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RENASCENT II: First in Human Evaluation of a Novel Sirolimus-Eluting Ultra-High Molecular Weight APTITUDE® Bioresorbable Scaffold: 9-and 24-Months Imaging and Clinical Results

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SHORT RUNNING TITLE

RENASCENT II: 9- and 24-months imaging and clinical results of novel APTITUDE® Bioresorbable scaffold.

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Conflict of Interest

Alaide Chieffo, MD: Proctorship fees from Amaranth Medical Inc

Juan F. Granada, MD: Scientific advisor and equity shareholder Amaranth Medical Inc.

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ABSTRACT

Aims: The novel sirolimus-eluting ultra-high molecular weight 115-microns strut thickness APTITUDE® Bioreabsorbable vascular scaffold (BRS) (Amaranth Medical Inc., Mountain View, CA) displays higher mechanical strength, expansion capabilities and resistance to fracture compared to clinically available BRS technologies. RENASCENT II is a prospective, multi-center first-in-human clinical study to evaluate the clinical performance of the APTITUDE® BRS in the treatment of single de novo coronary lesions among patients undergoing percutaneous coronary intervention.

Methods and results: APTITUDE® BRS was tested in a prospective study in two countries (Italy and Colombia). Study objectives were angiographic in-scaffold late lumen loss (IS-LLL) measured by quantitative coronary angiography (QCA) and target vessel failure (TVF) defined as the composite rate of cardiac death, target vessel myocardial infarction (TV-MI) or ischemia driven target lesion revascularization (TLR) at 9-and 24-months.

A total of 60 patients were enrolled. All patients underwent lesion pre-dilatation and 46 patients (76.7%) underwent post-dilatation. Clinical device and procedural success were 98.3% (59/60 patients) and 100% respectively. Angiographic late lumen loss was 0.19 ± 0.26mm at 9-months and 0.3 ± 0.41mm at 24-months. At 9-months, TVF occurred in 2/59 (3.4%) due to TV-MI but no TLR. No further cases of TVF, MACE or stent thrombosis were reported upto 24-months follow-up.

Conclusions: In this multi-center prospective study, the APTITUDE® BRS was shown to be safe and effective in the treatment of single coronary lesions at 24-months clinical follow up.

CLASSIFICATIONS

Bioresorbable scaffolds
QCA
Optical coherence tomography

CONDENSED ABSTRACT

In this multicenter first-in-human clinical study evaluating a novel sirolimus-eluting PLLA 115-microns strut thickness APTITUDE® BRS (Amaranth Medical Inc., Mountain View, CA), a total of 60 patients were enrolled. All patients underwent lesion pre-dilatation and 46 patients (76.7%) underwent post-dilatation. Clinical device and procedural success were 98.3% (59/60 patients) and 100% respectively. At 9-months, TVF occurred in 2/60 patients (3.4%) due to TV-MI but not needing TLR. In-scaffold angiographic late loss was 0.19 ± 0.26 mm at 9-months and 0.3 ± 0.41mm at 24-months. There were no further TVF reported between 9-to 24-months follow-up, showing the APTITUDE® BRS to be safe and effective at 2-year follow-up.

ABBREVIATIONS

BRS:Bioresorbable Scaffolds

BVS:Bioresorbable Vascular Scaffold

DES:Drug Eluting Stent

DS:Diameter stenosis

EES:Everolimus Eluting Stent

IS-LLL:In scaffold-Late Lumen Loss

IVUS:Intravascular Ultrasound

LVEF:Left Ventricle Ejection fraction

MACE: Major Adverse Cardiovascular Events

MLD:Minimal Luminal Diameter

OCT:Optical Coherence Tomography

PLLA:Poly-L-Lactic Acid

QCA:Quantitative Coronary Angiography

TIMI:Thrombolysis in Myocardial Infarction

TVF:Target Vessel Failure

TLR:Target Lesion Revascularisation

TV-MI:Target Vessel-Myocardial Infarction

Introduction

Current DES are safe and have very low thrombosis rates (1). However, potential limitations of DES include the permanent presence of a metallic foreign body within the artery and often a durable polymer, either of which may cause vascular inflammation, neoatherosclerosis and restenosis or perpetuate the risk of very late stent thrombosis. Moreover, metallic stents indefinitely impair physiological vasomotor function of the vessel and also the potential for future grafting within the stented segment (2). In this context, bioresorbable scaffolds (BRS) represent the latest innovation in the field of PCI. They aim to provide a transient vessel scaffold, preventing acute vessel closure/recoil and subsequently dissolve. In addition, complete bioresorption of the scaffold is associated with plaque regression, late vessel lumen enlargement and restoration of vasomotion within a few years. Thus, BRS hold the potential to achieve the paradigm of vascular restoration therapy, restoring both vessel lumen and vascular function eliminating the risk of late stent-related events.

However, BRS have several limitations including thicker, wider struts, less radial strength and limited expansion capabilities. These limitations require altered implantation techniques to standard DES, especially in complex coronary artery disease. To counteract the lower radial strength ascribable to the nature of their manufacturing, some companies have designed their BRS products with thicker struts than most second-generation DESs. **Furthermore BRS have shown to have an increased stent thrombosis risk compared to metallic DES, particularly very late stent thrombosis (10,11). Scaffold dismantling related to scaffold reabsorbtion was found to be the commonest mechanism of VLST in the INVEST registry (5).**

New generation thinner BRS implanted with optimal technique might offer early and intermediate-term outcomes comparable to contemporary metallic DES (prior to complete bioresorption), with improved long-term event-free survival.

The reduction of strut thickness from the current 150µm BRS to the newer generation scaffolds having 100 – 120µm struts may reduce flow disturbances and hence thrombogenicity (6) . **There are multiple newer generation BRS at different stages of development with varying mechanical or bioresorbtion properties. RENASCENT III is a first-in-man clinical safety trial of Amaranth Medical's newest BRS MAGNITUDE® (98µm strut**

thickness). These new BRS have to first show clinically safety in FIM trials and subsequently be further tested in RCT with proven metallic DES.

The aim of the RENASCENT II trial is to evaluate the clinical and safety performance of the APTITUDE® BRS.

