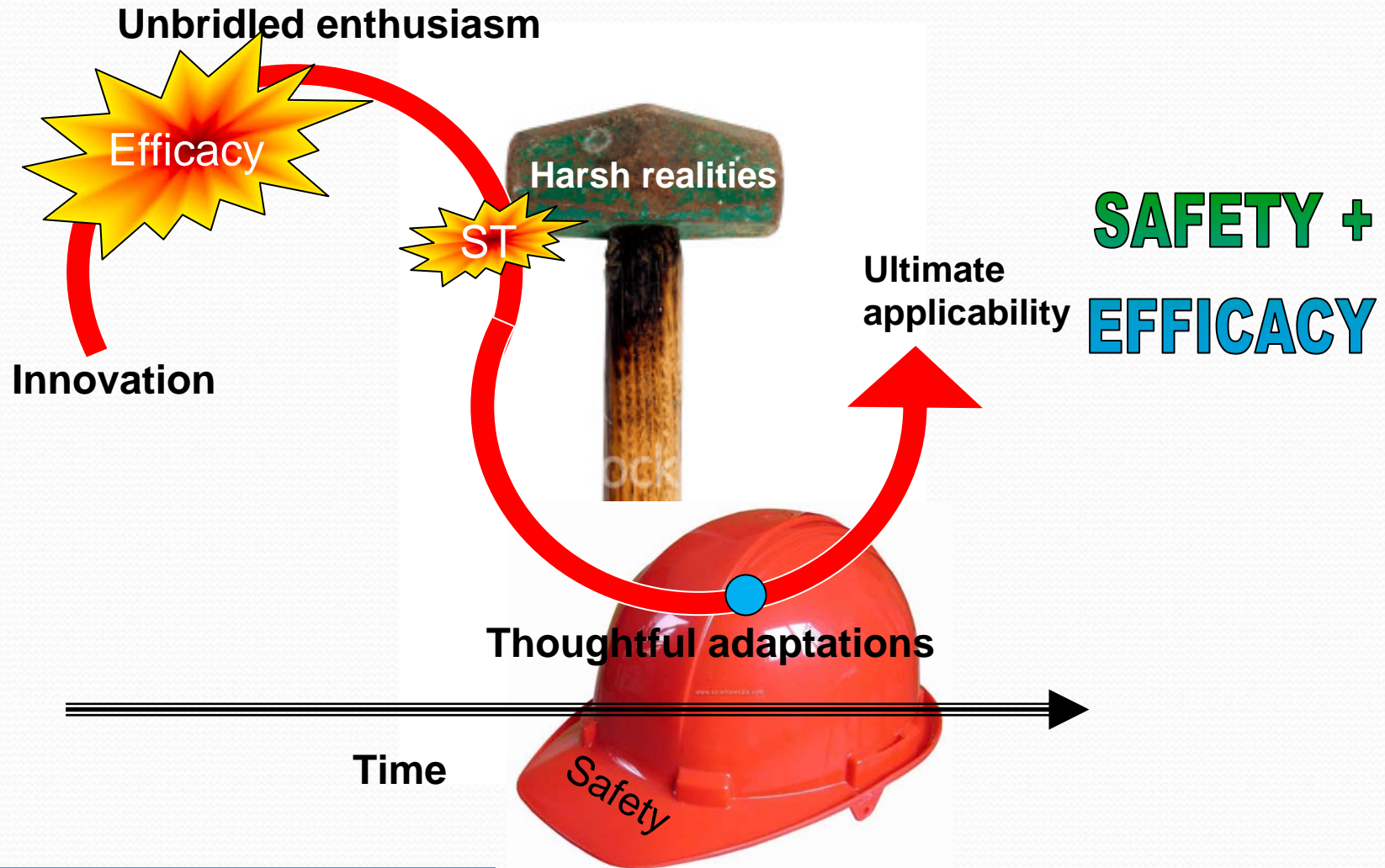# Evolution of

Sirolimus Eluting Coronary Stent System BIOMIME™

Novel Approach to DES Creation

Prof. Teguh Santoso

Medistra Hospital, Indonesia

TCT AP 2011
Seoul

DES use – Paradigm Shift

Unbridled enthusiasm

Efficacy

Harsh realities

ST

Innovation

Ultimate applicability

SAFETY + EFFICACY

Thoughtful adaptations

Time

Safety

BioMime entry point

Thin Struts and Restenosis

- Thin Struts allow for-

  - Low blood flow perturbance

  - Easy struts nesting to the vessel wall

  - Added flexibility and conformability

- **Improved clinical outcome***

- **Improved, faster endothelialization ****

- * Kastrati A, Schömig A, Dirschinger J, et al. **Strut Thickness Effect on Restenosis Outcome (ISAR STEREO Trial)**. Circulation 2001; 103:2816-2821

