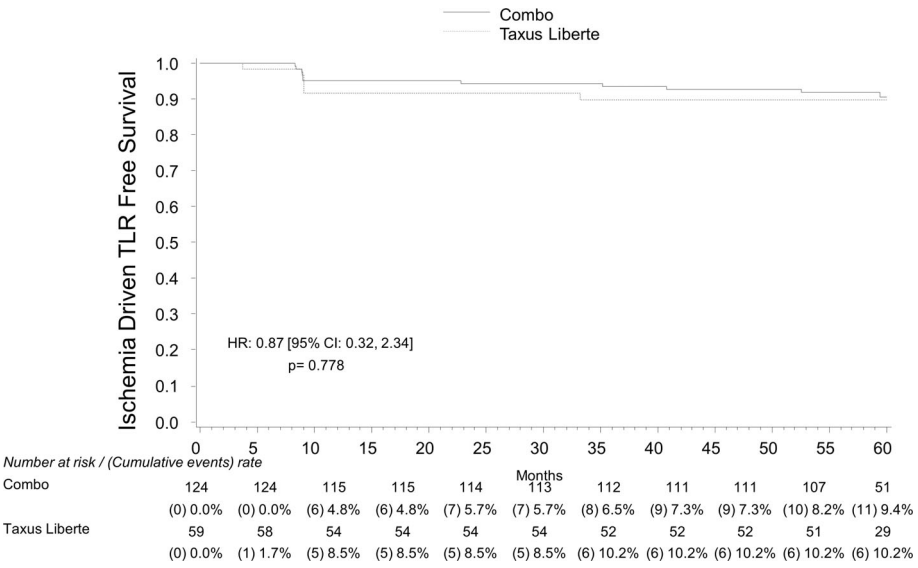


FIGURE 5 Kaplan–Meier plot of target lesion revascularization-free survival. Kaplan–Meier estimates of 5-year cumulative rates of target lesion revascularization

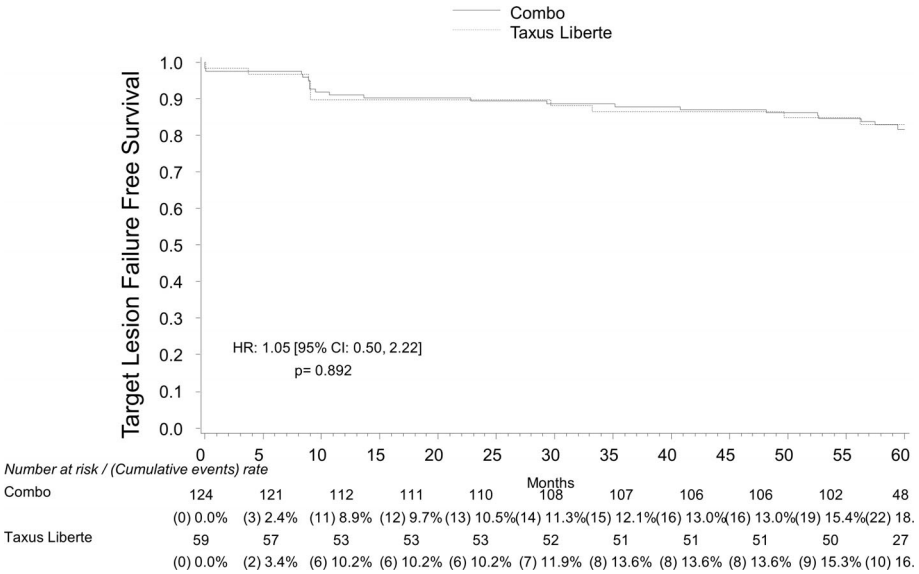


FIGURE 6 Kaplan–Meier plot of target lesion failure-free survival. Kaplan–Meier estimates of 5-year cumulative rates of target lesion failure

The main limitations of this first-in-man study were the small sample size and the fact it was not powered to detect differences in clinical adverse events or IVUS surrogate endpoints. Also, the fact that the patients had relatively low-risk lesions precludes the conclusions of REMEDEE from being extrapolated to other patient populations. An extensive study program is underway to investigate the benefits of the Combo stent in comparison with contemporary DES.

5 | CONCLUSIONS

REMEDEE is the first study in an extensive clinical program exploring the potential of a novel combined sirolimus-eluting and EPC capturing stent. Through 5 years of clinical follow-up, the Combo stent had low and similar rates of MACE, death, MI, and repeat revascularization procedures as those of Taxus, which supports the long-term safety profile of Combo. The initial 9-month clinical benefits of Combo stents in reducing in-stent LLL were sustained as demonstrated by the continued low rates of TLR. Finally, the implantation of Combo was not associated with the occurrence of either early or late stent thrombosis.

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CONFLICT OF INTERESTS

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