METHODS

Study Design and Patient Population

The RENASCENT II study is a prospective, non-randomized, non-inferiority study of the APTITUDE® Bioresorbable Drug-Eluting Coronary Scaffold (NCT02568462) that enrolled 60 patients from Colombia and Italy. The ethics committee at each participating institution approved the protocol and each patient gave written informed consent before inclusion. As required by national regulations, the approval of the relevant national regulatory agency was also obtained.

Inclusion and exclusion criteria have been shown in supplemental material (Supplemental Table 1)

Study Device

The APTITUDE® design is based on the FORTITUDE® scaffold. The FORTITUDE® scaffold has demonstrated to be biocompatible and maintain mechanical integrity with controlled drug release in previous trials. Key design difference between the two is a reduction of strut thickness (115µm APTITUDE® vs 150µm FORTITUDE®). The scaffold material (**ultra-high** poly-L-lactic acid), manufacturing process and delivery system have not changed.

APTITUDE® BRS is made with a continuous "closed cell" zigzag helical design made of **ultra-high** PLLA and coated with a polymer- antiproliferative drug matrix (poly-L-lactic acid + Sirolimus) mixed in a 1:1 polymer to drug ratio with 90% of the drug being released by 90 days.

In vitro studies have shown that the scaffold degrades over time with the reduction in molecular weight reaching approximately 50% at 8 months and greater than 85% at 18 months. The radial support is maintained for 8 to 10 months (7). As the scaffold degrades, the polymer is converted into lactic acid, which is metabolized through the Krebs cycle. The degradation process takes approximately two years and is very similar to that of the Abbott BVS bioresorbable scaffold.

The polymer and design of the scaffold provides uniform strength in all directions. This uniform strength also makes the scaffold less likely to fracture or crack in high stress areas..

Supplemental Table 2 shows features of the study APTITUDE® BRS device. Figure 1 shows OCT images comparing Abbott BVS, Amarnath FORTITUDE® and APTITUDE®.

Study Procedure

Target lesions were treated using standard interventional techniques; successful pre-dilatation of the target lesion was mandatory (1:1). Baseline IVUS assessment was performed during the index procedure to evaluate vessel size, degree of calcification and to determine the appropriate scaffold size. The target lesion had to be treated with a single study device and planned overlapping with another stent was not allowed. Post-dilatation was not mandatory but allowed at the operator's discretion (if sub-optimal angiographic result) using a non-compliant balloon with diameter ≤0.5 mm larger than the nominal scaffold size. **Bailout stenting with DES for non-flow limiting edge dissection was recommended and as per clinical practice, required for flow limiting dissection.** Post-procedural intravascular imaging with OCT was required in all cases.

Treatment with aspirin was started at least 24 hours before the procedure and ≥ 75mg/day dose was required for the duration of the study. A loading dose of ≥300mg clopidogrel (or 60mg of prasugrel/180 mg of ticagrelor) was administered before the procedure, followed by daily 75mg clopidogrel (or 10mg prasugrel daily / 90mg ticagrelor twice daily) for a minimum of 12 months. The duration of dual antiplatelet therapy beyond 12-months was left to the discretion of the physician.

The 30-day follow-up was performed via an office visit or by phone call. At 9-months, angiographic follow-up with OCT was performed. **Coronary computed tomography**

angiography or invasive coronary angiography was done at 24-months, depending on center preference. Colombian centers performed invasive coronary angiography while Italian centers preferred to use coronary CT. All data was collected in dedicated electronic Case Report Forms. The study terminated at end of 24-months.

Study Objectives

Primary performance endpoint was in-scaffold late lumen loss (IS-LLL) defined as the amount of vessel lumen diameter lost/gained at the time of angiographic follow-up measured by quantitative coronary angiography (QCA) at 9-months. The assessment was made within the segment of vessel including the scaffold.

Primary safety endpoint was the incidence of target vessel failure, defined as cardiac death (Academic Research Consortium [ARC] definition) (8), target vessel myocardial infarction (TV-MI) (using the Expert Consensus Document From the Society for Cardiovascular Angiography and Interventions [SCAI]) (9), or clinically indicated target lesion revascularization (TLR) (ARC definition) at 9-months. Although the adjudication of periprocedural MI was performed using the SCAI definition, additional analysis were performed using the Third Universal Definition of MI (10). Stent thrombosis was defined using the ARC "definite" or "probable" stent thrombosis definitions (8).

Furthermore, both "clinical device success" defined as successful delivery and deployment of the clinical investigation scaffold with a final residual stenosis of <50% by QCA after the index procedure and "clinical procedure success" defined as clinical device success using any adjunctive device without occurrence of major adverse clinical events related to ischemia up to day of discharge were assessed.

Meditrial Europe Ltd. (Zürich, Switzerland) was responsible of the submission of the protocol to the relevant Ethic Committees and authorities, monitoring of the patients' data and the reporting of Serious Adverse Events to the respective authorities for the RENASCENT II trial. **Adverse events were adjudicated by an independent clinical event committee.** An independent core lab (Cardiovascular Research Foundation, New York, USA) performed angiographic (QCA), OCT and CTA data analysis.

Angiographic, QCA, OCT image acquisition and data analysis have been described in supplemental materials (and supplementary Figures 1 and 2).

Statistical Analysis

Angiographic IS-LLL at 9-months was analyzed using a one-sample t-test for non-inferiority. If the assumptions for normality were not met, then a Wilcoxon signed-rank test was used. When provided, the 95% confidence intervals were computed with the gaussian approximation, taking into account the paired analysis. Paired comparisons between post-procedural and follow-up results were done by a Wilcoxon signed-rank test. The results for the endpoints are presented using summary statistics and 95% confidence intervals. For discrete outcomes, the total number and percentage are presented.

