10.2

MeRes100™—A sirolimus eluting bioresorbable vascular scaffold system

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BACKGROUND

The concept of a "temporary stent" to provide acute benefits in treatment of severe coronary stenosis and its eventual disappearance in order to free the vessel of metal caging is not just attractive but also represents an ultimate long-term goal of returning the arteries to their original physiological state [1]. The research on bioresorbable scaffolds (BRS) has been challenging over the last 15 years. Increasing insight into biomaterial science of polymers and technological innovation among polymer scientists, device industry, and experienced interventionalists has led to the creation of the first generation of BRS. The front-runner in this development process with pivotal randomized trials, large registry data, routine "real life" clinical use, and approval in more than 60 countries has been the Absorb™ Bioresorbable Vascular Scaffold System (Abbott Vascular, Santa Clara, CA) [2]. The potential long-term benefits, which have been identified and outlined as the "final frontier," are only going to be proven over long-term studies though more and more supportive data keeps appearing every month [3].

However, there are limitations of the first-generation BRS like Absorb™. It is a thick strut device with restrictive implantation characteristics (like gradual inflation deployment over 45–60 seconds, limited expansion characteristics of no more than 0.5 mm above its nominal size), limited sizes up to 3.5 mm in diameter (and hence meant only for vessels up to 4 mm in diameter) [4], limited lengths, and inadequate radiopacity. The device is difficult to track and cross especially in calcified and tortuous anatomy. In simple terms, it is not a stent but a new device and hence has its learning curve [5]. This limits its use in complex real life cases. Thus, newer device modifications are needed to expand the use of BRS from a niche device to a workhorse stent. The increased applicability would also be determined by economics of the procedure in most parts of the world. Thus, the target is to progress to an economical BRS with performance characteristics that bring it as close as possible to the metallic drug eluting stent (mDES) in most lesion subsets, thus overcoming some of the limitations of the first-generation BRS.

The MeRes100–Sirolimus Eluting Bioresorbable Vascular Scaffold System is an investigational device (developed by Meril Life Sciences Pvt. Ltd., Vapi, Gujarat, India), which is undergoing first-in-human clinical trials in India. It has a novel scaffold architecture, low strut thickness, low profile delivery system, high radial strength, high flexibility and deliverability, improved radiopacity, convenient side branch access, multiple length and size matrix, and conventional storage methods (Table 10.2.1).

Table 10.2.1 Advantages of MeRes100 over first-generation BRS

Low strut thickness	100 μm (±10%)
Low profile delivery system	Low crimping profile of 1.2 mm for a 3.00 mm diameter scaffold
Hybrid design	Closed cells at the edges and open cells along the length of the device
High radial strength	Strut-width variability in design maintains high radial strength starting above 22N without any loss in flexibility despite low strut thickness
High flexibility and deliverability	MeRes100 samples (3.00 × 19 mm scaffolds) produced low ultimate forces of 1.85N required to track the device and 8.77N of ultimate force required to push the device versus 2.09N and 8.81N required, respectively, to track and push the commercially available Absorb™ control samples (3.00 × 18 mm scaffolds)
Improved radiopacity	Couplets of three triaxial platinum radiopaque markers are fixed circumferentially 120° apart from each other at either end of the scaffold
Convenient side branch access	Open cells allow easy access of side branch
Multiple length and size matrix	Diameters of (mm) 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 4.00, 4.50 and lengths of (mm) 8, 13, 16, 19, 24, 29, 32, 37, 40
Conventional storage methods	MeRes100 BRS is sterilized using e-beam radiation and can be stored below 25°C

DEVICE DESCRIPTION

The MeRes100–Sirolimus Eluting BRS comprises the following components:

1. A balloon expandable BRS made from polymer—poly-L-lactide (PLLA)
2. A topcoat comprising an antiproliferative agent—sirolimus (1.25 μgm/mm2) eluting from PDLLA polymer base
3. A rapid exchange PTCA balloon catheter that acts as the scaffold delivery system

Poly-L-lactide (PLLA) is one of the commonly available commercial aliphatic polyesters that possess excellent biocompatibility, biodegradability, a high mechanical strength, and good shaping and molding properties. PLLA used in MeRes100 construction is a semicrystalline polymer with the glass transition temperature of around 55–60°C and the melting temperature of around 180°C.

PLLA is a recognized biocompatible and bioresorbable polymer that undergoes hydrolytic degradation in the body producing lactic acid, lactides, and oligomers which are decomposed in the body via well-known Kreb's cycle and eventually eliminated as carbon dioxide and water.