- ** Simon C, Palmaz JC, Sprague EA. **Influence of topography on endothelialization of stents: clues for new designes**. J Lon Term Eff Med Implants. 2000;10:143-151
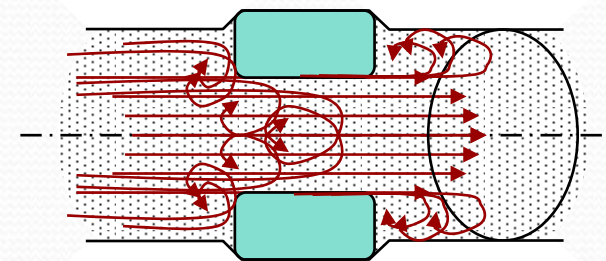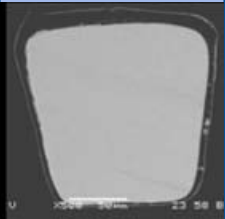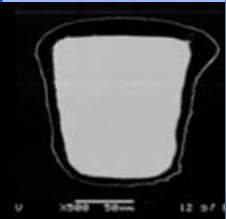
NO Stent: Laminar Flow
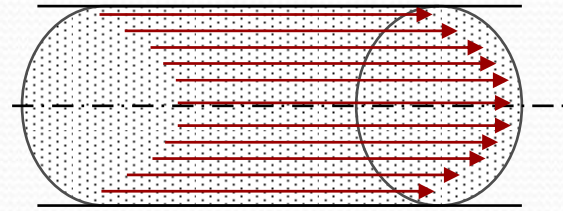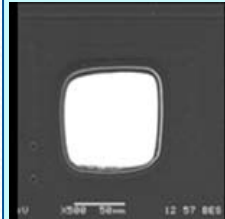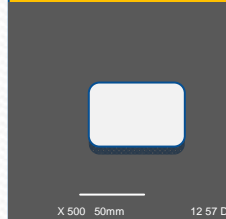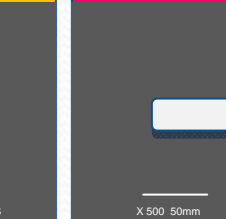
Stent Thickness S1:
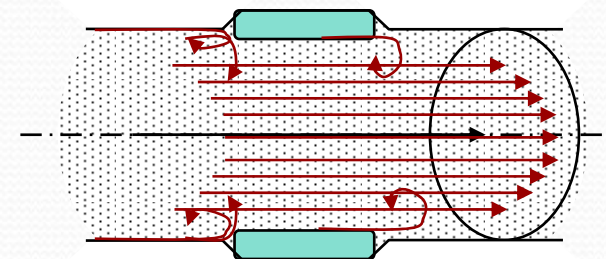
Stent Thickness S2>S1: Turbulent Flow

Moving towards biomimicry

	Cypher	Taxus	Endeavor	Xience V	BioMime	Mitsu
Strut thickness	140 µm	132 µm	91 µm	81 µm	65 µm	40 µm
Coating thickness	12.6 µm	16 µm	5.3 µm	7.6 µm	2 µm	< 2 µm
Polymer	PEVA-PBMA	SIBBS	PC	Fluoro	PLLA + PLGA	None
Drug	Sirolimus 1.4 µg/mm²	Paclitaxel 1.0 µg/mm²	Zotarolimus 10.0 µg/mm	Everolimus 1.0 µg/mm²	Sirolimus 1.25 µg/mm²	Merilimus 0.45 µg/mm²
	1st Gen	1st Gen	2nd Gen	2nd Gen	3rd Gen	4th Gen
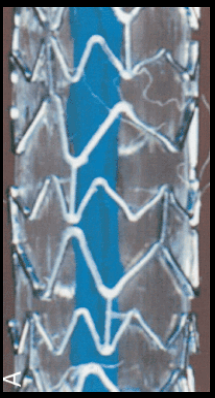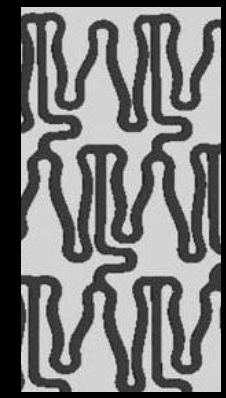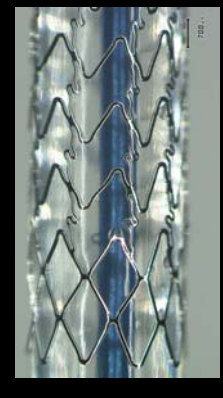
3.0 mm diameter stents, 500X magnification

Stent design makes a difference!

Closed Cells 140µm	Open Cells 132µm	Open Cells 132µm	Open Cells 90µm	Open Cells 81µm	Hybrid Cells 65µm	Hybrid Cells 40µm
Bx Velocity	Express	Liberte	Driver	Multi-Link	BioMime	Mitsu

Closed cells Open cells

The "hybrid" design coupled with strut width variability eliminates the need for high strut thicknesses as required in earlier stent technologies

BioMime Stent Architecture

- Cobalt chromium (L605) platform. 65μm strut thickness.
- Hybrid cell design, an intelligent mix of open and close cells.
- Excellent radial strength & high flexibility.
  - <3% recoil and 0.29% foreshortening
- Special electro-polishing technique eliminates surface nickel oxides

Hybrid design
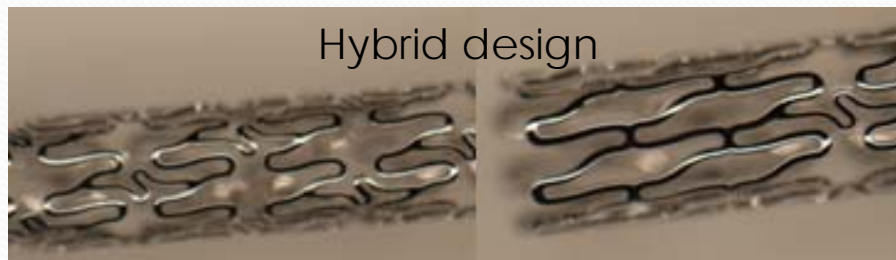
Open cells in mid segment   Close cells at edges

Y-connector   S-link   Mirror Polish

Strut width variability

Morphology Mediated Expansion

biomime™

Sirolimus Eluting Coronary Stent System

Mimes so well, you can't tell.