RESULTS

Baseline Clinical and Angiographic Characteristics

Baseline clinical and angiographic characteristics of the study population are shown in Table 1. A total of 60 patients were enrolled: 23 in Colombia and 37 in Italy. The mean reference vessel diameter was 2.8 ± 0.4mm and lesion length 12.4 ± 3.6mm. Most of the lesions were type ACC/AHA B1-C (83.3%, n=50). There was moderate-severe calcification in 6 cases (10%). **Figure 2 shows RENASCENT II study flow-chart.**

Procedural Characteristics

Table 2 shows the procedural characteristics of the study population. Baseline IVUS assessment was performed during the index procedure in all patients to evaluate vessel size, grading of calcification and to select the appropriate scaffold size. Appropriate pre-dilatation was performed in 100% of the lesions. In 76.7% (n=46) of cases, post-dilatation was performed. There were no dissections requiring a bail out DES.

The clinical device success was 98.3% (n=59); in one case the scaffold was not implanted due to inability to track through a calcified and tortuous vessel proximal to the target lesion. The resulting clinical procedure success rate was 100% (n=60).

Study Objectives

Table 3 shows results of major adverse cardiovascular events during the trial up to 24-months follow-up. There were no major in hospital cardio-vascular events and up to 30 days follow-up.

At 9 months, 59 (98%) patients completed clinical and mandatory angiographic follow up. 1 patient did not receive the study device and per protocol exited the study at 30 days. At 9-months TVF was 3.4% (n=2) due to 2 non- Q wave MIs (target vessel MIs) but no target lesion revascularization (TLR). Details of these 2 cases are provided in Supplemental Table 3. No ischemia driven TLR and scaffold thrombosis have been reported up to 24-months follow-up. There were 2 cases of binary stenosis at 24-months follow-up (Supplemental Table 4). However, these patients were asymptomatic and no intervention was required as not clinically indicated. **At 24-months follow-up, 24 out of 55 patients (43.6%) were still on dual antiplatelet therapy.**

Angiographic and QCA Analysis

Table 4 reports QCA measurements at baseline, post-scaffold implantation, 9- and 24-months follow-up. In-Scaffold late lumen loss (IS-LLL), was 0.35 ± 0.33mm at 9 months and 0.37 ± 0.44mm at 24-months (Figure 3). Other significant QCA measurements were: In-Segment MLD 1.0 ± 0.3 at baseline, In-Scaffold MLD 2.9±0.4mm post-BRS implantation, 2.5±0.4mm at 9-months and 2.3±0.6mm at 24-months. There was an acute gain of 1.9 ± 0.4mm post BRS insertion.

OCT Analysis

OCT pullbacks were analyzed in 53 lesions during the index procedure (post-scaffold implantation) and 58 lesions at 9-months angiographic follow-up. Supplementary Table 5 shows the in-scaffold OCT measurements. The percentage of intra-scaffold NIH volume at 9 months was very low (13.3±6.1%). The total percentage of covered struts at 9 months was 97.0%, of which 96.52±5.02% were apposed to the vessel wall. The total percentage of uncovered struts at 9-months was very low (2.97%). Figure 4 shows Mean Outer Scaffold Area in matched 51 patients at 9-months.

DISCUSSION

The major findings of the international, multi-center study of the novel thin walled 115µm APTITUDE® bioresorbable scaffold were the following: a) high clinical device success rate; b) low MACE rate up to 24 month follow-up (3.4%; both non-Q wave MIs related to non-TLR) as expected in this population, c) no scaffold thrombosis, d) scaffold stability maintained upto at 24-months, e) high level of strut coverage (97.0%) and low rate of malapposition (0.037%, all covered) evident by OCT.

One of the major challenges in the BRS field has been the development of scaffolds displaying stent-like mechanical strength and resistance to the compressive load imposed by vessel recoil following deployment in challenging anatomical conditions. In first generation BRS, crystalline polymeric structures provided mechanical strength to the scaffold. However, the highly crystalline polymer structure limited the scaffold's expansion capabilities and its resistance to fracture. As a result, current generation BRS display limited expansion capabilities beyond pre-determined limits and are prone to fracture if not deployed properly.

The ultra-high molecular weight PLLA-based BRS have already displayed higher expansion capabilities and resistance to fracture under static and dynamic loading conditions (7). At EuroPCR 2018, RENASCENT trial showed good safety performance of the FORTITUDE® BRS with lumen patency and vessel wall stability up to 24-months. This is once again reproduced in this trial with the low angiographic late lumen loss rate (0.35mm at 9-months and 0.37mm at 24-months). Furthermore, OCT analysis showed high strut apposition and coverage rates at 9-months.

Acute Gain and Late Lumen Loss

In our analysis the APTITUDE® BRS showed an acute gain of 1.9 ± 0.4mm, the same reported for FORTIDUDE® BRS. Ormiston et al reported an acute gain of 1.22 ± 0.38mm for the second generation of Absorb BVS in the ABSORB Cohort B trial which was numerically lower compared to the EES (1.32 ± 1.26mm) (10). The numerically higher EES acute gain, (11) could be secondary to higher recoil rates or more conservative post-dilatation techniques used during BVS deployment aiming to avoid strut fractures. The in vivo acute gain of the FORTITUDE® BRS has been reported to be higher compared to BVS. Cheng et al (7) reported

in vitro analysis that compared the capability of Amaranth Medical BRS to resist fracturing under high load conditions. They reported that the number of fractures was higher in BVS vs. FORTITUDE® BRS with lower percentages of late scaffold recoil at 3 months.

Numerous studies have shown that Late Lumen Loss (LLL) is a predictor of MACE. LLL provides an indirect angiographic evaluation of the vessel wall response to the metallic stent related to neointimal proliferation in metallic stents (11). In BVS, LLL also depends on the late scaffold expansion (12). Current BVS data show a LLL of 0.16 ± 0.18mm at 6-months and 0.27 ± 0.20mm at 2-years follow-up for the second generation of BVS (10), while a LLL of 0.21± 0.34mm at 6-months was reported for DESolve scaffold (13). Recent analysis have reported that the LLL for the FORTITUDE® scaffold is 0.29 ± 0.43mm at 9-months of follow-up, that is comparable with the current BVS previously reported. In our analysis, In-Scaffold LLL for the APTITUDE® BRS is comparable with ABSORB and FORTITUTE® at 9-months (0.35 ± 0.33mm) and comparable at 24-months (0.37 ± 0.44mm).