The MeRes100 scaffold strut thickness is maintained around 100 μm (±10%). The scaffold is laser cut to form an articulating mix of crowns and connectors. The resultant design (Figure 10.2.1) is an intelligent "hybrid" comprising closed cells at the edges and open cells along the length of the device. Additionally, the design incorporates strut-width variability; thus, the scaffold maintains high radial strength without any loss in flexibility despite low strut thickness. The open cells ensure sufficient side branch access. The percentage of vessel wall area covered by the scaffold is 28.5% for the 3.0 mm device. In order to address the inadequate radiopacity with current generation of BRS, in the MeRes100, couplets of three triaxial platinum radiopaque markers are fixed circumferentially 120° apart from each other at either end of the scaffold.

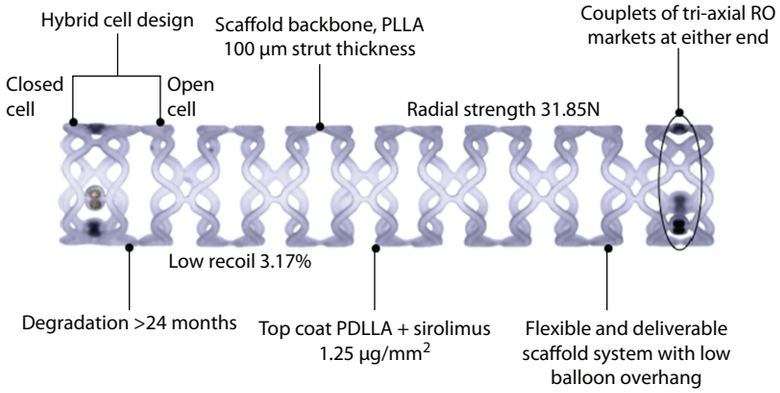

Figure 10.2.1 MeRes100–sirolimus eluting bioresorbable vascular scaffold.

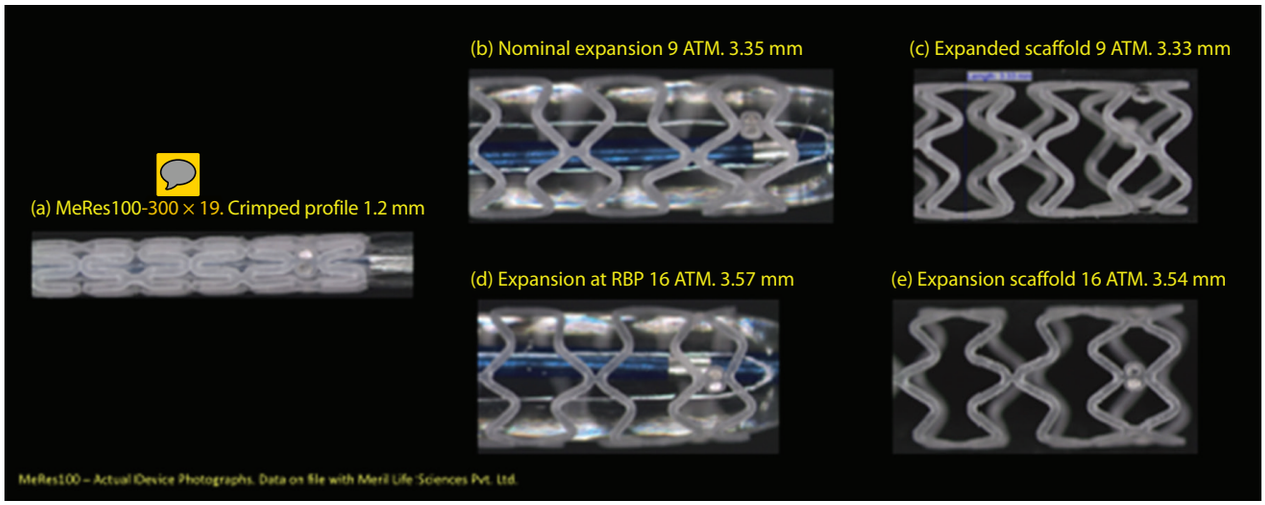

Figure 10.2.2 MeRes100–Crimped and expanded actual device images at NP 9 ATM and RBP 16 ATM.

These markers assist scaffold positioning when viewed in two orthogonal planes and ensure adequate visibility during postdeployment high-pressure dilatations.