Low Injury Stent Design

Sirolimus Drug Loading

- BioMime has *1.25µgm/mm² of Sirolimus* loading on stent (Cypher has 1.4µgm/mm²)
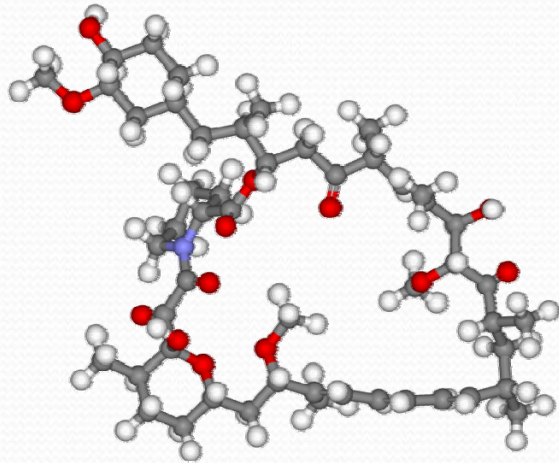
Sirolimus is an ideal choice considering that it acts on the common final pathway of cell division cycle without exceptional risk of necrosis induction

Stent Length	Vessel Size & Drug Loading		
	2.5 mm (Drug Loading in mcg.)	2.75-3.5 mm (Drug Loading in mcg.)	4.0-4.5 mm (Drug Loading in mcg.)
8 mm	39	51	63
13 mm	62	82	103
16 mm	79	104	128
19 mm	92	121	151
24 mm	117	154	190
29 mm	142	187	225
32 mm	155	202	254
37 mm	181	237	287
40 mm	193	252	316

Data on file with Meril Life Sciences.

pK / pD of BioMime

BioMime In Vivo drug elution

75% in 2 weeks

>98% in 4 weeks

(Y-axis: Cumulative Drug Percentage, 0–100; X-axis: Days, 0–30)

— % Cumulative Drug Release
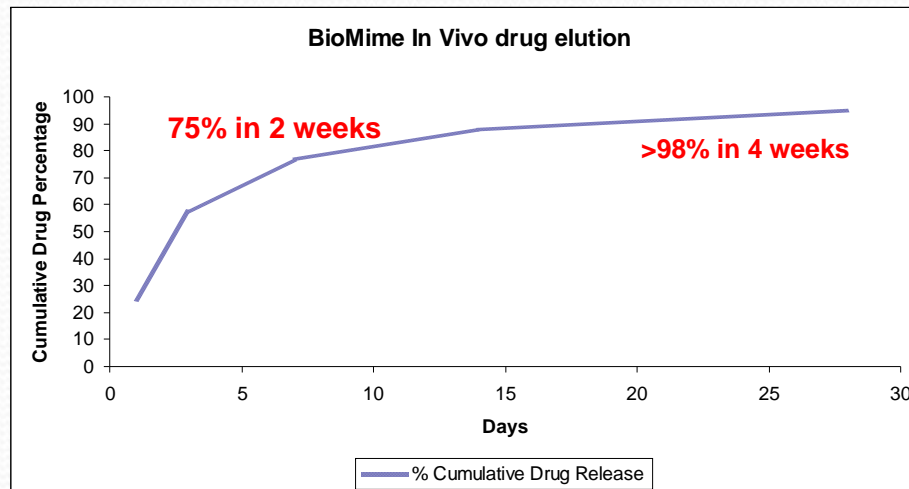
Similar tissue concentrations as Cypher

BioMime Sirolimus Concentration in Rabbit artery homogenate

(Y-axis: Mean Drug Concentration (ng/mg), 0–15; X-axis: Time(days), 0–30)

— Mean Drug Concentration(ng/mg)

Cypher Sirolimus concentration in artery homogenate

(Y-axis: Mean Drug Concentration (ng/mg), 0–15; X-axis: Time(Days), 0–100)

— Mean Drug Concentration(ng/mg)
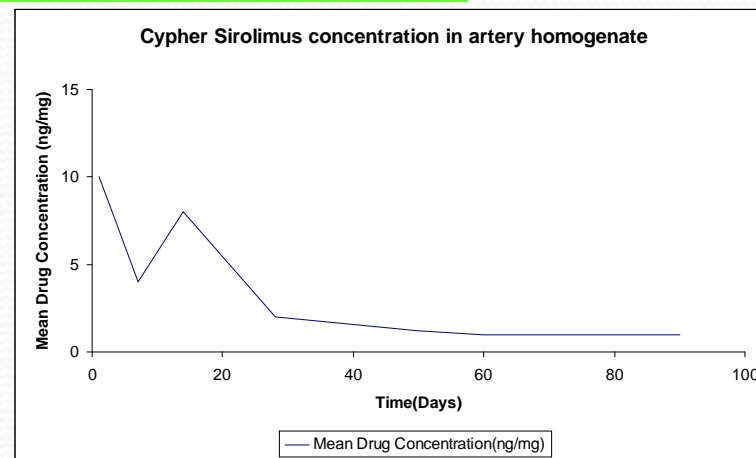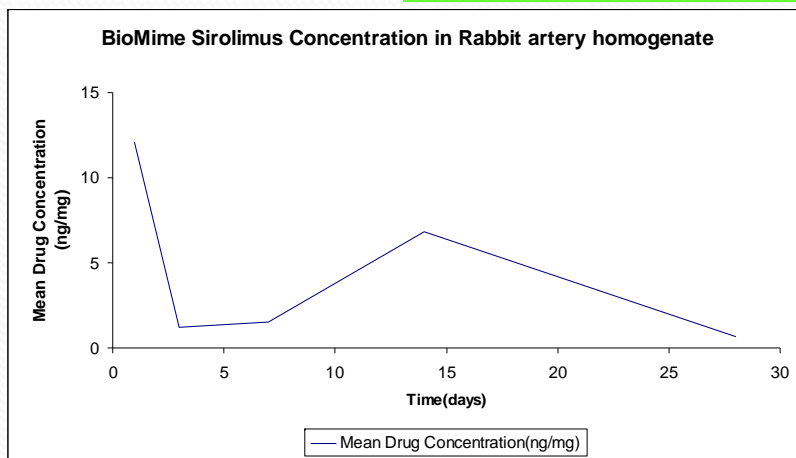
Data on file with Meril Life Sciences. Rabbit illiac model.

Biodegradable Polymers
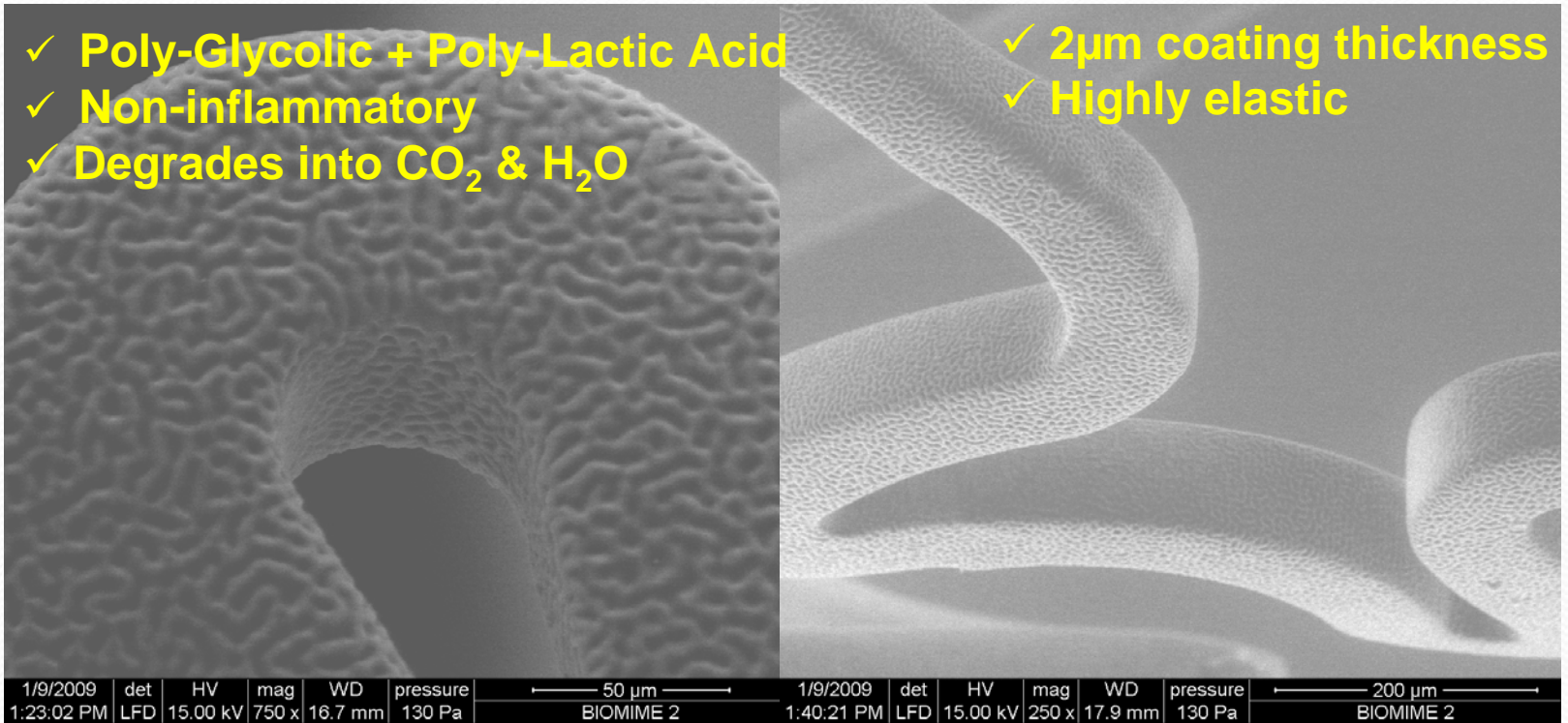
✓ **Poly-Glycolic + Poly-Lactic Acid**
✓ **Non-inflammatory**
✓ **Degrades into CO_2 & H_2O**

✓ **2µm coating thickness**
✓ **Highly elastic**

| 1/9/2009 1:23:02 PM | det LFD | HV 15.00 kV | mag 750 x | WD 16.7 mm | pressure 130 Pa | 50 µm BIOMIME 2 |

| 1/9/2009 1:40:21 PM | det LFD | HV 15.00 kV | mag 250 x | WD 17.9 mm | pressure 130 Pa | 200 µm BIOMIME 2 |

After inflation   **After inflation**

Post inflation BioPoly™ adjusts to stresses generated at vulnerable areas – s-links & y-connectors due to its elasticity.

Data on file with Meril Life Sciences. SEM pictures BioMime Stent

BIOMIME
Sirolimus Eluting Coronary Stent System

Closed Cell
Open Cell
Hybrid cell design

65 μm strut thickness Cobalt Chromium stent

Crimped stent

Morphology Mediated Expansion™ for optimal conformability

Fully expanded stent

0.29% foreshortening

<3% recoil
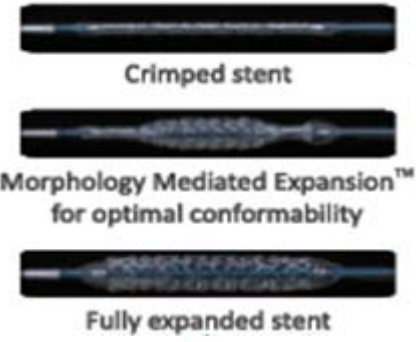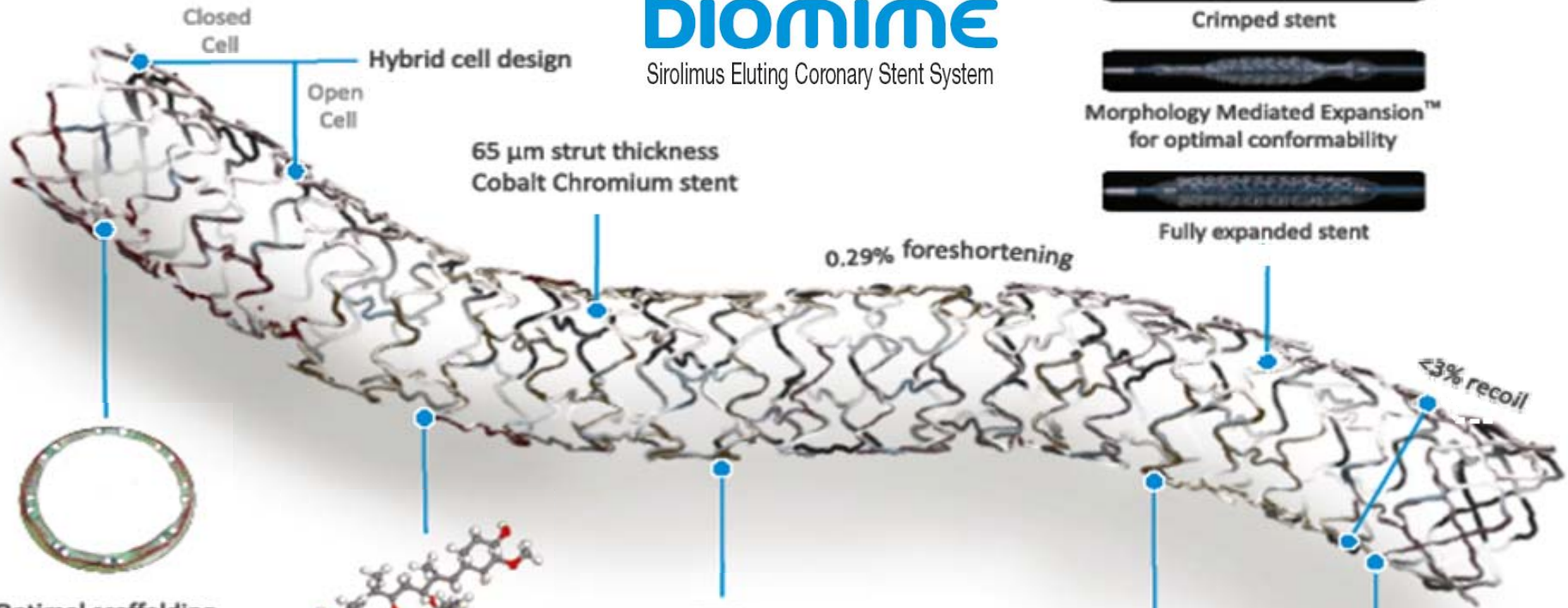
Optimal scaffolding, wall apposition with superior acute gain[1]
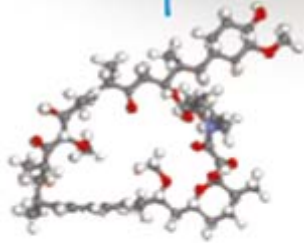
Sirolimus 1.25 μg/mm² of stent surface, 30-days elution kinetics
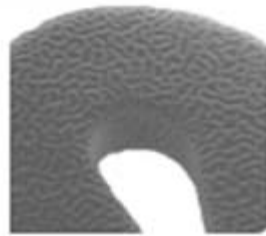
Stable, elastic non - inflammatory BioPoly™- Biodegradabl hick.

PLLA

+

+

PLGA
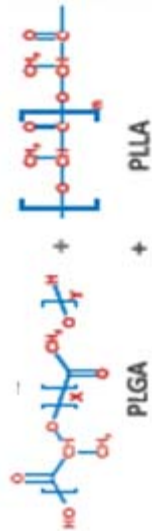
Highly flexible and deliverable stent system

Low balloon overhang, short, abrupt balloon shoulders for low balloon - related edge injury

CE & ANVISA approved

40mm Lengths

Available in 54 sizes-
Diameters (mm): 2.50, 2.75, 3.00, 3.50, 4.00, 4.50
Lengths (mm) : 8, 13, 16, 19, 24, 29, 32, 37, 40

Meril family of Trials – meriT series

MeriT – I is a prospective, single center primary safety and efficacy trial for BioMime™ Sirolimus Eluting Coronary Stent System.
Principal Investigator – Dr. Sameer Dani, India

MeriT – II is a prospective, multi-centric, non-randomized, all-comers study to asses safety and efficacy of BioMime™ Sirolimus Eluting Coronary Stent System.
Principal Investigator – Dr. Ashok Seth, India

meriT-1 Study Design

- Study – to assess the safety and efficacy of BioMime Stent in 30 patients with single de-novo lesions in a single centre

- Stent diameters – 2.50 to 3.50 mm

- Stent lengths – 13 to 24 mm

- Primary Safety and Efficacy End-points – MACE at 30days, Late loss by QCA at 8months

- 1 year follow-up completed.

Baseline Demographics

Baseline Characteristics	Details
Number of patients	30
Mean age, years	50.5 ± 7.7
Gender, Males	25 (83%)
Previous MI	*13 (43%)*
Prior PCI	1 (3%)
Prior CABG	1 (3%)
Diabetes	*9 (30%)*
Hyperlipidemia	4 (13%)
Hypertension	*16 (53%)*
Smokers	7 (23%)
BMI	24.3±4.7