OCT Analysis

The OCT analysis conducted at 9-months showed no statistically difference in mean scaffold area (7.82 ± 1.81mm^2 baseline to 7.84 ± 1.79mm^2 at 9-months). Almost all struts were covered by neointimal tissue (97%) and completely apposed to the vessel wall (96.5 ± 5.02%). A total of 3% of all struts were uncovered and but fully apposed. A very low percentage of all struts analyzed were either covered but malapposed (0.037% ± 0.16%). No uncovered, malapposed struts were detected. Strut apposition and coverage have been important predictors of late stent thrombosis in DES trials. In our study, the high percentage of strut apposition (~99%) and very low percentage of uncovered-malapposed struts may result in an improvement of long term clinical outcomes. **However these OCT findings indicate stent struts still present at 9-months, indicating active resorbtion process still ongoing. These OCT findings observed during the active process of resorption need to be confirmed at long term with the use of serial imaging.**

Clinical Outcomes

Serruys et al. (10) reported for the second generation of BRS in the ABSORB Cohort B trial a MACE rate at 1-year of 7.1%. In the FIM DESolve scaffold study the overall MACE rate

was 20% at 1-year follow-up (13). RENASCENT II showed very high clinical device and procedural success rates with no MACE reported at hospital discharge. 2 non-Q wave MIs (TV-MIs) were reported because of troponin rise but without ECG changes or clinical symptoms at 9-months follow-up without any TLR. No cardiac death or stent thrombosis were seen at 9-month follow-up. Our analysis demonstrated that the APTITUDE® BRS is safe and effective for use in the treatment of de novo stenotic native coronary artery lesions in patients undergoing elective percutaneous coronary intervention.

Furthermore there are other new BRS at various stages of testing in the market. These all need to undergo FIM and then eventual RCTs with current DES to evaluate their safety and clinical performance. (14)

LIMITATIONS

This study is limited by number of patients and also the follow-up period. It would also be worth noting that BRS implantation during RENASCENT II was guided by IVUS and OCT assistance. Further studies are required to analyze results of the APTITUDE® BRS using routine implantation techniques as well as assessing clinical outcomes in longer patient follow-up.

CONCLUSIONS

24-months clinical experience with the PLLA BRS APTITUDE® (Amaranth Medical Inc., Mountain View, CA) has demonstrated that the polymer is safe and effective in improving coronary luminal diameter in patients undergoing elective percutaneous coronary intervention. The APTITUDE® BRS has shown that despite reduction in struct thickness, it matches previous safety clinical endpoints seen with FORTITUDE® BRS.

IMPACT ON DAILY PRACTICE

Renascent II was first-in-human study to analyse the APTITUDE® BRS and was found to be safe and effective upto 24-months. It had low levels of target vessel failure and late lumen loss, warranting further BRS studies with longer follow-up and implantation using routine implantation techniques.

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Table 1. Baseline Clinical and Angiographic Characteristics of the Study Population

Baseline Clinical Characteristics	APTITUDE® BRS (n=60) Mean ± SD or % (n)
Male	78.3% (47)
Age (Years)	65.2 ± 8.0
History of Smoking	60.0% (36)
Medically Treated Diabetes	18.3% (11)
Medically Treated Hypertension	73.3% (44)
Clinical Presentation	
Stable Angina	50.0% (30)
Acute Coronary Syndrome	33.3% (20)
Silent Ischemia	16.7% (10)
Previous MI	51.7% (31)
History of PCI	63.3% (38)
History of CABG	0%
LVEF	54.9% ± 8.1%
Target Artery	
LAD	40.0 % (24)
LCX	30.0 % (18)
RCA	30.0 % (18)
Lesion Location	
Proximal-Mid	81.7% (49)
Reference Vessel Diameter (mm)	2.8 ± 0.4
QCA Diameter Stenosis	63.2 ± 10.8%
QCA Length (mm)	12.4 ± 3.6
ACC/AHA Lesion Classification	
Type B1-C	83.3 % (50)
Any Bifurcation/Side Branch	5.0 % (3)
Calcification	
Moderate-Severe	10.0 % (6)
Pre-Procedure TIMI 3 Flow	100 % (60)

MI=myocardial infarction; PCI=percutaneous coronary intervention: CABG=coronary artery bypass grafting; LVEF=left ventricular ejection fraction; QCA=Quantitative Coronary Analysis; TIMI=Thrombolysis In Myocardial Infarction

Table 2. Procedural Characteristics of the Study Population

Index Procedure Characteristics	APTITUDE® BRS (n=60) Mean ± SD or % (n)
Pre-Procedure Diameter Stenosis	63.2% ± 10.8%
Pre-Dilatation Prior to Implant	100% (60)
Single Post-Dilatation using NC Balloon	76.7% (46)
Max. Scaffold Deployment Inflation Pressure (atm)	11.8 ± 2.4
Final In-Segment Diameter Stenosis	7.1 ± 6.8%
Failure to Cross Due to Severe Calcification/Tortuosity	1.7% (1)
Distal Dissection Treated with drug eluting stent	0%
Clinical Device Success	98.3% (59)
Clinical Procedure Success	100%

NC balloon=non compliant balloon ; atm=atmospheres.

Table 3. Major Adverse Cardiac Events- Safety Endpoints in Hospital, at 30 days, 9-and 24-months Clinical follow Up

Safety Endpoints % (n)	In Hospital (n=60)	Discharge to 30 Days (n=60)	1 to 9 Months (n=59)	9 to 24 Months (n=56)	0 to 24 Months (n-56)
TVF (Cardiac Death, TV-MI, or ID-TLR)	**0%**	**0%**	**3.4% (2)**	**0%**	**3.4% (2)**
All Death	**0%**	**0%**	**0%**	**0%**	**0%**
Cardiac Death	0%	0%	0%	0%	**0%**
Non Cardiac Death	0%	0%	0%	0%	**0%**
Target Vessel MI	**0%**	**0%**	**3.4% (2)**	**0%**	**3.4% (2)**
Q-wave MI	0%	0%	0%	0%	**0%**
Non Q-wave MI	0%	0%	3.4% (2)	0%	**3.4% (2)**
Ischemia Driven TLR	**0%**	**0%**	**0%**	**0%**	**0%**
PCI	0%	0%	0%	0%	**0%**
CABG	0%	0%	0%	0%	**0%**
ARC Stent Thrombosis	0%	0%	0%	0%	**0%**
Definite or Probable	0%	0%	0%	0%	**0%**
Possible					