The scaffold is mounted between the radiopaque markers of a rapid exchange balloon expandable delivery system. This thin strut BRS has low crimping profile (1.2 mm for a 3.00 mm diameter scaffold) and higher trackability and pushability. In a series of MeRes100 samples tested on ASTM standard test equipment for flexibility and deliverability, MeRes100 samples (3.00 × 19 mm scaffolds) produced low ultimate forces of 1.85N required to track the device and 8.77N of ultimate force required to push the device versus 2.09N and 8.81N required, respectively, to track and push the commercially available Absorb™ control samples (3.00 × 18 mm scaffolds) [6].

The device demonstrates uniformity of expansion without any strut deformity or minor or major notching, no strut fractures at nominal pressures of 9 ATM and this is evenly observed beyond the balloon rated burst pressures (RBP) of 16 ATM (Figure 10.2.2).

MeRes100 side branch accessibility tests demonstrate that the struts withstand the balloon expansion pressures without any link fractures or trauma to surrounding cells and the remaining structures. Figure 10.2.3 demonstrates the circular diameter available after expansion of a cell with 3.00 mm diameter balloon at 16 ATM.

The active drug coating is sirolimus in the dose of 1.25 μgm/mm^2. The drug is formulated in a 1:1 mixture with biocompatible bioabsorbable polymer, i.e., poly-DL-lactide (PDLLA), which acts as a drug reservoir and controls drug release rate. The coating is thin (<5 μm), uniform, and does not web, crack, or lump. The drug is timed to elute over a period of 90 days with 75% of drug elution happening during the first 30 days (Figure 10.2.4) [7].

MeRes100 is manufactured in a wide range of sizes—diameters (mm) of 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 4.00, 4.50 and lengths of (mm) 8, 13, 16, 19, 24, 29, 32, 37, 40 thus allowing the operators to choose from a wide matrix partially resolving the unmet clinical need to treat a variety of real life lesion morphologies. The device is sterilized using e-beam radiation and can be stored below 25°C, thus ensuring ease of transport and storage at various points along the distribution system.

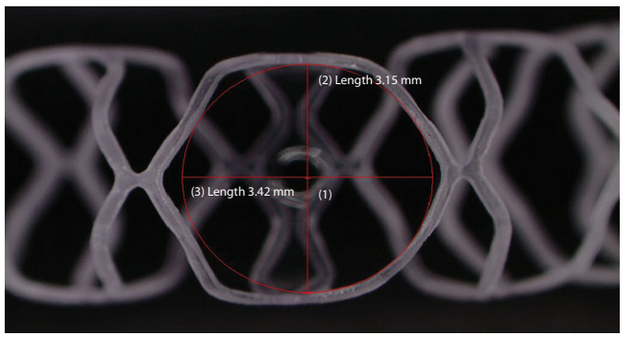

Figure 10.2.3 MeRes100 3.00 × 19. Open cell expansion using a 3.00 mm balloon at 16 ATM.

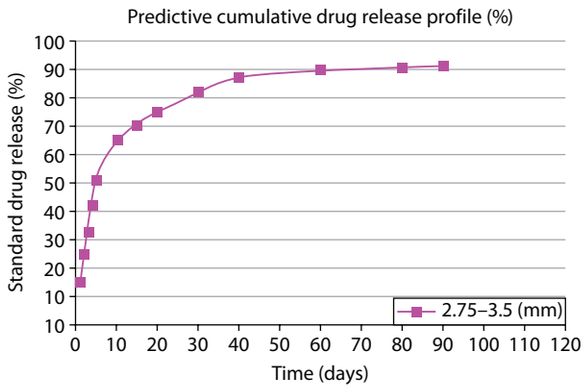

Figure 10.2.4 MeRes100—*In-vitro* drug release kinetics.

DEGRADATION, LOSS IN RADIAL STRENGTH, MOLECULAR WEIGHT AND CHANGE IN CRYSTALLINITY

Simulated in-vitro degradation study performed as per ASTM standards demonstrates that MeRes100 BRS retains its radial strength beyond 3 months. Breakdown of PLLA on further hydration occurs leading to loss in molecular weight. Inversely the crystallinity increases shortly as the amorphous base degrades faster and then drops over a period of 6 months. The scientific hypothesis here is that during the 6 months postdeployment the scaffold endothelializes and the vessel no longer needs additional support allowing for its ultimate degradation estimate to be beyond 2 years, liberating the vessel of its primary implant [1]. Both animal model testing and in-house sophisticated degradation models developed by Meril have substantiated this correlation.

