Orsiro Hybrid Drug Eluting Stent
Insights into the Sirolimus-eluting DES with bioabsorbable polymer

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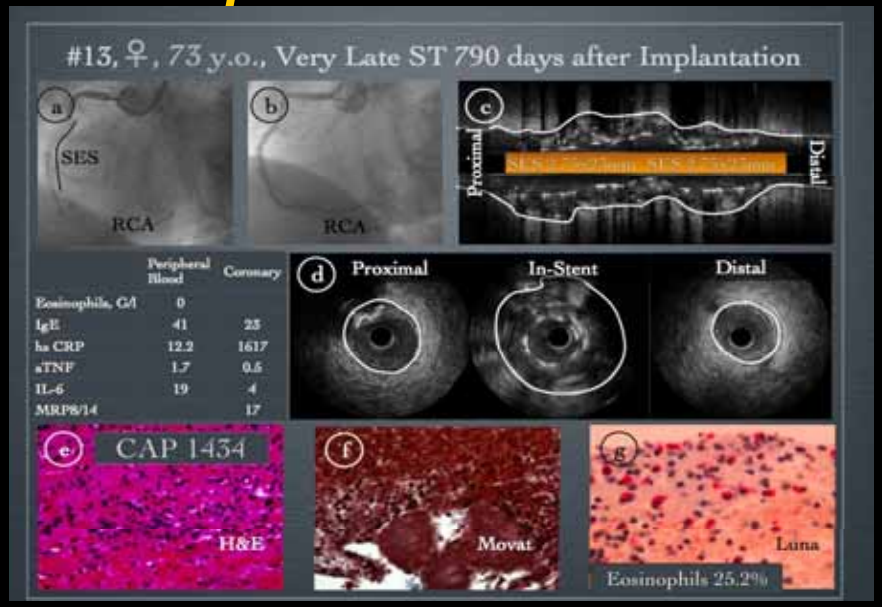
ANGIOPLASTY SUMMIT
TCTAP 2013
TRANSCATHETER CARDIOVASCULAR THERAPEUTICS ASIA PACIFIC

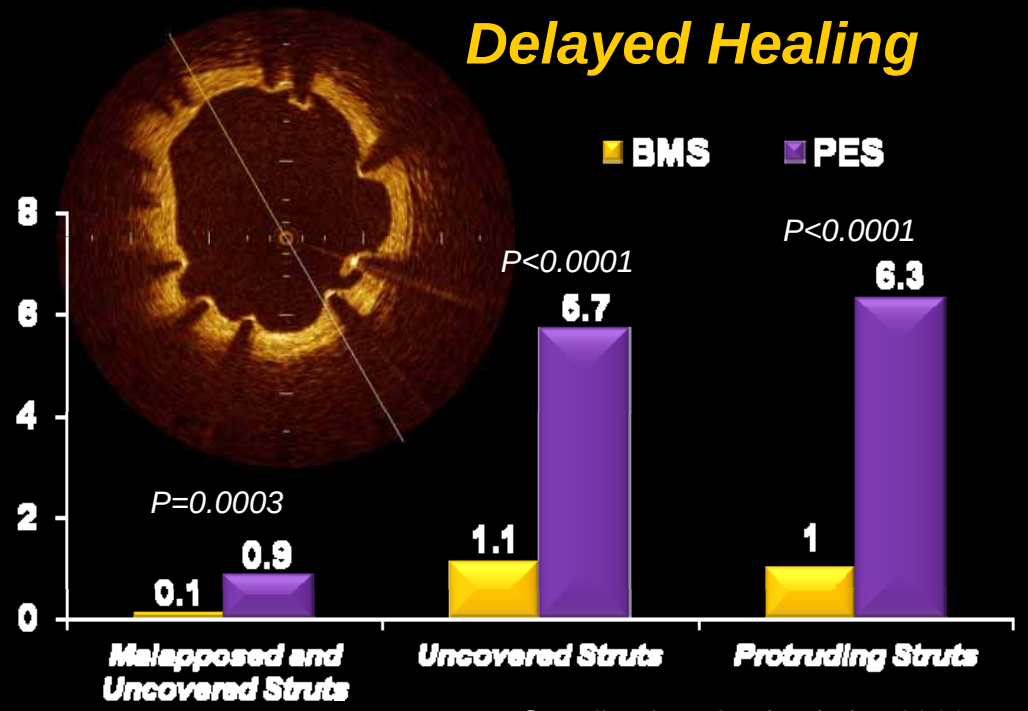
Pathological Healing Response to Implantation of Early Generation DES

Eosinophilic Infiltrates



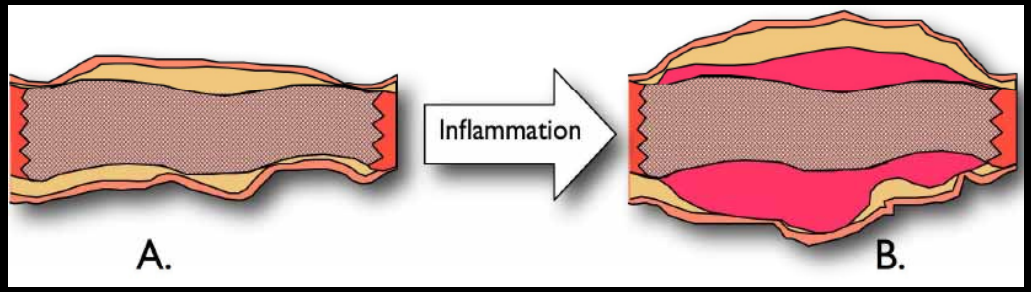
Cook et al. *Circulation* 2009

Delayed Healing



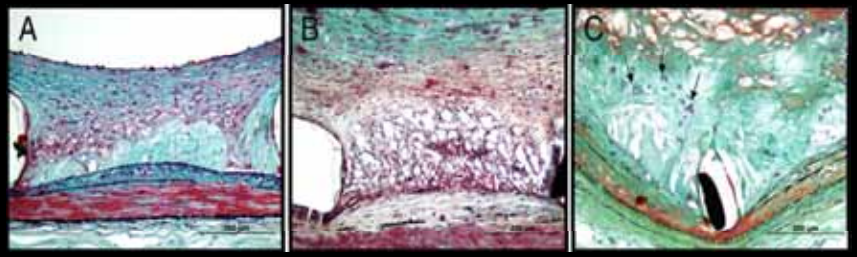
Guagliumi et al. *Circulation* 2011

Vessel Remodeling



Cook et al. *Circulation* 2007

Neoatherosclerosis

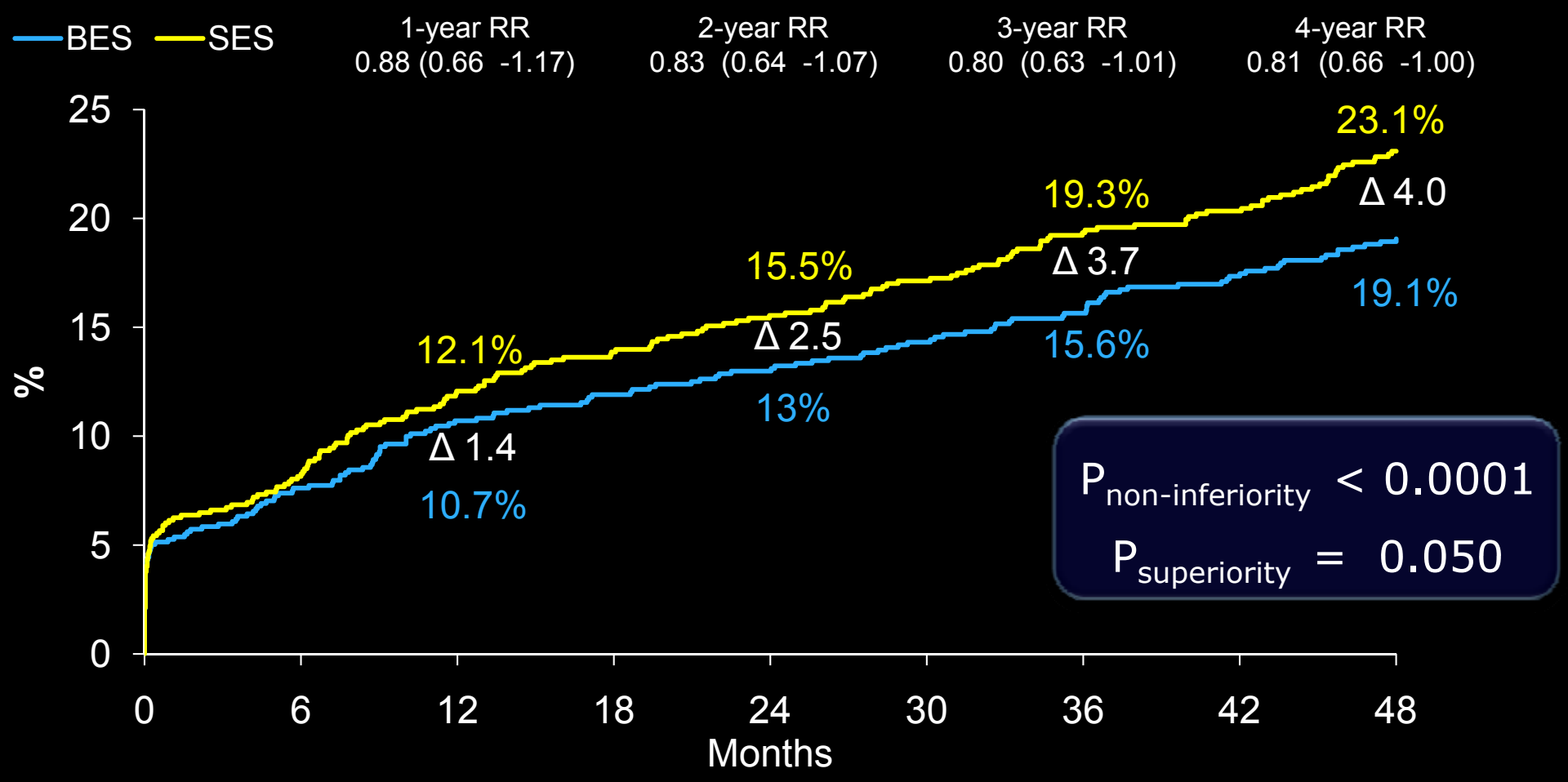


Nakazawa *JACC* 2011

Comparison of Biolimus- and Sirolimus-Eluting Stents

Cardiac Death, MI, or indicated-TVR @ 4 years

Stefanini G et al. *Lancet* 2011



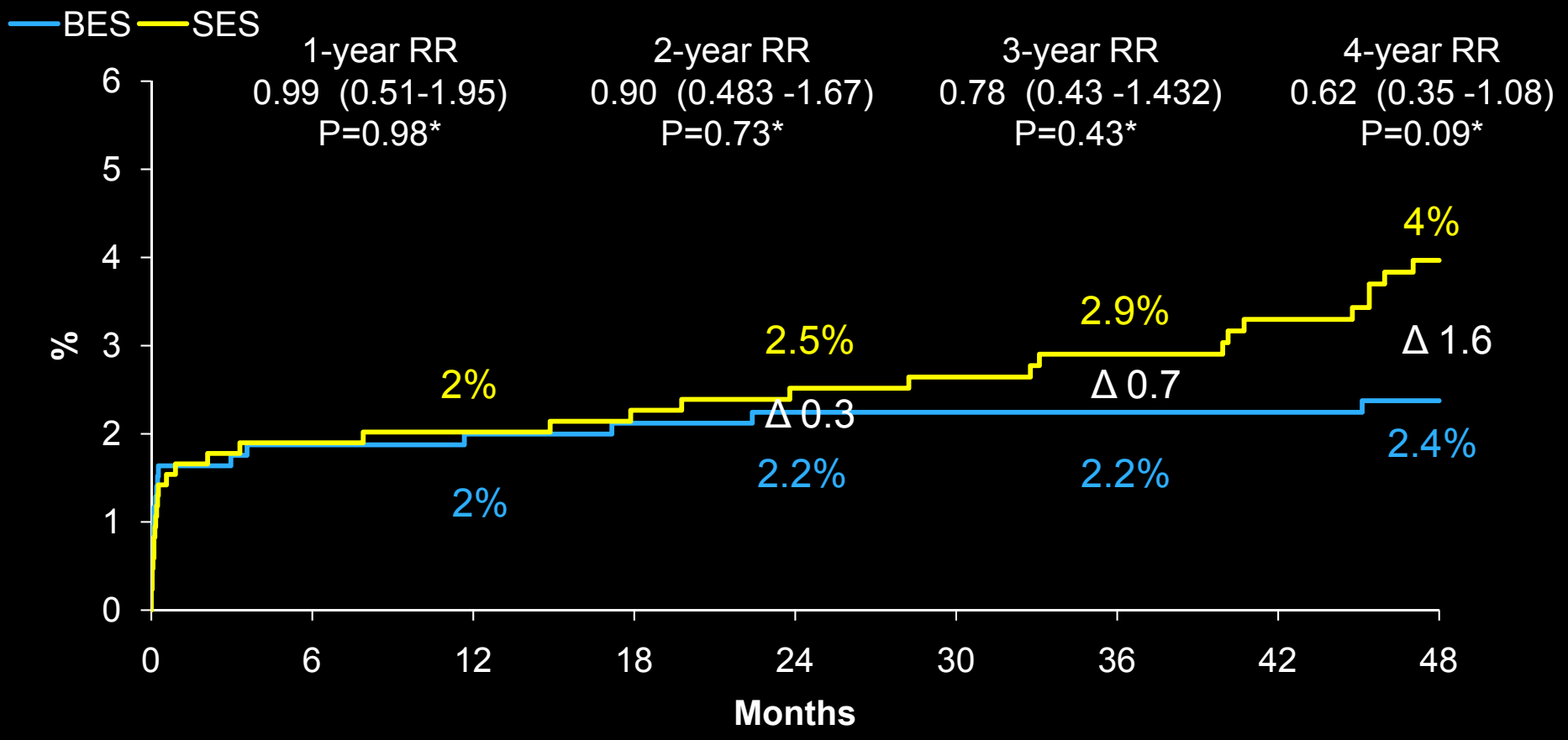
Numbers at risk

SES	850	775	738	718	702	676	656	639	614
BES	857	781	749	733	723	710	697	677	659

Comparison of Biolimus- and Sirolimus-Eluting Stents

Definite Stent Thrombosis @ 4 years

Stefanini G et al. *Lancet* 2011

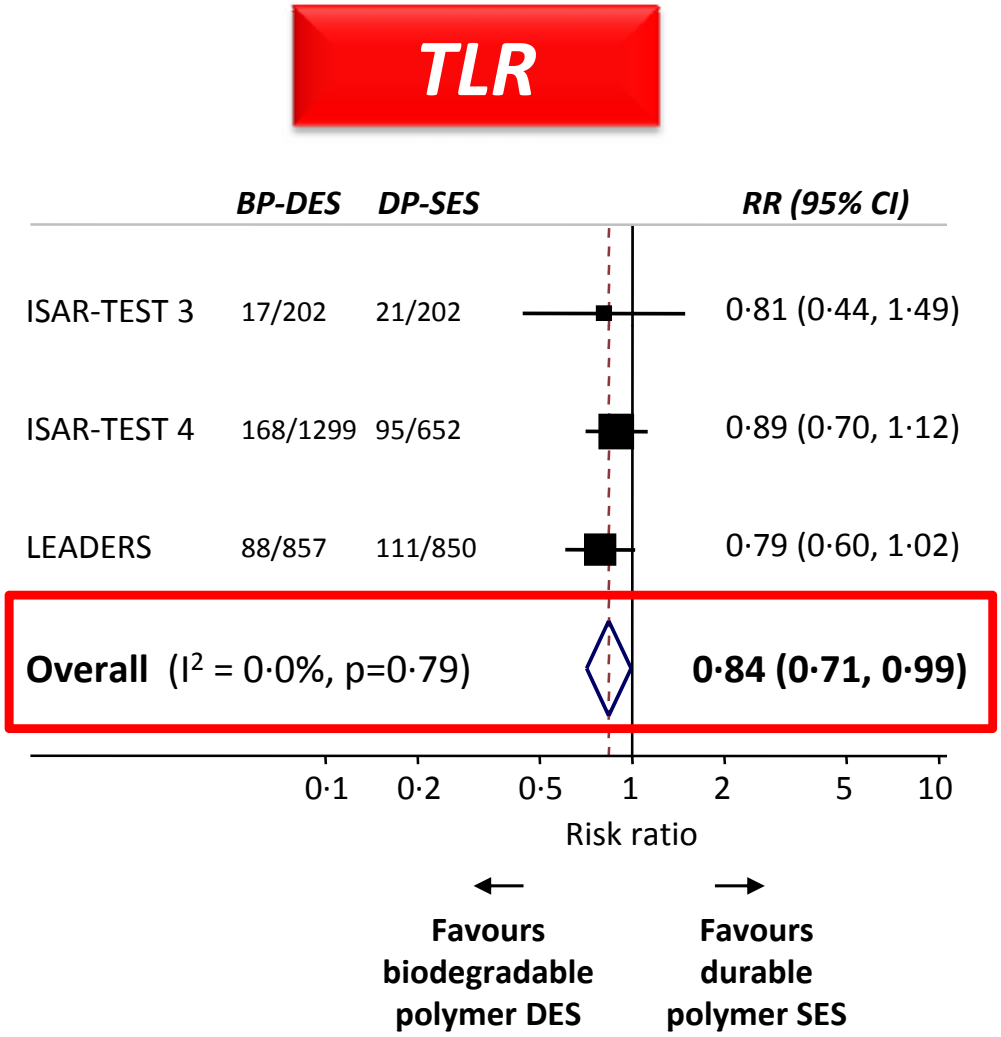


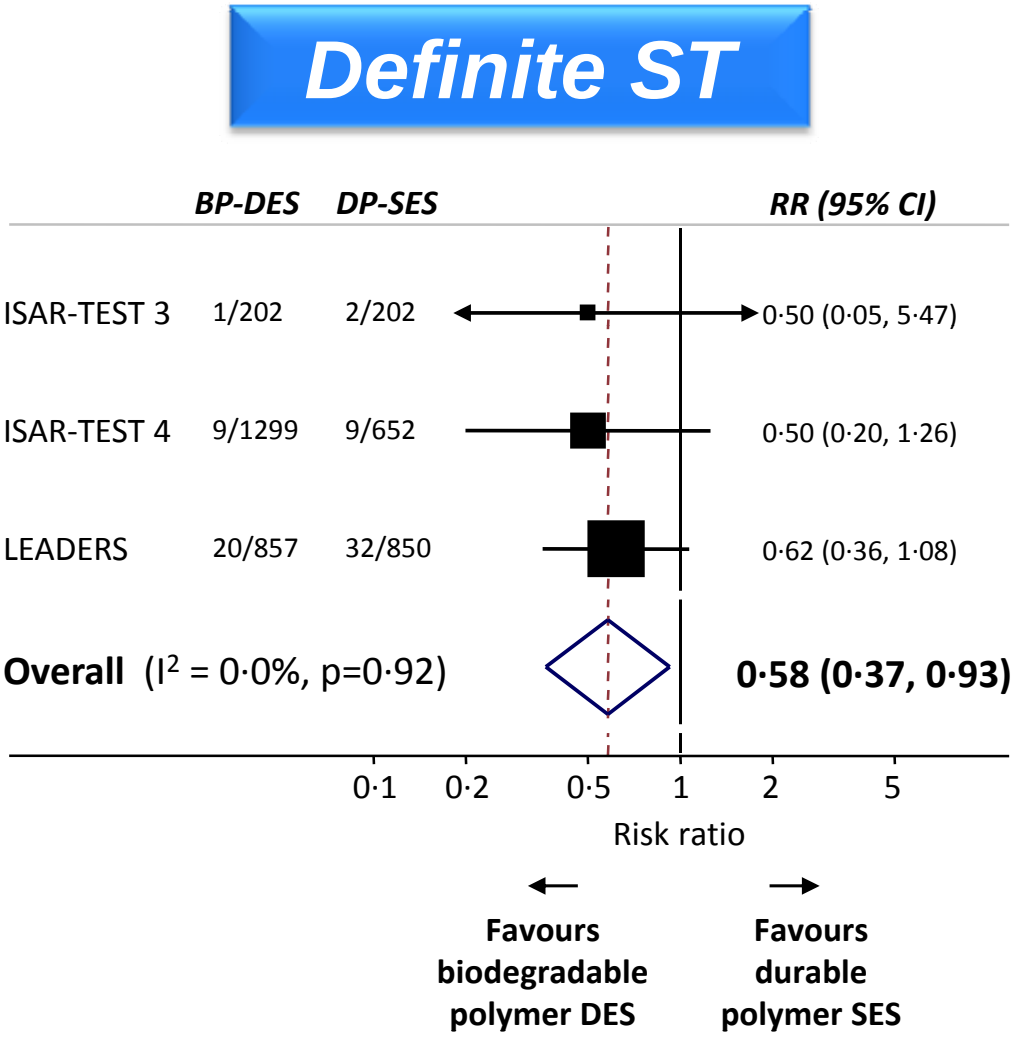
Numbers at risk

SES	**850**	**817**	**801**	**787**	**776**	**759**	**750**	**730**	**714**
BES	**857**	**821**	**804**	**792**	**787**	**780**	**774**	**757**	**746**

* P values for superiority

Efficacy and Safety with Biodegradable Polymer DES versus Durable Polymer Sirolimus-Eluting Stent During Long-Term Follow-up





Stefanini G et al. *Lancet* 2011

Are absorbable polymers the future?

- Biodegradable polymer DES represent the first newer generation DES that improves efficacy and safety outcomes compared to the earlier generation gold-standard SES
- Other newer generation durable polymer DES have not shown superiority over SES in randomized clinical trials to date
- Further studies are needed to investigate whether biodegradable polymer technology improves clinical outcomes compared to newer generation durable polymer DES

BIOTRONIK Orsiro Hybrid DES
Hybrid coating contains active and passive layers

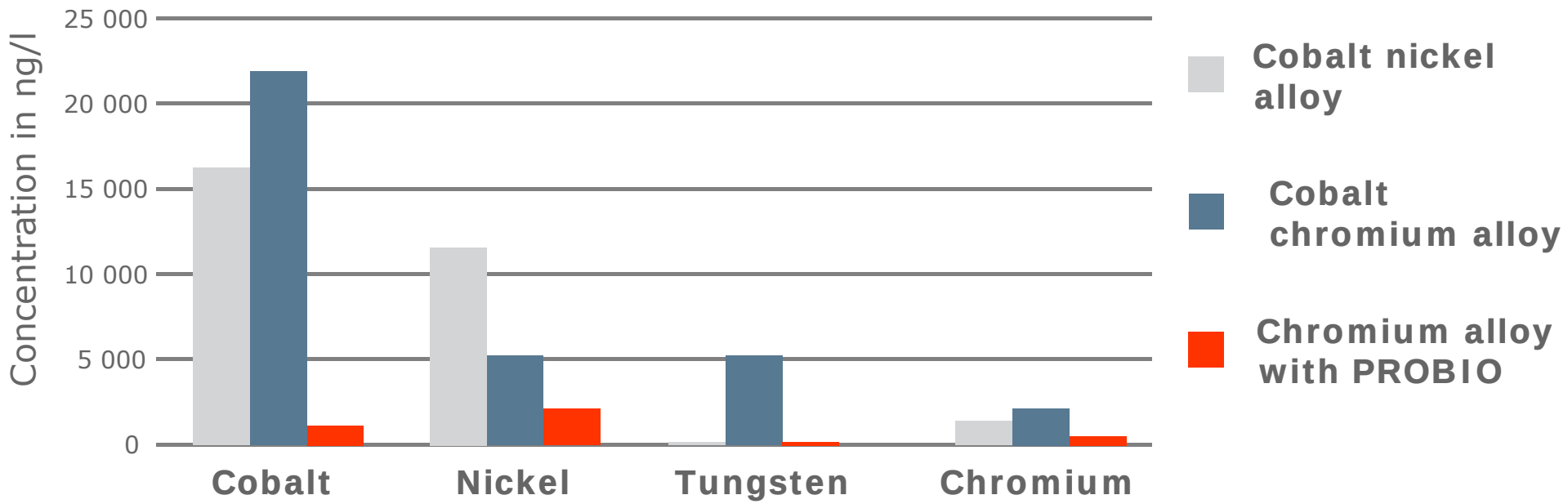
Passive coating
- PROBIO silicon carbide barrier
- Encapsulates the stent surface, reducing ion release

Active coating
- BIOlute PLLA bioabsorbable polymer
- Limus drug (1.4 µg/mm^2)

Stent platform
- PRO-Kinetic Energy, Cobalt Chromium, L-605
- 60 µm struts, double helix design

Passive Coating: PROBIO
Semi-Conductive Silicon Carbide Coating

- PROBIO reduces the interaction between tissue/blood with the metallic stent
- In vitro studies show up to a 96% reduction of metal ions

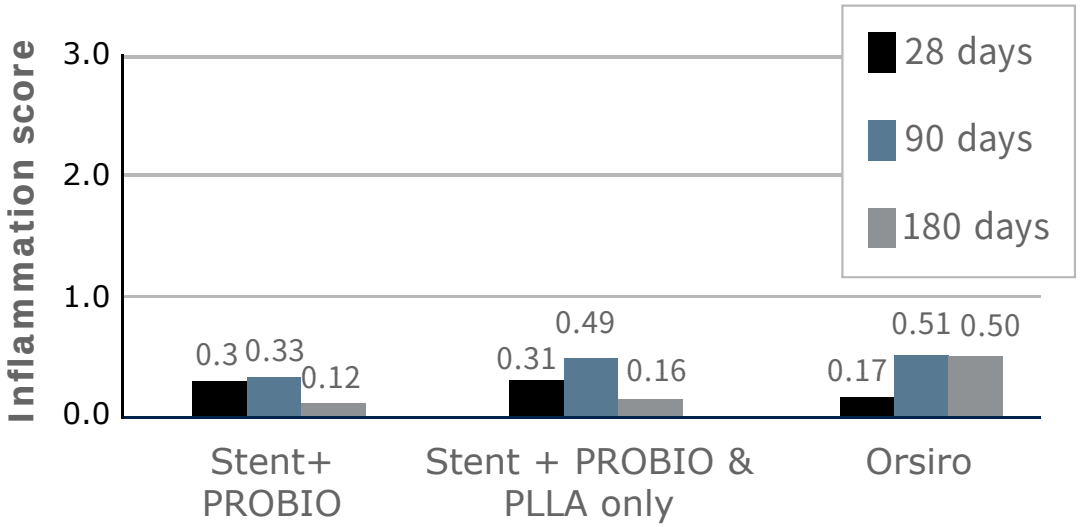


Source: Data on file, BIOTRONIK AG.

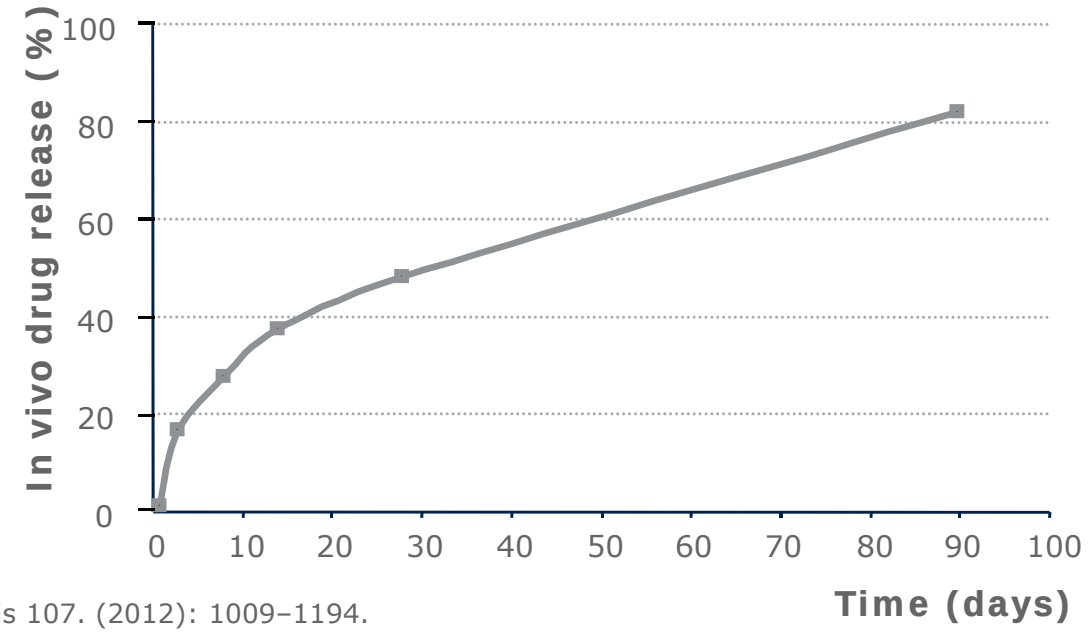
Active Coating: BIOlute

Bioabsorbable PLLA and Active Drug

- PLLA was chosen for its biocompatible and controlled drug release
- Metabolizes into CO_2 and H_2O

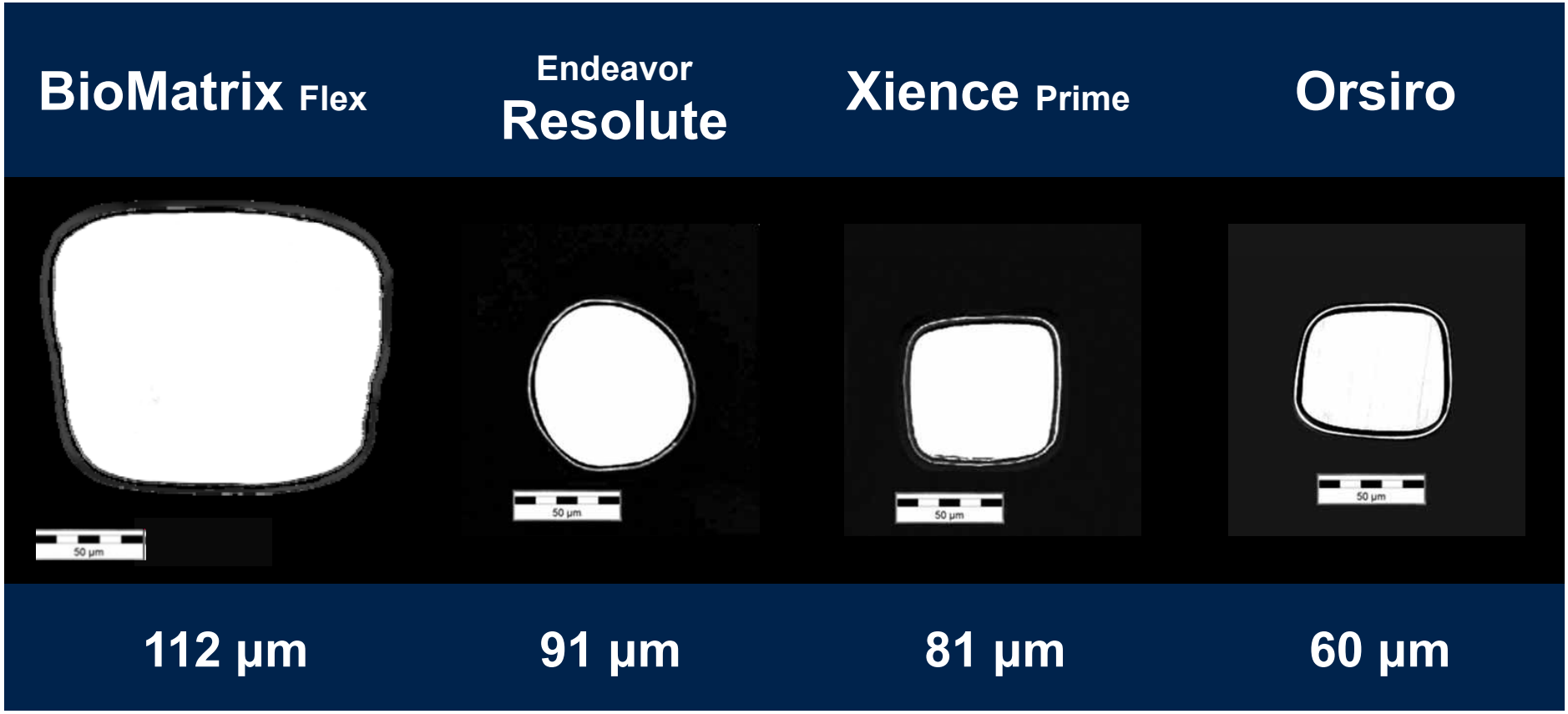


- Drug dose 1.4 µg/mm² with complete elution in about 100 days
- Elution curve is in-line with other Limus-based stents

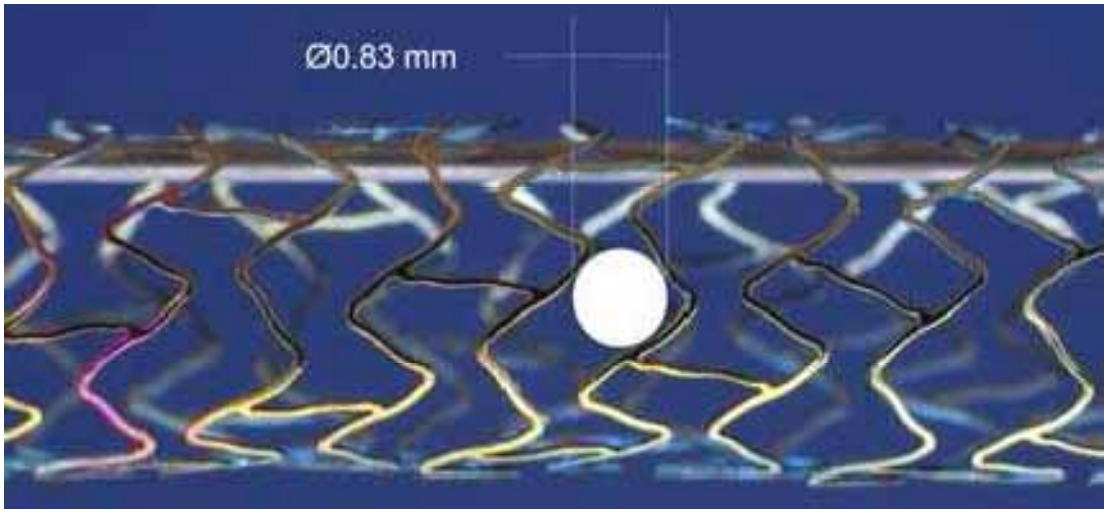


Source: Koppara, T., et al.Thrombosis and Haemostasis 107. (2012): 1009–1194.

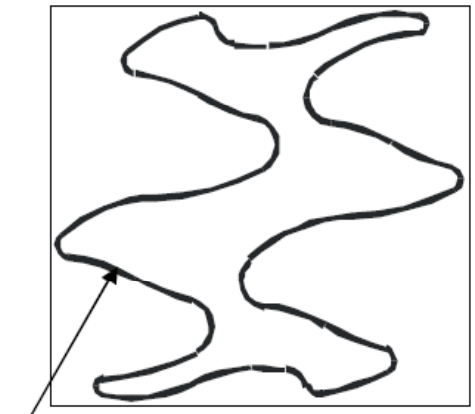
Stent Strut Thickness
New Generation DES



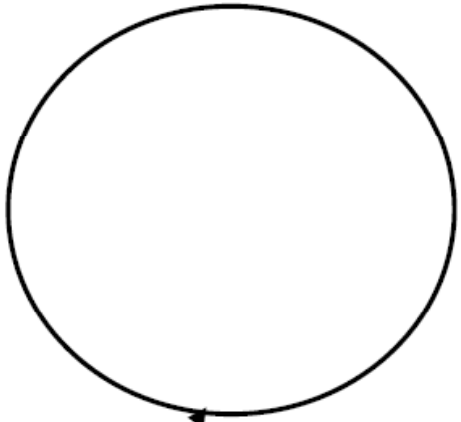
Orsiro Cell Size



- Two different platform designs
  - Small (ø2.25-3.0mm)
  - Medium (ø3.5, 4.0mm)



Entire length of cell edge

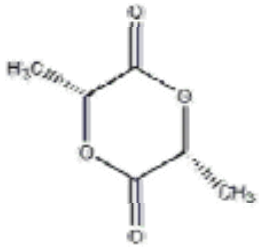


Corresponding circumference after maximum expansion of cell

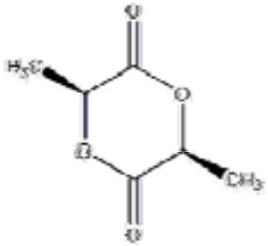
Design	Length of cell edge (mm)	Corresponding Circle Diameter (mm)
Small	11.28	3.59
Medium	13.90	4.42

Biodegradable Polymers

L- and D- isomer of polylactides



L-Lactid

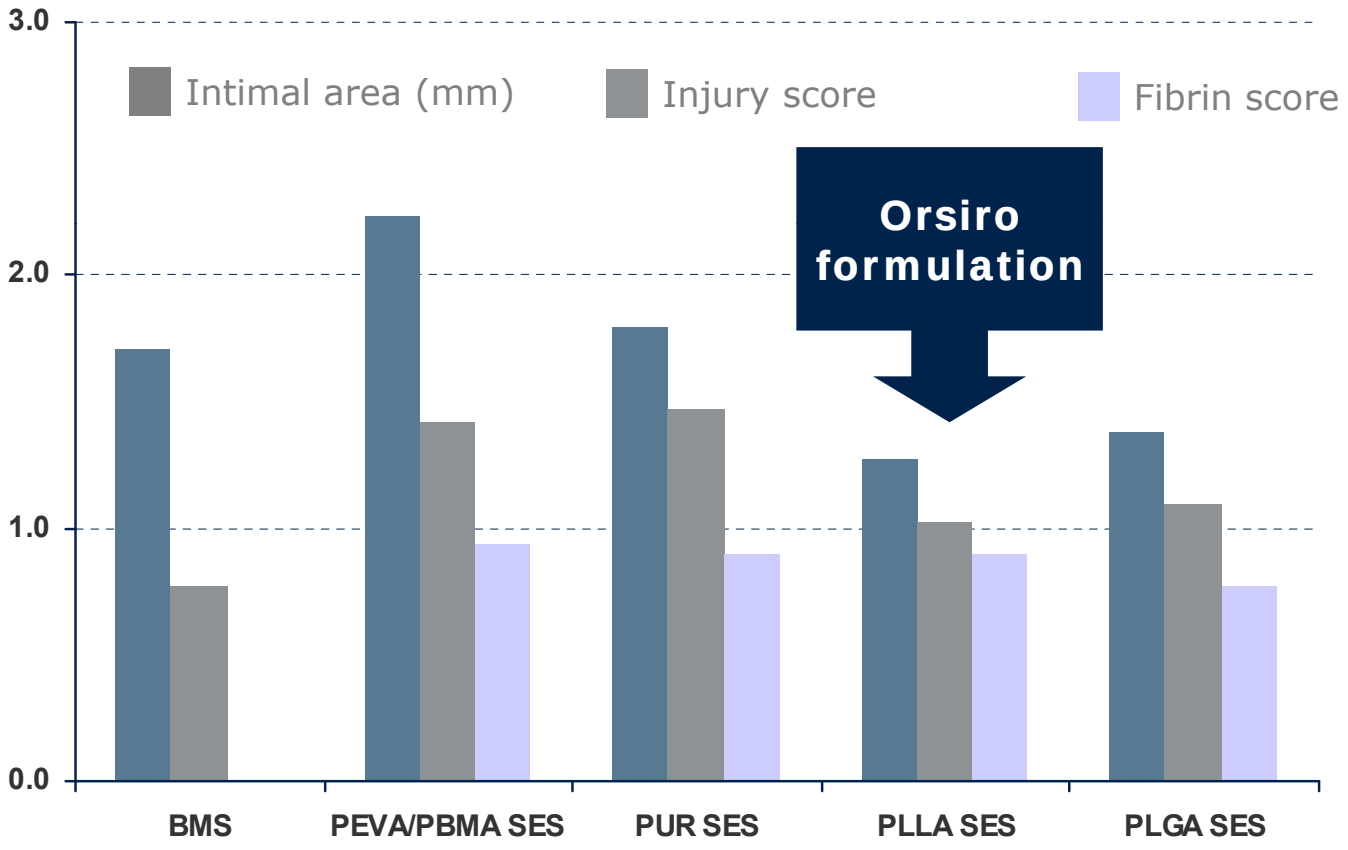


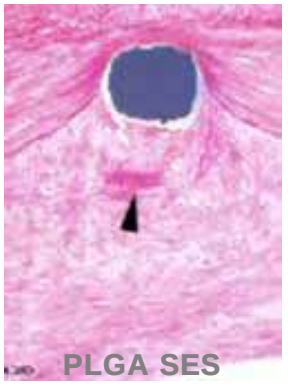
D-Lactid

P-L-LA	P-D-LA or P-DL-LA	P-L-GA
Poly-L-Lactid Acid	Poly-D-Lactid Acid; PDLA or Poly-D-L-Lactid acid	Poly-lactid co - glycolic acid
Contains only the L-isomer	Contains a mix of the L and D-isomer	Combination of lactid acid monomers and glycolic acid monomers
Naturally occurring	Synthetically produced	
Orsiro, ABSORB	BioMatrix, Nobori	Nevo, CoStar, Synergy
Absorbs slower than PDLLA, but is more biocompatible	In medical device industry the PDLLA is often called PDLA	Has less mechanical strength and release control than PLA type polymers. Absorbs quickly.
Less than 2 years	About 9mo - 1 year	About 3-9 months

Differences among bioabsorbable and permanent polymer DES

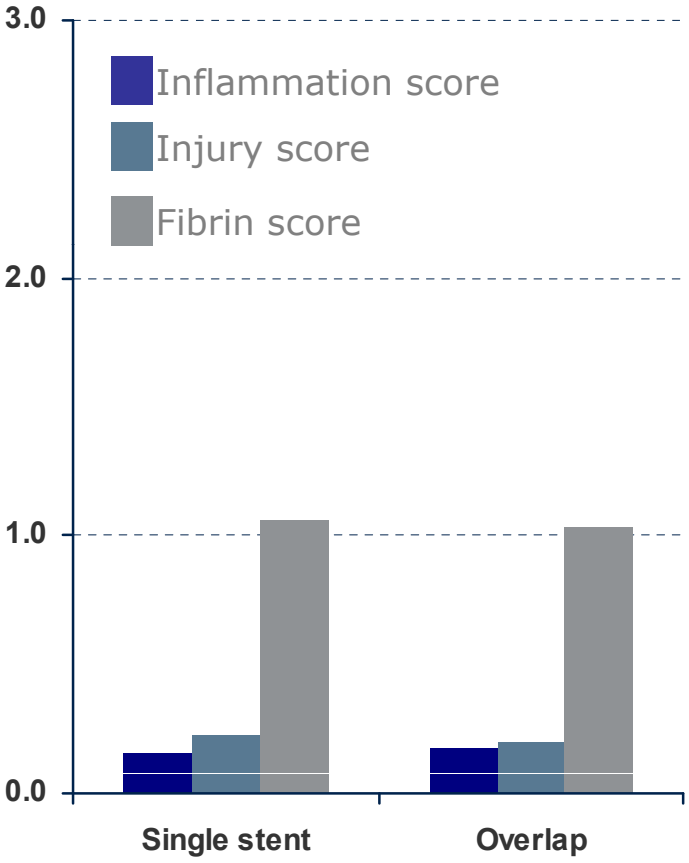
Pre-clinical histology, mean values at 28 day





Pre-clinical histology shows benign affects with overlapped Orsiro devices

Pre-clinical histology
Mean values at 28 day



Orsiro Clinical Program

	Study	Study design	n	1° endpoint	Status
BIOTRONIK initiated	BIOFLOW-I	FIM	30	9 mo LLL	Published
	BIOFLOW-II	International, RCT vs. Xience Prime	440	9 mo LLL	Enrollment completed
	BIOFLOW-III	International registry	1,000	12 mo TLF	Enrollment completed
		Satellite registries	3,000+	12 mo TLF	Enrollment ongoing
	BIOFLOW-INDIA	Indian single-armed trial	120	9 mo LLL	Enrollment completed
	BIOLUX RCT	RCT vs. Pantera Lux in ISR	210	6 mo LLL 12 mo TLF	Enrolling
Investigator initiated	BIOSCIENCE	Swiss RCT vs. Xience Prime	2,100	12 mo TLF	Enrolling
	HAT-TRICK-OCT	Finnish RCT vs. Endeavor Resolute	40	3 mo strut coverage	Enrollment completed
	PRISON-IV	RCT vs. Xience Prime in CTO	330	9 mo LLL	Enrolling
	BIO-RESORT	Dutch, RCT vs. Xience Prime	3,500	12 mo TVF	Enrolling
	ISAR-ORSIRO	German, RCT vs. Xience Prime	60	6 & 24 mo Strut coverage	Enrolling
		Total	**10,830+**		

BIOFLOW-I (FIM)

- **DESIGN:** Prospective, multi-centre, non-randomized, first in man trial
- **OBJECTIVE:** To assess the safety and clinical performance of the ORSIRO in coronary de-novo coronary artery lesions
- **PRIMARY ENDPOINT:** LLL at 9 months
- **Clinical coordinate investigator:** Prof. Martial Hamon, University Hospital of Caen, France
- **PRINCIPAL INVESTIGATORS:** Dr. Rodica Niculescu, MD, PhD, FESC, Dr. Dan Deleanu, MD, FESC

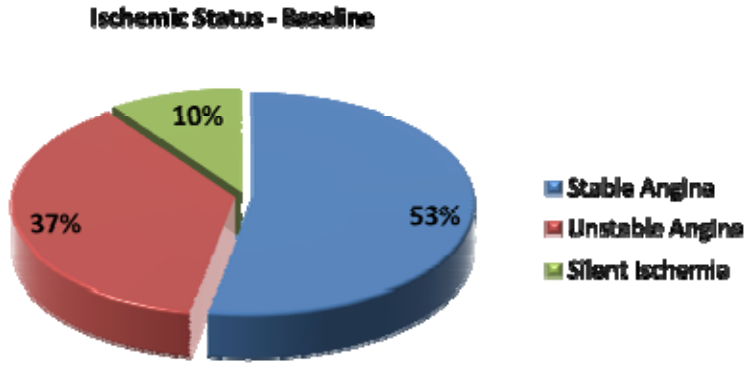
Source: Hamon M., et al. EuroIntervention 2013;8:1006-1011.

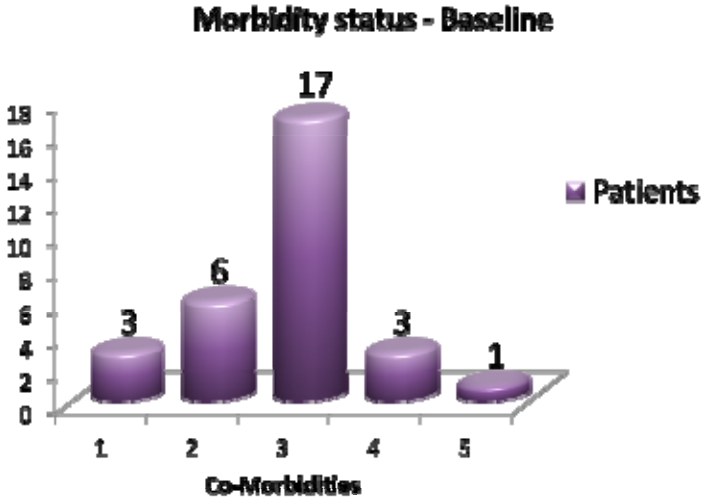
Baseline clinical characteristics

BIOFLOW-I

N = 30

Age, years	58.10 yrs ± 9.80	
Male sex	60.0%	18/30
Hyperlipidemia	93.3%	28/30
History of MI	73.3%	22/30
Hypertension	66.6%	20/30
Smoker	53.3%	16/30
Diabetes	23.3%	7/30
CHF	20.0%	6/30

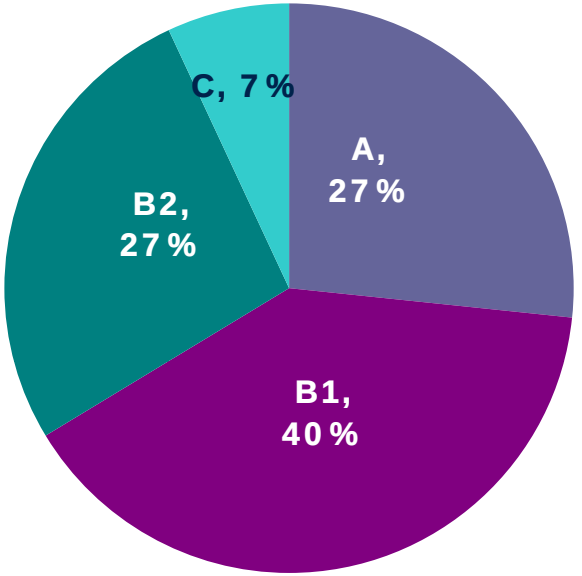


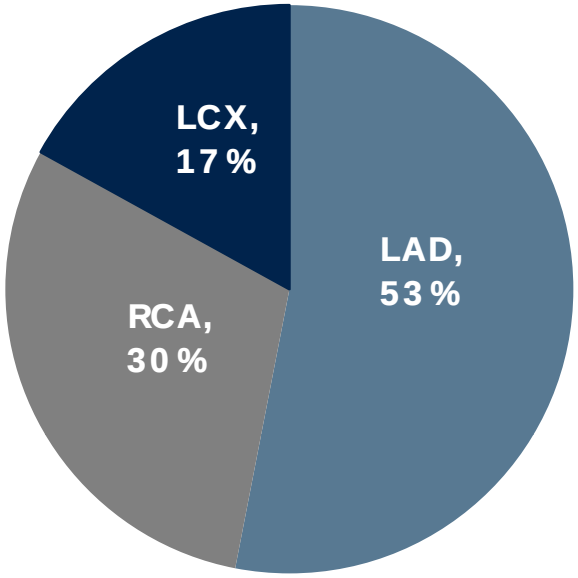


Baseline lesion characteristics

Pre-Procedure	N=30
RVD (mm)	2.75 ± 0.34
MLD (mm)	0.95 ± 0.29
% Diameter stenosis	65.52 ± 9.47
Mean Lesion length (mm)	11.71 ± 4.40

Procedural	N=30
Stent length per lesion (mm)	19.93 ± 5.33
Stent diameter per lesion (mm)	3.08 ± 0.37
Direct stenting	20.0%
Device success*	100.0%



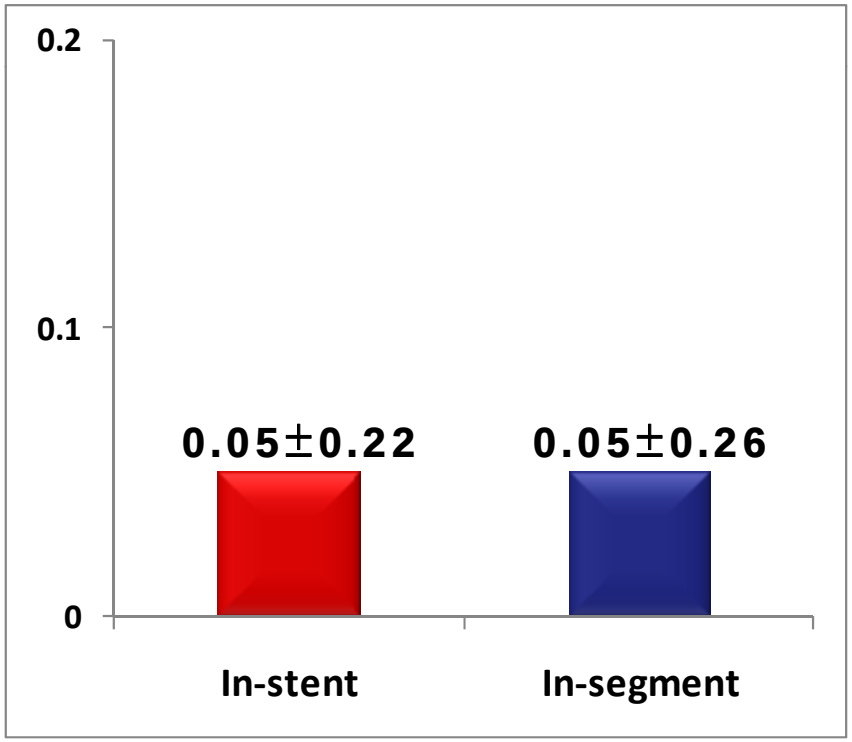


* Defined as In-Stent < 30% residual stenosis by offline QCA

Angiographic follow-up results

BIOFLOW-I

Primary Endpoint Late Lumen Loss @ 9 Months



	4-month	9-month
RVD (mm)	2.81 ± 0.28	2.81 ± 0.30
Minimal Lumen Diameter		
In-stent (mm)	2.50 ± 0.36	2.56 ± 0.38
In-segment (mm)	2.20 ± 0.35	2.21 ± 0.31
Diameter Stenosis		
In-stent (%)	15.19 ± 4.55	13.60 ± 4.27
In-segment (%)	23.66 ± 9.80	23.55 ± 8.06
Late Loss		
In-stent (mm)	0.12 ± 0.19	0.05 ± 0.22
In-segment (mm)	0.06 ± 0.23	0.05 ± 0.26
Binary Restenosis		
In-stent (mm)	0%	0%
In-segment (mm)	0%	0%

Source: Hamon M., et al. EuroIntervention 2013;8:1006-1011.

Clinical outcomes at 9 months

BIOFLOW-I

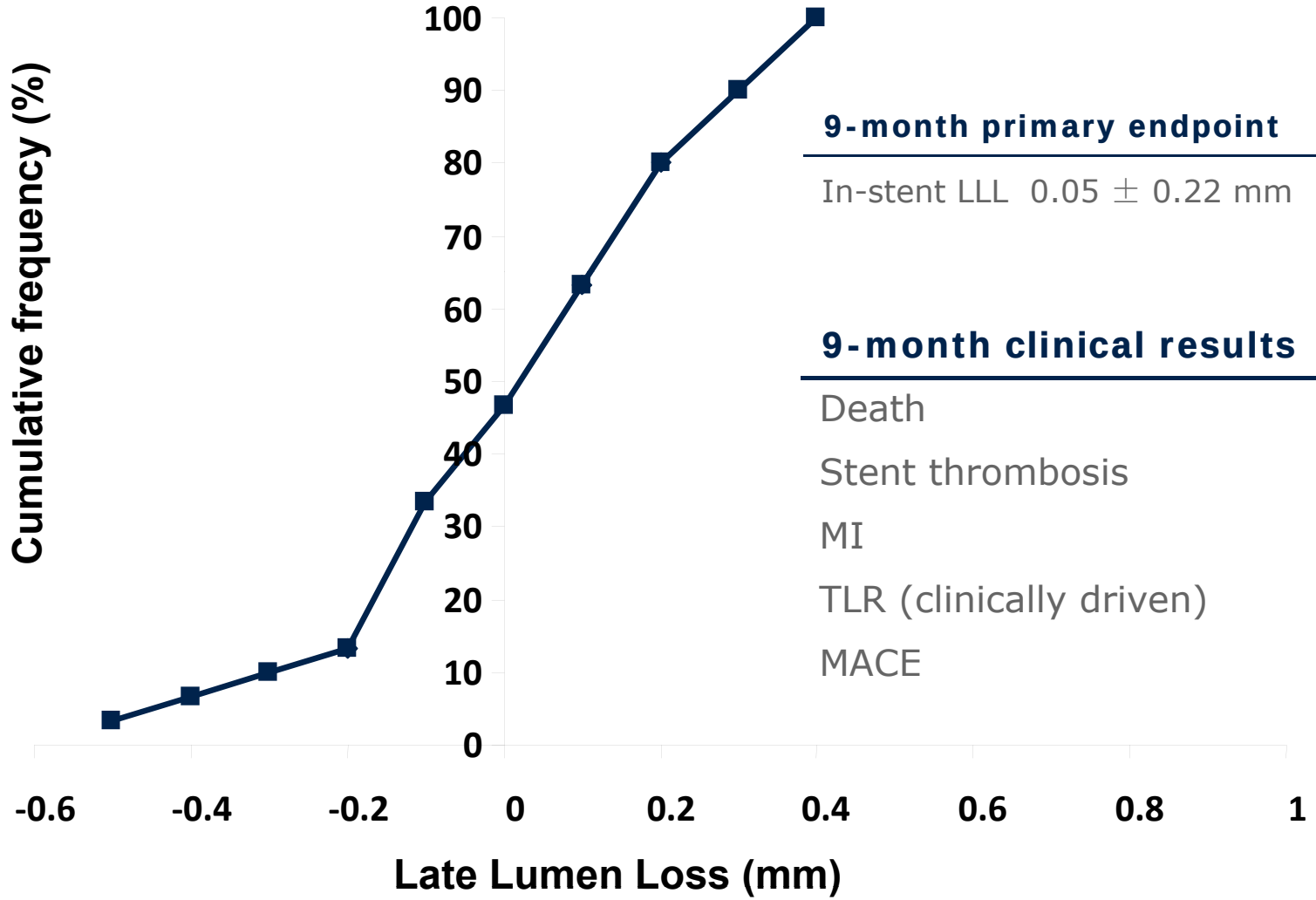
9-month clinical results	N	%
MACE	2	6.7
Cardiac Death	0	0.0
MI	0	0.0
Stent thrombosis	0	0.0
TLR (clinically driven)	2	6.7

MACE defined as:

Composite of cardiac death, MI attributed to the target vessel, stent thrombosis and clinically driven target lesion revascularization

Source: Hamon M., et al. EuroIntervention 2013;8:1006-1011.

The Orsiro FIM BIOFLOW-I showed promising results



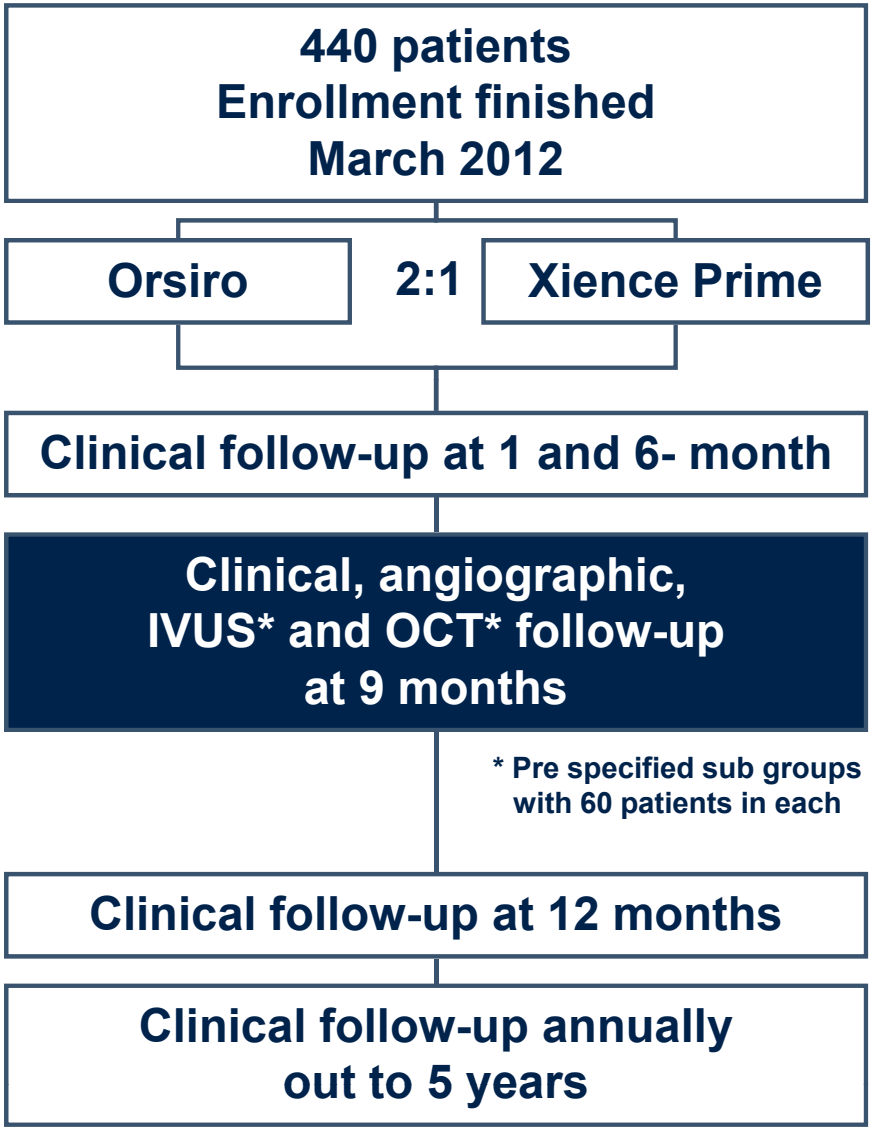
9-month primary endpoint	n=30
In-stent LLL 0.05 ± 0.22 mm	

9-month clinical results	n	%
Death	0	0.0
Stent thrombosis	0	0.0
MI	0	0.0
TLR (clinically driven)	2	6.7
MACE	2	6.7

Source: Hamon M., et al. EuroIntervention 2013;8:1006-1011.

BIOFLOW-II

- **DESIGN:** A prospective, multicenter, international, non-inferiority, randomized controlled study
- **OBJECTIVE:** To compare the Orsiro to Xience Prime in de novo coronary lesions
- **PRIMARY ENDPOINT:** In-stent late lumen loss at 9 months
- **Co-PIs:**
  Prof. Stephan Windecker
  University Hospital Bern, Switzerland
  Dr. Thierry Lefevre
  Hospital Jacques Cartier, Massy, France

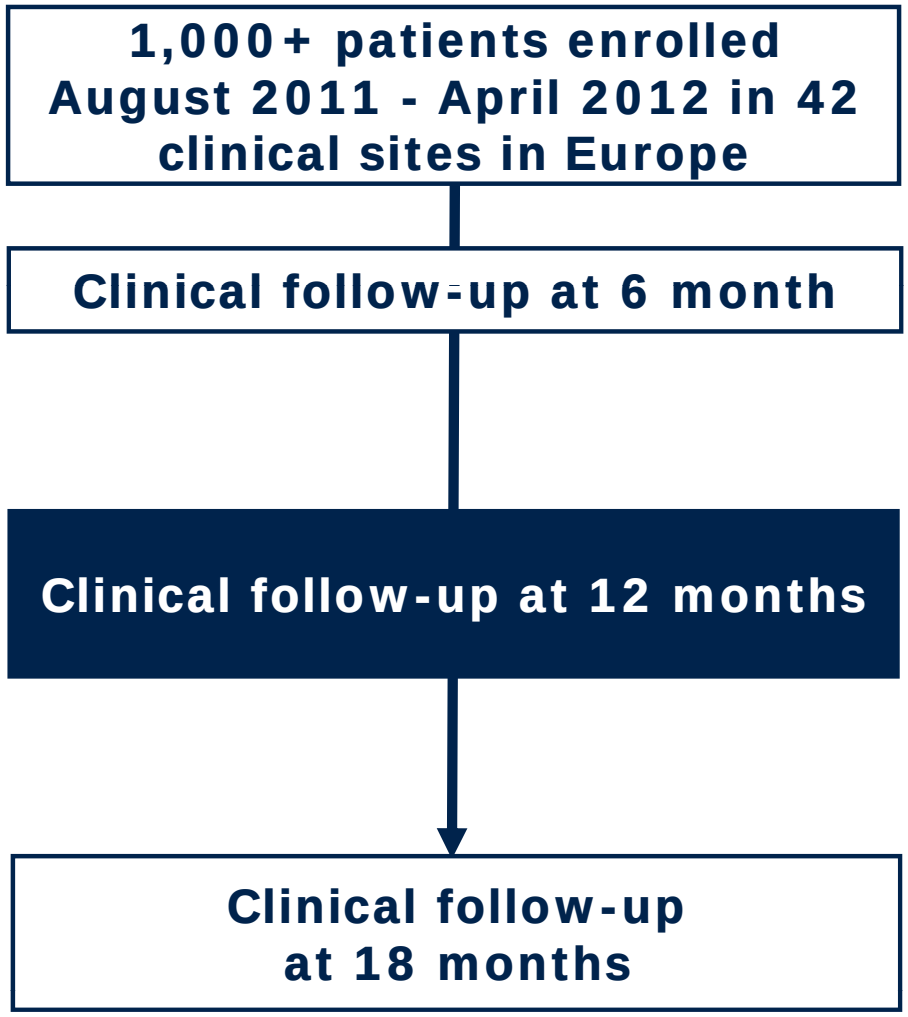


Source: ClinicalTrials.gov Identifier: NCT01356888

BIOFLOW-III

BIOFLOW-III

- **DESIGN:** International, prospective, non-randomized, multicenter, open-label clinical evaluation
- **OBJECTIVE:** To assess the clinical performance of the ORSIRO in coronary arteries in an "all comers" population
- **PRIMARY ENDPOINT:** TLF at 12 months
- **COORDINATING INVESTIGATOR :** Johannes Waltenberger University Hospital Muenster, Germany



Source: ClinicalTrials.gov Identifier: NCT01553526

BIOSCIENCE

- **DESIGN:** Prospective, multi-center, randomized, non-inferiority trial
- **OBJECTIVE:** To compare the safety and efficacy of SES with a biodegradable polymer with an EES with a durable polymer
- **PRIMARY INVESTIGATOR:** Prof. Stephan Windecker University Hospital Bern, Switzerland
- **PRIMARY ENDPOINT:** TLF at 12-month.

Source: ClinicalTrials.gov Identifier: NCT01443104

Conclusions

- Biodegradable polymer technology has shown to improve outcomes compared with the previous gold-standard of durable polymer SES
- Orsiro Hybrid DES applies biodegradable polymer based drug elution with an attractive platform, and has shown promising results in a FIM study
- Further BIOFLOW studies will provide further data on this novel device by directly comparing angiographic outcomes with durable polymer EES (Xience Prime) and in broader populations