TV-MI= target vessel myocardial infarction; ID-TLR= ischemia driven target lesion revascularization; ARC= Academy research consortium

Table 4. Baseline, post-BRS implantation, 9- and 24-months coronary angiography and QCA measurements

QCA Measurements Mean ± SD (n)	Baseline Procedure (n=60)	Post-BRS Implantation (n=59)	9-Month Follow-up (n=59)	24-Month Follow-up (n=17)
In-Segment QCA Analysis				
Interpolated RVD (mm)	2.8 ± 0.4	2.9 ± 0.4	2.9 ± 0.4	2.7 ± 0.4
MLD (mm)	1.0 ± 0.3	2.5 ± 0.4	2.3 ± 0.4	2.1 ± 0.5
Late Lumen Loss (mm)	--	--	0.18 ± 0.26	0.24 ± 0.36
Diameter Stenosis (%)	63.2 ± 10.8	13.7 ± 6.2	17.7 ± 9.1	19.6 ± 13.8
In-Scaffold QCA Analysis				
Interpolated RVD (mm)	--	3.1 ± 0.4	2.9 ± 0.4	2.7 ± 0.4
MLD (mm)	--	2.9 ± 0.4	2.5 ± 0.4	2.3 ± 0.6
Acute Gain (mm)	--	1.9 ± 0.4	--	
Late Lumen Loss (mm)	--	--	0.35 ± 0.33	0.37 ± 0.44
Diameter Stenosis (%)	--	6.5 ± 5.5	13.4 ± 9.4	15.3 ± 16.6

RVD=reference vessel diameter; MLD=minimal lumen diameter

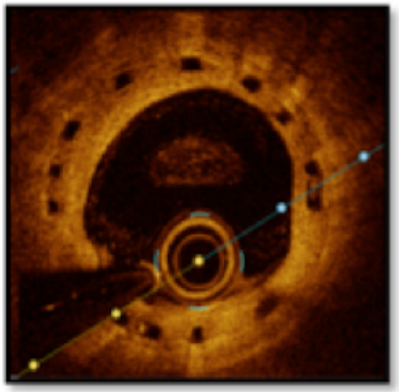
Figure Legends

Figure 1. OCT images showing APTITUDE® BRS with thinner struts (9-months post implantation), in comparison with Abbott BVS and FORTITUDE BRS.

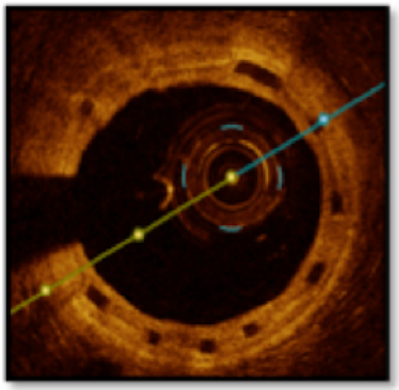
Figure 2. A flow-chart of the APTITUDE® Study Design showing the enrollment of the patients.

Figure 3. Cumulative frequency of In-Scaffold Late lumen loss at 9- and 24-months.

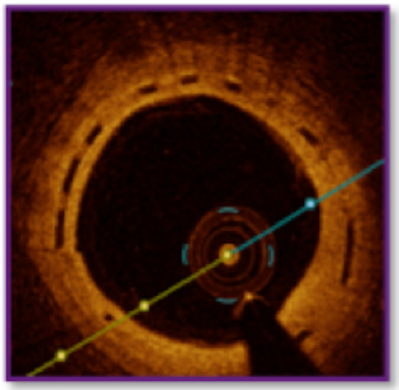
Figure 4. Scaffold Integrity at 9-Months: Mean Outer Scaffold Area by OCT in 51-patients matched data.



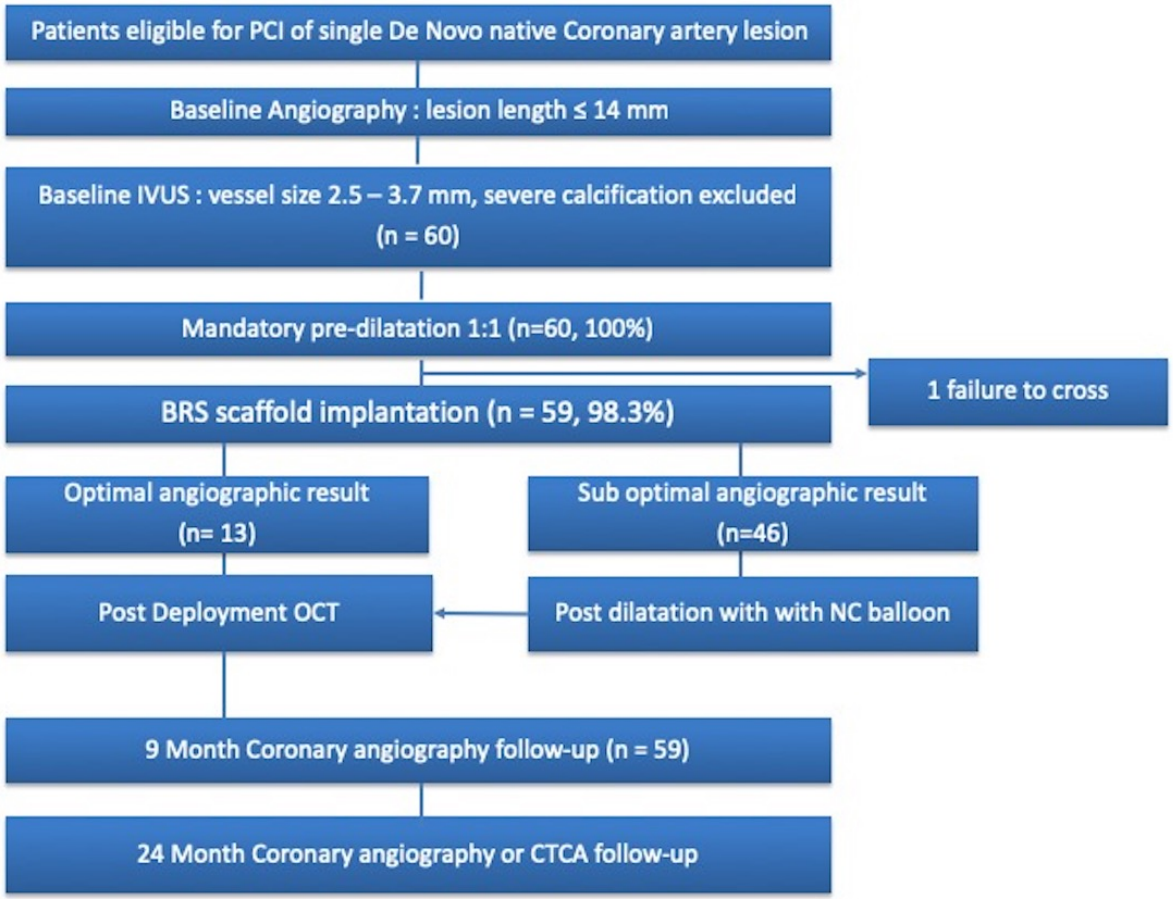
1st Generation:
Abbott BVS (156 µm)