In-vitro degradation testing demonstrates three critical parameters of the *in-vitro* scaffold degradation analysis (Figures 10.2.5, 10.2.6, and 10.2.7). The scaffold is made

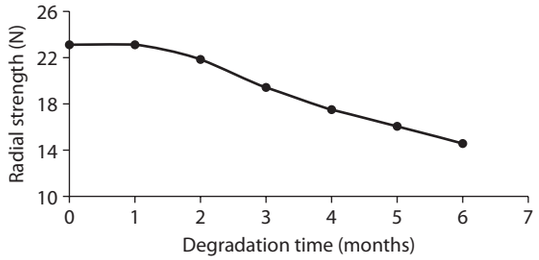

Figure 10.2.5 Loss in radial strength.

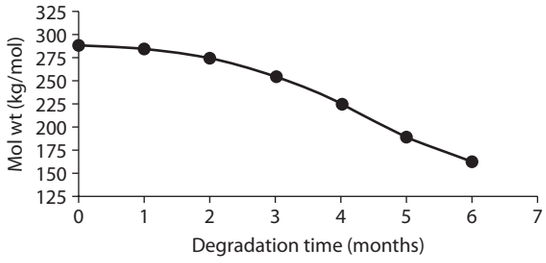

Figure 10.2.6 Loss in molecular weight.

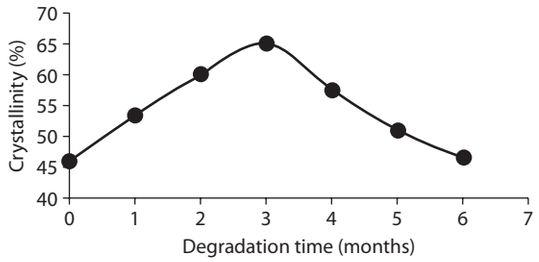

Figure 10.2.7 Change in crystallinity.

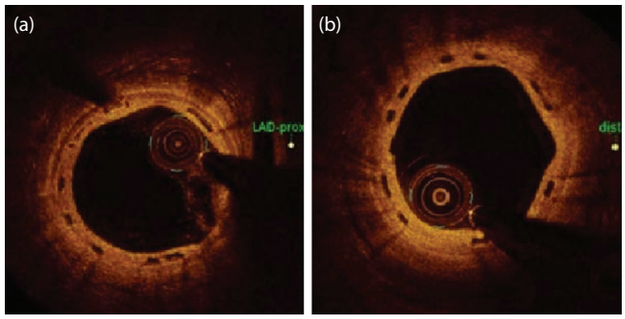

Figure 10.2.8 Ninety-day OCT image of MeRes100 3.00 × 19 implanted in **(a)** proximal LAD and **(b)** distal LAD porcine coronary artery.

of high molecular weight PLLA ranging 275,000–300,000 Daltons. The design coupled with improved manufacturing process generates a scaffold with high radial strength starting above 22N. As the scaffold undergoes hydrolytic degradation, there is a gradual reduction in radial strength and beyond 3 months, the values drop to 14N, which is still sufficient to maintain the hoop strength while the vessel undergoes simultaneous healing and prevents recoiled restenosis. An inversely proportional relationship is observed between molecular weight loss and temporary spike in crystallinity, which is momentary aggregation of large chain semicrystalline PLLA, which populates as the smaller chain PLLA cleaves preferentially [8]. This can be correlated along with representative OCT images (Figure 10.2.8) from porcine coronary artery implantation at 90-day's time point demonstrating intact scaffold, no loss in vessel diameter, uniform and thin neointimal coverage, and absence of scaffold fractures [9].

IN-VIVO AND *IN-VITRO* BENCH PERFORMANCE

Extensive *in-vivo* biocompatibility tests and *in-vitro* performance testing has been undertaken as per standard stent and BRS testing guidelines prescribed as per ISO guidelines; US FDA guidance document; ASTM standard guidelines; D-618 -stent practice document and WK-35909–standard guide to test absorbable stents [6]. Tests involved radial strength measurement, percentage recoil, fatigue resistance, 3-point bend test, pushability, trackability, radial force, percentage change in length, dislodgement force, uniformity of expansion, and ring strength test. All the samples passed both biocompatibility and engineering bench tests as per the guidelines.

PRECLINICAL PROOF OF CONCEPT

The purpose of the preclinical studies of MeRes100 were to evaluate the acute operational performance, acute and intermediate biomechanics, intermediate durability and patency, biocompatibility, and pharmacokinetics (pK) of

sirolimus elution, in a porcine model in comparison to Absorb™ BRS (Abbott Vascular, Santa Clara, CA), a mDES, i.e., Xience V everolimus eluting stent (Abbott Vascular, Santa Clara, CA), and BioMime Sirolimus Eluting Stent (Meril Life Sciences, India).