0% MACE, 0% ST

Follow-up Time Points	Total Patients Followed up		Death		Myocardial Infarction		Target Lesion / Vessel Revascularization	
			Cardiac	Non-Cardiac	Q-wave	Non-Q-wave	Repeat PCI	CABG
30-Days	All 30 patients	100%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6-Months	All 30 patients	100%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
8-Months	All 30 patients	100%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
1-Year	All 26patients	87%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Follow-up Time Points	Total Patients Followed up		Stent Thrombosis				Any Other Complications
			Acute (0D – 1D)	Sub-Acute (>1D – 1M)	Late (>1M – 1Y)	Very Late (>1Y)	
30-Days	All 30 patients	100%	0 (0%)	0 (0%)	N.A.	N.A.	0 (0%)
6-Months	All 30 patients	100%	N.A.	N.A.	0 (0%)	N.A.	0 (0%)
8-Months	All 30 patients	100%	N.A.	N.A.	0 (0%)	N.A.	0 (0%)
1-Year	All 26 patients	87%	N.A.	N.A.	0 (0%)	N.A.	0 (0%)

*4 patients refused Angiographic follow-up. NA = Not Applicable

QCA Analysis

Pre-Procedure QCA (N=26)	
Lesion length, mm	14.12 [12.16, 17.25]
Reference Diameter, mm	2.95 [2.77, 3.35]
MLD, mm	0.40 [0.30, 0.91]
% Diameter Stenosis	87.3 [67.2, 91.1]

Post Procedure QCA	(N=26)
Reference Vessel Diameter, mm	3.01 [2.89, 3.37]
In-Segment	
MLD, mm	2.57 [2.31, 2.98]
% DS	14.1 [9.4, 19.9]
Acute gain, mm	2.08 [1.70, 2.54]
In-Stent	
MLD, mm	2.86 [2.73, 3.10]
% DS	6.3 [4.6, 8.8]
Acute gain, mm	2.28 [1.91, 2.73]

Preliminary QCA analysis. Median values

QCA analysis done by – Dr. Ricardo Costa, Dr. Alexandre Abizaid
Cardiovascular Research Centre (CRC)
Sao Paulo, Brazil

*4 patients refused Angio follow-up.

QCA Analysis* – Follow up

Follow-up QCA – 8 months	(N=26)
Reference Vessel Diameter, mm	2.97 [2.80, 3.28]
In-Segment	
MLD, mm	2.32 [2.18, 2.62]
% DS	21.1 [14.9, 26.2]
Late Lumen Loss, mm	0.18 [0.06, 0.35]
Binary Restenosis, %	0 (0)
In-Stent	
MLD, mm	2.67 [2.32, 2.83]
% DS	10.9 [8.2, 15.6]
Late Lumen Loss, mm	0.15 [0.09, 0.33]
Binary Restenosis, %	0 (0)

Preliminary QCA analysis. Median values

meriT-2 Study Design

- Design : Prospective, Non-Randomized, Multi- Centre, Complex, Real world study involving 250 patients

- Objective : Assess the safety and efficacy of the BioMime™ Sirolimus Eluting Coronary Stent System in Complex Real World patients

Ongoing study. Preliminary Roll-in phase data

Study Design

- Inclusion Criteria : To include most lesions (CTO's included)
  - *Vessel Diameter : >2.5 and <3.5mm*
  - *Lesion lengths upto 37mm treated with maximum stent length of 40mm*

- Exclusion Criteria : SVG's, AMI's, LM disease, LVEF <30%

- Trial would therefore be representative of real-life complex patients and practice

- All patients *Rx DAPT for 6 months to 1 year* as per standard institutional practices

Study Follow Up Regimen

- Clinical
  - At 30 days, 8months and 1 year
  - Additional follow-up at 3 years and 5 years

- Angiographic
  - 8 months

Study Endpoints

- End-Points : Primary (Safety & Efficacy)
  - MACE at 30 days
  - Late Loss (In-stent & In-segment) at 8months angiography

Study Endpoints

- Secondary Endpoints – (safety & efficacy)
  - MACE until 12 months
  - Device Related SAE's until 12 months
  - Angiographic Stent Thrombosis
  - Procedural Success

Study Research Partners

- Core Laboratory Analysis :
  - *Cardiovascular Research Center (CRC), Sao Paulo, Brazil*
    - *Dr. Ricardo Costa, Dr. Alexandre Abizaid*

- Clinical Research Organization (CRO)
  - SIRO Clin Pharm, Thane, Mumbai

PI – Dr. Ashok Seth

S. No.	Investigating Site	Site Investigator	City
01	EHIRC	Dr. Upendra Kaul	New Delhi
02	PGI	Dr. Rohit Manoj	Chandigarh
03	Hero DMC	Dr. G. S. Wander	Ludhiana
04	Fortis	Dr. Suresh Vijan	Mumbai
05	Poona Hospital	Dr. Suhas Hardas	Pune
06	Narayan Hrudayalaya	Dr. Sunitha Abrahim	Bengaluru
07	Columbia Asia	Dr. Prabhakar Shetty	Bengaluru
08	Apollo Jubilee Hills	Dr. P. C. Rath	Hyderabad
09	Apollo Vikrampuri	Dr. J. Shiv Kumar Rao	Hyderabad
10	Apollo Chennai	Dr. Samuel Mathew	Chennai
11	MMM	Dr. Ajit Mullasari	Chennai
12	KMCH	Dr. Thomas Alexander	Coimbatore

Patient Characteristics

52% Lesions constituted of Type B2+C

ACC / AHA Lesion Classification
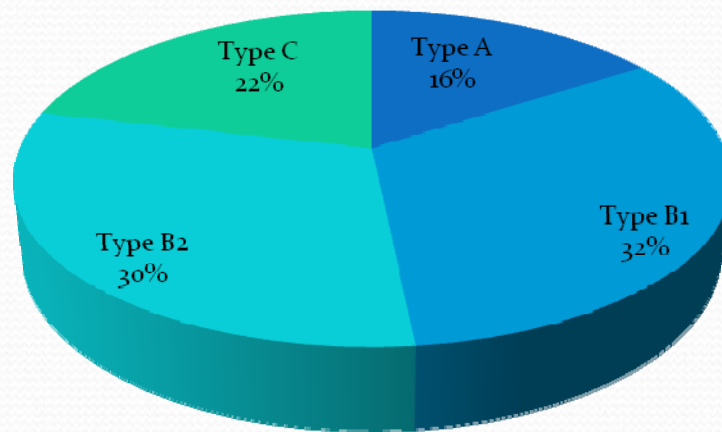
41 (22%) Mild to moderate Calcification

Type C 22%
Type A 16%
Type B2 30%
Type B1 32%

Lesion Site Location

OM 7%
LPDA 1%
Diagonal 1%
LCx 12%
RCA 36%
LAD 43%
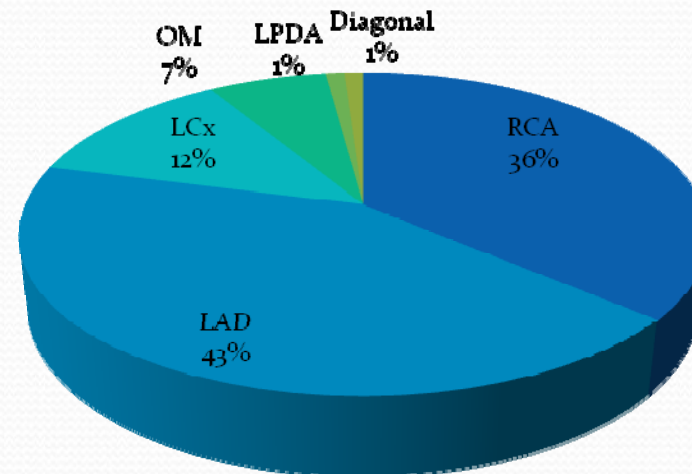
Treatment Details

Stenting details	
# of lesions treated	283
# of stents used in total population	278
# of stents/patient	1.5
# of stents > 24mm	126 (45%)
Average Diameter, mm	2.9 ± 0.4
Average Stent lengths, mm	22 ± 8

Stent Lengths used

Stent Lengths

13 mm	16 mm	19 mm	24 mm	29 mm	32 mm	37 mm	40 mm
44	50	66	49	26	20	8	19
16%	18%	23%	17%	9%	7%	3%	7%
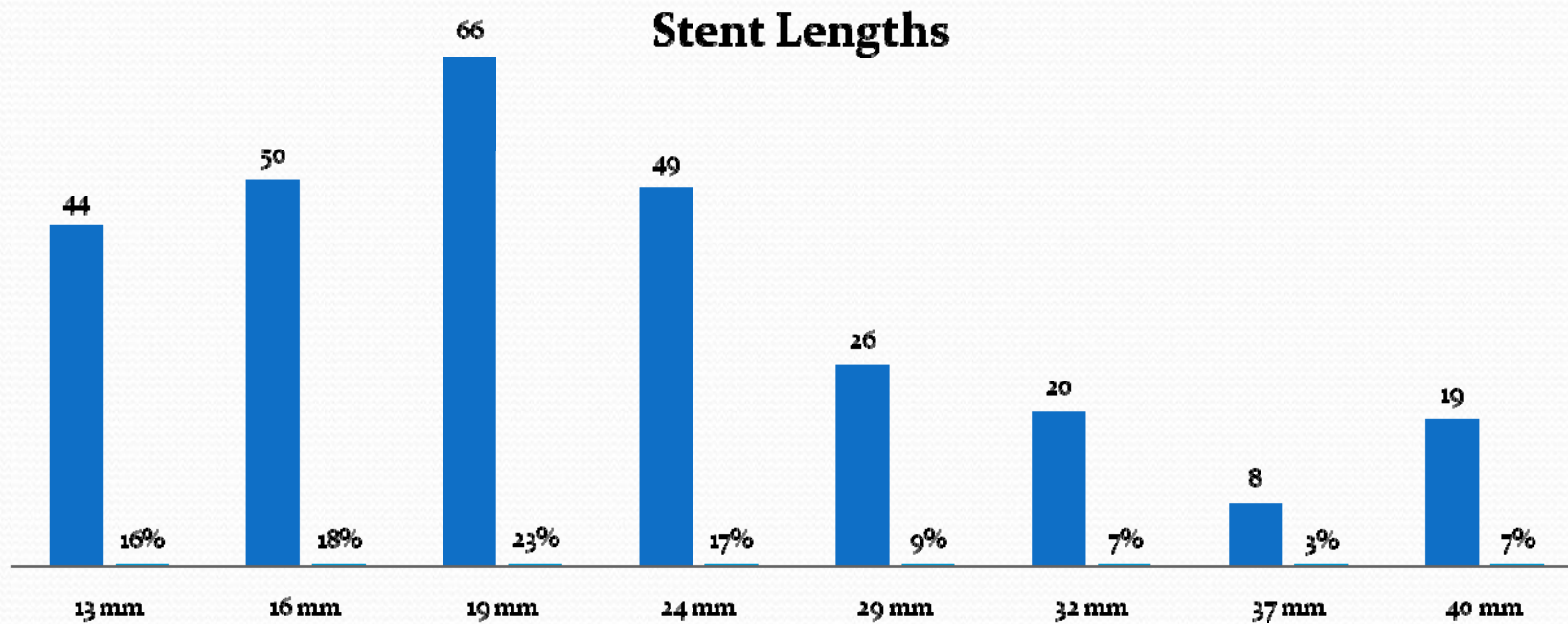
Baseline Demographics

Baseline Characteristics	Details
Number of patients enrolled	217
Mean age, years	57.5 ± 10.2
Gender, Males	171 (84%)
Body Mass Index (BMI)	25 ± 3.6
Previous MI	*75 (37%)*
Acute Coronary Syndromes	177 (87%)
Prior PCI	14 (7%)
Prior CABG	4 (2%)
Diabetes	*82 (40%)*
Hyperlipidemia	27 (13%)
Hypertension	*116 (57%)*
Smokers	*65 (32%)*
Family History	18 (9%)

Ongoing study

MACE & ST

- On going study.
- 217 patients have been treated-
  - 0% MACE at 30days
  - 1 non-cardiac death at 4 months
  - 2 (0.9%) patients had ischemia driven TLR at 4 months
  - 4 (1.8%) patients had TLR at 8 months Angio follow-up
  - 1 (0.5%) patient had SAT and was successfully treated. Doing well.
  - 100 patient QCA to be declared during EuroPCR 2011

Preliminary QCA Analysis

Pre-Procedure QCA	n=30
Lesion length, mm	15.39 [12.95, 20.47]
Reference Diameter, mm	2.79 [2.36, 2.98]
MLD, mm	0.29 [0.19, 0.58]
% Diameter Stenosis	89.3 [78.4, 92.8]

Post Procedure QCA	n=30
Reference Vessel Diameter, mm	2.90 [2.47, 3.07]
In-Segment	
MLD, mm	2.48 [2.12, 2.67]
% DS	12.5 [9.3, 16.4]
Acute gain, mm	2.10 [1.68, 2.43]
In-Stent	
MLD, mm	2.53 [2.37, 2.80]
% DS	6.4 [5.3, 10.8]
Acute gain, mm	2.28 [1.75, 2.54]

QCA analysis done by – Dr. Ricardo Costa, Dr. Alexandre Abizaid
Cardiovascular Research Centre (CRC)
Sao Paulo, Brazil

n=30, MEDIAN VALUES PRELIMINARY QCA ANALYSIS

Roll-in phase data. Ongoing study

QCA Analysis* – Follow up

| Follow-up QCA – 8 months	n = 30
Reference Vessel Diameter, mm	2.85 [2.47, 3.03]
In-Segment	
MLD, mm	2.05 [1.73, 2.43]
% DS	20.2 [14.5, 32.2]
Late Lumen Loss, mm	0.19 [0.09, 0.44]
Binary Restenosis, %	0 (0)
In-Stent	
MLD, mm	2.56 [2.06, 2.52]
% DS	11.2 [9.1, 16.3]
Late Lumen Loss, mm	0.18 [0.09, 0.44]
Binary Restenosis, %	0 (0)

n=30, MEDIAN VALUES PRELIMINARY QCA ANALYSIS

Roll-in phase data. Ongoing study

Late Loss Comparison

Late Lumen Loss, mm at 8 months

■ meriT-1   ■ meriT-2

In-Stent
- 0.15
- 0.18

In-Segment
- 0.18
- 0.19
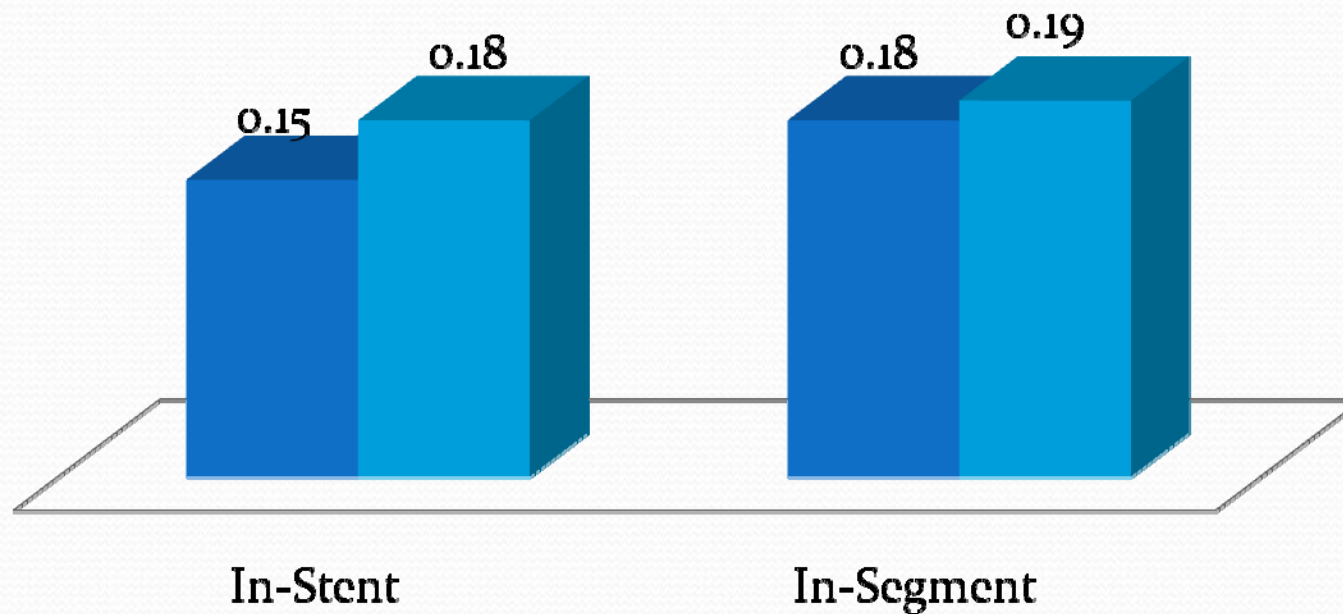
Roll-in phase data. Ongoing study

meriT Trial conclusions

Demonstrable product science

MERIT-1 STUDY (n = 30)

1.   0% MACE or 0% Stent thrombosis at 1 year

2.   0.15mm Late Loss at 8m QCA

MERIT-2 STUDY (n = 217)

1.   0% MACE at 30days

2.   1 non-cardiac death,

3.   2 cases of clinical TLR, 4 cases of angiographic TLR

4.   1 case of SAT

BioMime is CE marked and ANVISA approved.