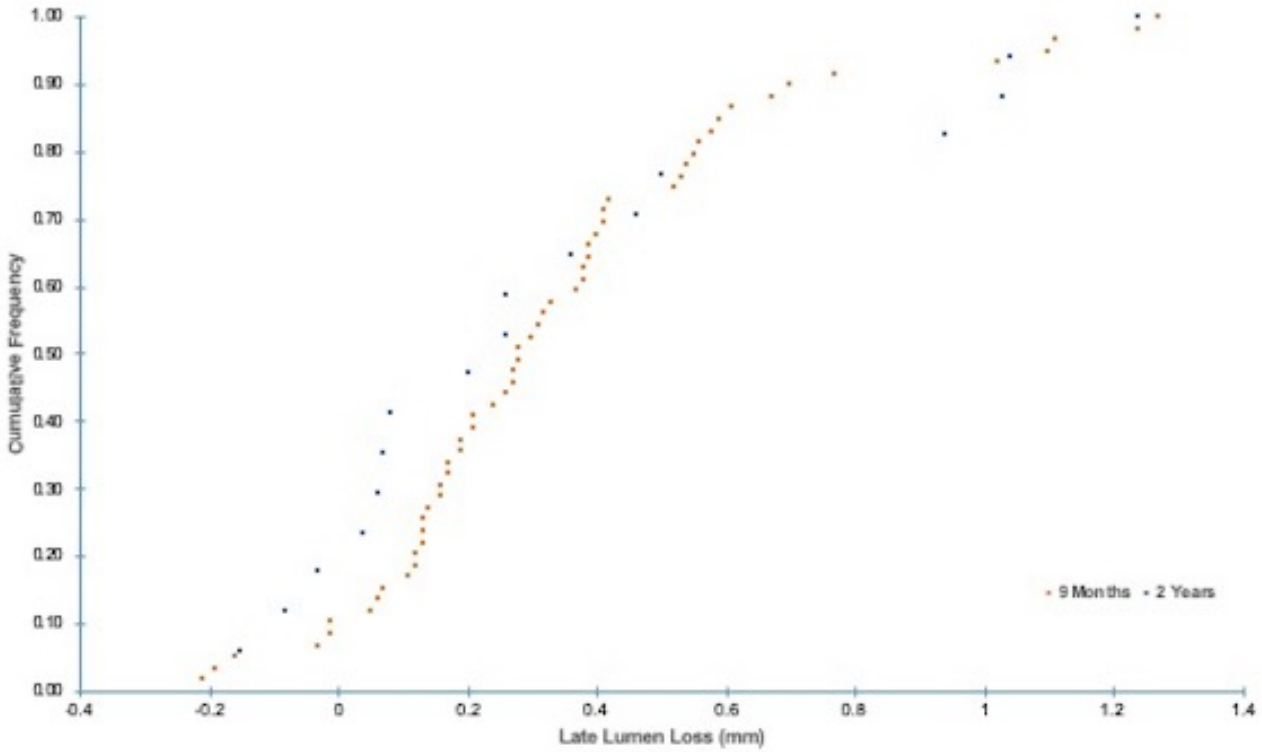


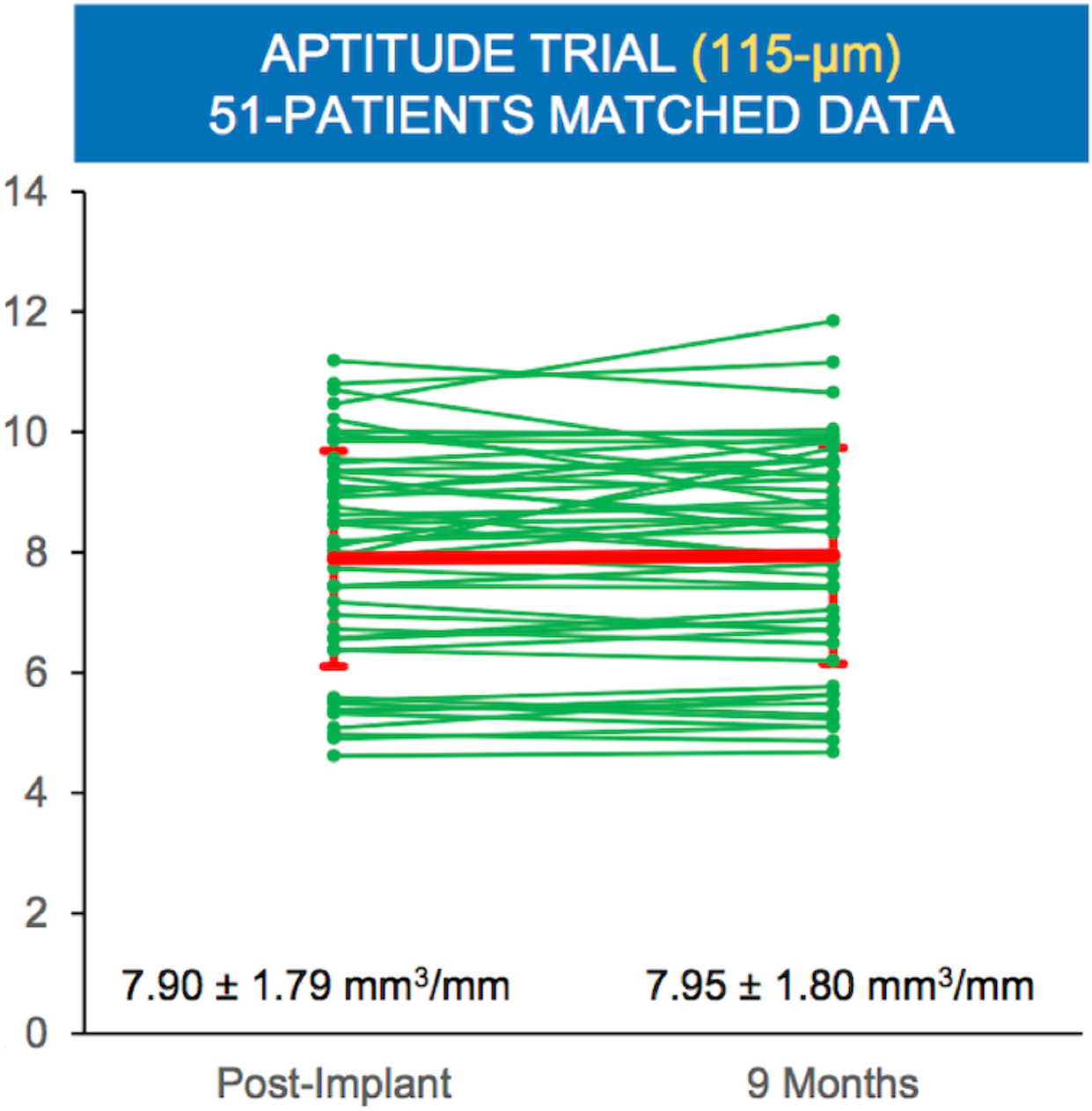
1st Generation (RENASCENT Study):
Amaranth Medical FORTITUDE® (150 µm)



2nd Generation (RENASCENT II Study):
Amaranth Medical APTITUDE® (115 µm)







SUPPLEMENTAL MATERIAL

Supplemental Table 1. Inclusion and Exclusion criteria for RENASCENT II study.

Inclusion Criteria • patients >18 and <85 years of age • stable, unstable angina pectoris or silent ischemia • Low or intermediate risk NSTEMI • de novo lesions in a native coronary artery with a diameter between 2.5 and 3.7 mm (by IVUS) and lesion length of <14 mm (by QCA) • a percentage diameter stenosis (DS) ≥50% and <100% • Thrombolysis in Myocardial Infarction flow grade of ≥1.
Exclusion Criteria • acute ST segment elevation myocardial infarction, unstable arrhythmias • left ventricular ejection fraction <30% • restenotic or severely calcified lesions • renal insufficiency with eGFR < 60 ml/kg/m2 or serum creatinine level of > 2.5 mg/dL • thrombus or another clinically significant stenosis in the target vessel. • lesions located in the left main coronary artery or located within ≤3 mm of the aorta junction or within ≤3 mm the origin of the left anterior descending or left coronary circumflex, lesions involving an epicardial side branch >2 mm in diameter by visual assessment • another clinically significant stenosis in the target vessel.

Supplemental Table 2. APTITUDE® Scaffold's Design Features and Description.

Design Feature	Description
Polymer	Ultra-High Molecular Weight Poly-L-Lactide (PLLA)
Diameters	2.5, 2.75, 3.25, and 3.5 mm
Lengths	13 and 18 mm
Wall Thickness	115 µm All Scaffold Sizes
Surface Coverage Area	28 to 49%*
Drug Coating	1:1 Poly D L-Lactide:Sirolimus
Drug Content	95 to 160 µg*
Drug Density	96 µg/cm^2
Inflation Pressures	Nominal: 8 to 10 ATM RBP: 13 to 16 ATM
Guide Catheter Size	6 French Compatible

*Depending on scaffold size.

Supplemental Table 3. Details of patient events