The follow-up period for the study was 180 days. A subset of these animals was used to get pK data on release profile of sirolimus into blood and local arterial tissue surrounding the scaffold.

Test devices MeRes100 and control devices (Absorb EE BRS, Xience V EES, and BioMime SES) were implanted in Yucatan mini-swines in LCx, LAD, and RCA. All implanted arterial sites were imaged with angiography and OCT. There was no animal mortality or any serious adverse event (such as device thrombosis, MI, hypersensitivity, or acute/chronic mechanical device failure). No clinically relevant abnormalities were observed in the health status of animals nor in the clinical pathology (hematology and serum chemistry). Acute operational performance, acute and chronic biomechanics, and chronic patency were found satisfactory. MeRes100 BRS demonstrated appropriate acute operational performance, adequate acute and chronic biomechanics, and favorable patency and neointimal growth when compared to benchmark Absorb BRS, mDES Xience V, and BioMime [9].

The purpose of the pK substudy was to evaluate release of sirolimus into the blood stream and in surrounding arterial tissue following implantation of MeRes100 BRS in a porcine model up to 180 days. There was no animal mortality or any serious adverse event within the period of the study. MeRes100 BRS demonstrated gradual release of sirolimus with a minor proportion released into the blood stream, and sustained presence with gradual decline in arterial tissue up to 180 days. The blood concentrations peaked between 1 and 4 hours. The levels were clinically acceptable as the peak was never higher than 9 ng/ml. The levels gradually declined below quantifiable limit (<0.100 ng/ml) in all animals at day 14 and beyond. The arterial tissue concentration gradually declined over time. At 90 days, the concentrations were about 50% lower than at 28 days. At 180 days, the concentrations were detectable, yet about 90% lower than at 28 days [10].

MERES-1 FIM CLINICAL TRIAL

MeRes100 is currently an investigational device and is being studied in a phase-II safety and feasibility study in India. MeRes-1 is a prospective, multicenter, single arm, open label, pilot clinical Study of MeRes100 Sirolimus Eluting Bioresorbable Vascular Scaffold System in the treatment of *de novo* native coronary artery lesions [11].

The study has been approved by the [DCG(I)] (Indian FDA) and is planned to recruit 108 patients in 16 sites across India. Angiographic inclusion criteria involves a maximum of two treatable *de novo* lesions (maximum one per native epicardial vessel) located in a major artery or branch, with a reference vessel diameter between 2.75, 3.0, and 3.5 mm by online QCA and target lesion length ≤20 mm. The MeRes-I Study is currently enrolling and thus far 80 out of 108 subjects have been enrolled.

The primary safety endpoint will be ischemia-driven major adverse cardiac event (ID MACE) at 6 months. Clinical endpoints include ischemia-driven MACE, ischemia-driven TVF, TLR, TVR, scaffold thrombosis at 30 days, 6 months, and at 1, 2, and 3 years. Additionally acute device and procedural success will be determined.

A subset population will undergo angiographic (n = 36), IVUS (n = 12), OCT (n = 12) follow-up at 6 and 24 months and MSCT (n = 12) follow-up at 12 months. A subset population will also undergo pK to measure time taken to reach maximum concentration (T_{max}) level in the blood after implantation of the scaffold, maximum concentration of the drug obtained in peripheral venous blood (C_{max}), mean initial ($T_{½i}$) and terminal ($T_{½T}$) half life period of the drug in venous blood, area under the curve (AUC) of the blood drug concentration, and time taken for the drug to go below detectable levels by LCMS.

SUMMARY AND CONCLUSIONS

The MeRes100 Sirolimus Eluting BRS represents a second generation BRS with a novel architecture, thinner struts, lower profile, and a variety of lengths and diameters, thus progressing closer to a user-friendly, workhorse device. Preclinical engineering and animal study data demonstrate extremely favorable characteristics and similar vascular tissue responses as seen with Absorb™ (Abbott Vascular, Santa Clara, CA) BRS up to 3 months. Longer animal data is awaited. The first-in-man clinical trial, MeRes-1, is underway in India and the 6-month results of this are expected by mid-2016. Development of MeRes100 from India would also help to lower the cost of BRS, which is a limitation for its widespread use not just in emerging countries but also in the developed world.

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