2 TVF due to TV-MI between 1 and 9-months (no TLR)
Patient 1: Patient had distal LAD PCI with APTITUDE®. The patient then presented with chest pain on day 144 post baseline procedure. The patient was diagnosed with MI and on angiography was found to have patent study stent but disease progression in the target vessel requiring PCI. The patient was adjudicated as TV-MI but no TLR.
Patient 2: Patient had LAD PCI with APTITUDE®. On day 273 post baseline procedure, patient had chest pain and subsequent angiography showed LAD disease progression, not related to previous treated lesion. Patient had LAD PCI and was judged to have TV-MI but no TLR.

Supplemental Table 4: Binary Stenosis

	9-months follow-up	24-months follow-up
Coronary angiography restenosis (%)	0% (0/59)	10% (1/10)
CT angiography restenosis > 50% (%)	N/A	6.7% (1/15)
Cumulative Binary stenosis rate (%)	0%	8.0% (2/25)

Supplemental Table 5. In-scaffold Optimal Coherence Tomography Measurements

OCT Measurements Mean ± SD (n)	Post-BRS Implantation (n=53)	9-Month Follow-Up (n=58)	Difference (Post vs. 9-Month)
Mean Lumen Area (mm^3/mm)	7.02 ± 1.69	5.98 ± 1.70	-1.03 (-14.7%)
Mean Outer Scaffold Area (mm^3/mm)	7.82 ± 1.81	7.84 ± 1.79	0.02 (0.3%)
Mean Inner Scaffold Area (mm^3/mm)	6.63 ± 1.60	6.79 ± 1.65	0.19 (2.9%)
Percent Intra-Scaffold NIH Volume (%)	--	13.3 ± 6.1	--
Post-Implantation Scaffold Fracture (%)	--	--	--
OCT Strut Measurements Mean ± SD (n)	**Percent Covered Struts (At 9 Months)**	**Percent Uncovered Struts (At 9 Months)**	**Total (%)**
Apposed of Total Struts (%)	96.522 ± 5.017	2.971± 4.757	99.493 ± 0.856
"Malapposed" of Total Struts (%)	0.037 ± 0.160	0.00 ± 0.00	0.037 ± 0.160
"Orifice of Branch" of Total Struts (%)	0.438 ± 0.844	0.032 ± 0.139	0.470 ± 0.839
Total (%)	96.996 ± 4.804	3.004 ± 4.804	100

NIH= neointimal hyperplasia

Supplementary definitions

Scaffold struts were classified as covered if the total thickness of the hyperintensity region (presumably including scaffold rim and neointima) was ≥0.03mm.

Follow-up scaffold dismantling was defined as isolated struts that could not be integrated into the expected circularity of the device without embedding it into neointima

OCT analysis.

The outer (abluminal) and inner (endoluminal) scaffold area and lumen area were analyzed every 1mm. Outer scaffold area was contoured as the abluminal leading edge of black strut

core and inner scaffold area was contoured as the endoluminal leading edge of black strut core (supplementary Figure 1). Lumen area was contoured as the interface between blood and the surface of plaque or neointima. Intra-scaffold neointimal area was calculated as inner scaffold area minus lumen area. Volume was calculated using Simpson's rule and shown as mean value (volume divided by analyzed length).

The strut level analysis was also performed every 1mm. As shown in Supplementary Figure 2, to determine scaffold coverage, we previously measured the thickness of the endoluminal hyper-intensity border for 150 randomly chosen APTITUDE® scaffold "struts" immediately after scaffold implantation; the mean was 0.0211 (Confidence Interval 0.0206, 0.0216) mm. Therefore, if the total thickness of the hyperintensity region (presumably including scaffold rim and neointima) was ≥0.03mm, it was considered to be "covered." A malapposed strut required visible blood between the outer scaffold border and the surface of the plaque. Acute scaffold fracture was defined if 1) two struts overlapped each other or 2) there was an isolated strut(s) that could not be integrated into the expected circularity of the device. Follow-up (laste) scaffold dismantling was defined as isolated struts that could not be integrated into the expected circularity of the device without embedding it into neointima. All quantitative analyses were done at a 1-mm sampling interval and total percentage of covered struts were calculated as number of covered struts divided by the total number of analyzed strut. Therefore, each lesion has one value (%), which was summarized as mean +- standard deviation (of percentage of covered strut).

CT analysis

CT stenosis was categorized visually as 1=normal, 2<25% of diameter stenosis, 3=mild 25-49% of diameter stenosis, 4=moderate 50-69%, 5=severe 70-99% diameter stenosis, 6=occluded. Binary restenosis was defined as >=50% of diameter stenosis.

Supplementary Background Information

As with BMS and DES, the impact of scaffold design, including strut thickness, is an important factor in the clinical outcome of BRS (16,17). With thicker struts comes increased foreign material and flow disturbances, including stagnation, hence increasing the risk of thrombosis (17).

The Absorb® (Abbott Vascular, Santa Carla, California), with a strut thickness of 157μm, was withdrawn from the market due to safety concerns (18).

The Amaranth bioresorbable scaffold technology has been shown to be biocompatible, maintain mechanical integrity, deliver controlled drug release and eventual scaffold resorption in pre-clinical and clinical studies of the FORTITUDE®, a novel sirolimus-eluting ultra-high molecular weight amorphous PLLA BRS. The FORTITUDE® scaffold is designed with strut thickness of 150 μm and was clinically evaluated in the RENASCENT study. The clinical results presented at EuroPCR 2018 demonstrated favorable safety and performance outcomes (19).

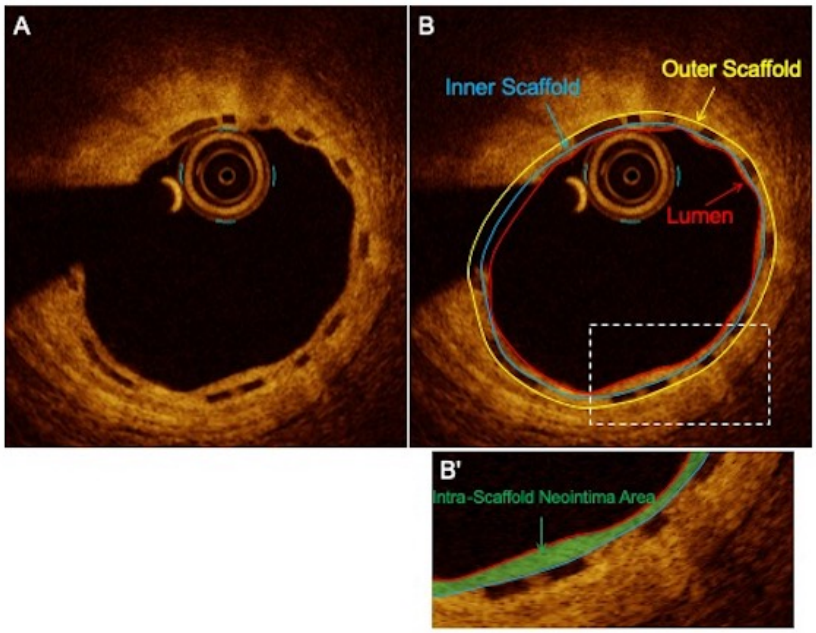
As a consequence of positive initial results from FORTITUDE®, Amaranth Medical developed a thinner scaffold with the same strength, flexibility and versatility seen in the previous product, but with 115μm wall thickness.

Supplementary Figure Legend

Supplemental Figure 1: Shows OCT imaging used to measure neointimal hyperplasia. The outer scaffold area (abluminal) was marked in yellow, inner scaffold area (endoluminal) in blue. Lumen was marked as interface between blood and plaque or neointima (red). Neointimal area was calculated between red and blue lines.

Supplemental Figure 2: Shows 9-month OCT imaging measurement used to calculate "strut coverage" if thickness was ≥0.03mm.

Supplementary figure 1:



Supplementary figure 2: