BIOFLOW V

Comparison of UltraThin Sirolimus-Eluting Bioresorbable Polymer with Thin Everolimus-Eluting Durable Polymer Stents

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Clinicaltrials.gov Identifier NCT02389946

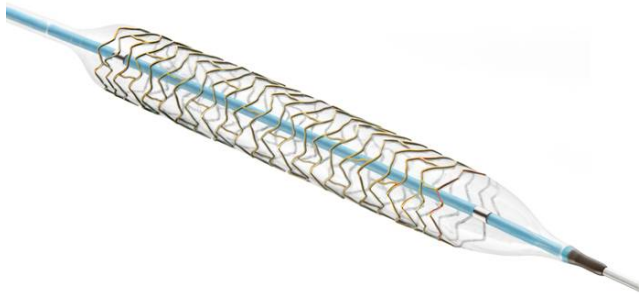
Drug Eluting Stent Innovation

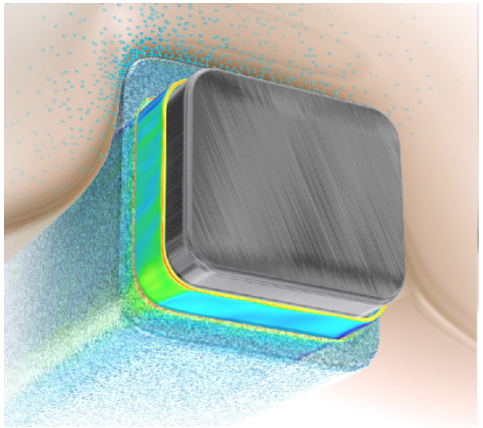
Perspective

- Persistence of adverse events with both first generation and contemporary permanent polymer-based DES presents an opportunity for iterative improvement
- Advancements include thinner struts, stent design modifications, improvement in polymer biocompatibility and most recently the development of bioresorbable polymers
  - BP control drug release while allowing simultaneous (or subsequent) dissolution of the polymer material, eliminating the stimulus for chronic inflammation and hypothetically restoring the stent phenotype to an inert bare metal stent
- Although previous comparative studies have reported statistical non-inferiority between bioresorbable and permanent polymer DES, no study to date has demonstrated a statistically meaningful difference in clinical outcomes

Orsiro UltraThin Strut (BP SES) Stent System

Stent material	L-605 Cobalt-Chromium
Strut thickness	60 µm*
Polymer material	Poly-L-lactic acid (PLLA)
Polymer type	Bioresorbable, asymmetric circumferential thickness; scission begins immediately with 24 month complete degradation
Passive coating	Amorphous silicon carbide
Antiproliferative drug	Sirolimus (1.4 µg/mm^2), >80% eluted in first 90 days





*For 2.25mm to 3.0mm diameter stents, 80 µm for >3.0 mm diameter stents

Randomised Clinical Trials Involving Orsiro BP SES

	BIOFLOW II	BIOFLOW IV	BIOSCIENCE	BIO-RESORT
Location	Europe	Europe, Japan	Switzerland	Netherlands
Design	Randomised 2:1 vs. Xience Prime	Randomised 2:1 vs. Xience Prime/Xpedition	Randomised (1:1 vs Xience Prime)	Randomised (1:1:1, Orsiro, Synergy, Resolute Integrity)
Primary Endpoint	LLL @ 9 Months	TVF @ 12 Months	TLF @ 12 Months	TVF @ 12 Months
Enrollment	452 (298 Orsiro, 154 Xience)	579 (387 Orsiro, 192 Xience)	2,119 (1,063 Orsiro, 1,056 Xience)	3,514 (1,172 Synergy, 1,169 Orsiro, 1,173 Resolute Integrity)
Inclusion	1 to 2 de novo lesions Separate arteries	1 to 2 de novo lesions Separate arteries	All-comers	All-comers
Follow-up	1, 6, 12 months and 2 to 5 year clinical 9 month clinical and angiographic (60 IVUS patients)	1, 6, 12 months and 2 to 5 year clinical	1, 6, 12 months and 2 to 5 year clinical	1 and 12 month and 2 to 5 year clinical

BIOFLOW V Trial Leadership and Organization

Steering Committee	Ron Waksman, MD (Chairman), David E Kandzari, MD (US Principal Investigator), Jacques Koolen, MD (EU Principal Investigator), Laura Mauri, MD, Joseph J Massaro, PhD
Core Laboratory	Hector Garcia-Garcia, MedStar Cardiovascular Research Network, Angiographic Core Laboratory, Washington, DC, USA
Study Management, Data Monitoring and Analysis	Baim Institute for Clinical Research, Boston, MA USA
Data Safety Monitoring Board	William Weintraub (Chairman) Baim Institute for Clinical Research, Boston, MA USA
Clinical Events Committee	Donald E Cutlip, MD (Chairman) Baim Institute for Clinical Research, Boston, MA USA
Sponsor	BIOTRONIK, Inc. and BIOTRONIK AG

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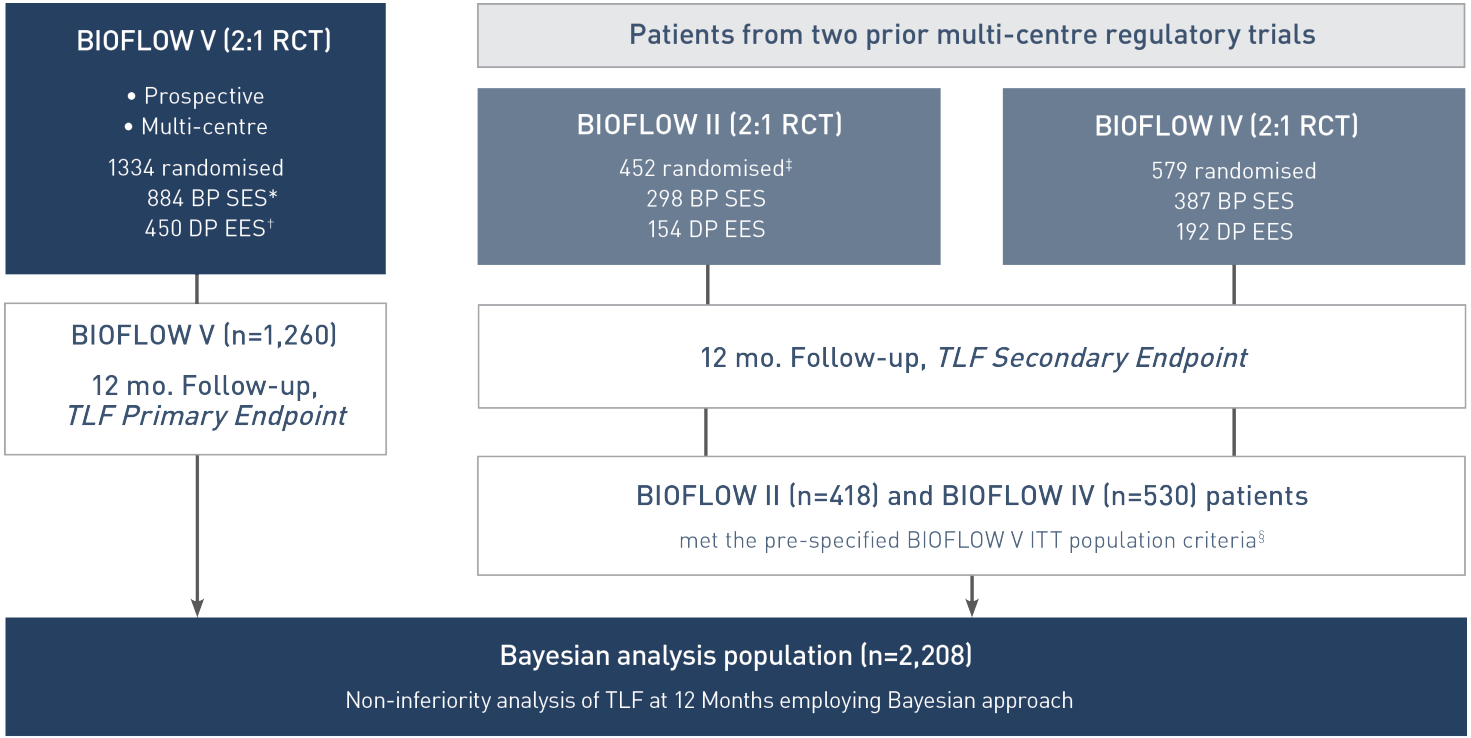
Trial Design



* BP SES: Bioresorbable polymer sirolimus-eluting stent(s)
†DP EES: Durable polymer everolimus-eluting stent(s)
‡Six additional patients were enrolled and received a randomization assignment in BIOFLOW II, 4 experienced procedural complications prior to stenting and two patients withdrew consent prior to stenting but did not receive any study stent, and were excluded from the ITT population.
§ BIOFLOW V ITT population criteria: BIOFLOW V enrolment criteria, at least 330 days of follow-up or experienced an endpoint event prior to 330 days.

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Primary and Secondary Endpoints

Primary Endpoint	Target Lesion Failure (TLF) at 12 months: cardiovascular death, target vessel-related myocardial infraction (MI), or ischaemia-driven TLR Noninferiority design, Event rate 7.0%, Delta 3.85%, Power 89%
Secondary Endpoints	Major Adverse Cardiac Events (MACE): all-cause death, MI, or ischaemia-driven TLR
	Target Vessel Failure (TVF): cardiac death, target vessel-related MI, or ischaemia driven TVR
	Individual components of composite endpoints at 30 days and 12 months
	Definite / probable stent thrombosis
	Device Success: achievement of <30% diameter stenosis of the target lesion within the study stent
	Procedure Success: final diameter stenosis <30% with the assigned stent and with no in-hospital MACE

Key Enrollment Criteria

Inclusion Criteria

- Age ≥ 18 years
- IHD, stable or unstable angina, or silent ischaemia
- ≤ 3 de novo target lesions in ≤ 2 native target vessels (TV)
- RVD ≥ 2.25 mm and ≤ 4.0 mm
- LL ≤ 36 mm
- TIMI flow > 1
- Eligible for DAPT therapy (aspirin + P_2Y_{12})
- Provided informed consent

Exclusion Criteria

- Recent (< 72 hours prior to procedure) STEMI or hemodynamically unstable NSTEMI/ ACS patients
- Chronic total occlusions, bypass grafts
- Bifurcations with side branch > 2.0 mm
- In-stent restenosis or active stent thrombosis
- LVEF < 30%
- Prior PCI within 30 days (non-TV) or within 9 months (TV).
- Planned staged PCI post-procedure
- Renal impairment > 2.5 mg/dL or 221 µmol/L or dialysis dependent
- Excessively tortuous/ angulated or severely calcified (operator visual assessment)

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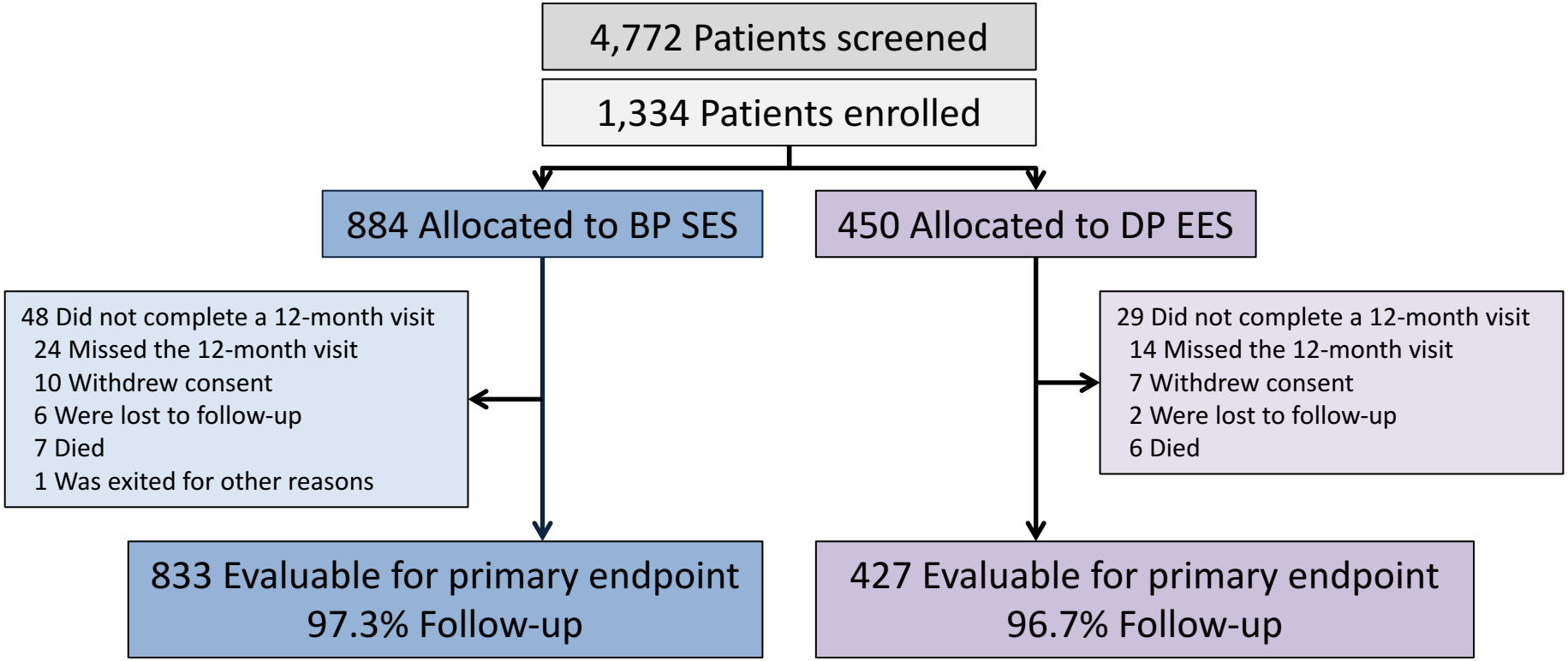
Enrollment

- 1,334 patients randomised between May 2015 and March 2016
  - 884 Orsiro and 450 Xience
- Patients enrolled in 13 countries in North America (665), Europe (390), Israel (231), Asia (36), and Australia and New Zealand (12)
- 12 month follow-up completed May 2017

Leading Enrollment Sites

Institution	Country	Number enrolled
UZ Leuven – Campus Gasthuisberg	Belgium	57
Rambam Medical Center	Israel	55
Kaplan Medical Center (Clalith Health Services)	Israel	52
Rabin Medical Center	Israel	48
Universitares Herzzentrum Hamburg	Germany	44
Ein-Kerem Medical Center	Israel	43
Charleston Area Medical Health Systems	USA	39
Florida Hospital Pepin Heart Institute	USA	35
Cardiovascular Associates, Ltd.	USA	34
Columbia Presbyterian University Medical Center	USA	33
Sourasky Medical Center Tel Aviv	Israel	33
Thomas Hospital	USA	31
University Hospital Lausanne	Switzerland	31

Patient Disposition



Bayesian Analysis

- Subjects from BIOFLOW II and BIOFLOW IV meeting all BIOFLOW V inclusion / exclusion criteria and having either an endpoint event or completing at least 330 days of follow-up
- To ensure consistency and validity of pooled events, all BIOFLOW II and BIOFLOW IV events were re-adjudicated by the BIOFLOW V CEC, including additional events not previously adjudicated for those studies

	Bayesian Population	BP SES	DP EES
BIOFLOW II	418	279	139
BIOFLOW IV	530	354	176
BIOFLOW V	1,260	833	427
Total	2,208	1,466	742

Clinical Characteristics	BP SES (N=884)	DP EES (N=450)
Age, years	64.5 ± 10.3	64.6 ± 10.7
Female	25.3%	27.1%
Hypertension	79.7%	80.5%
Hyperlipidemia	78.9%	82.4%
Diabetes mellitus	34.0%	37.0%
Prior MI	27.4%	25.9%
Prior PCI	36.8%	33.0%
Prior CABG	7.1%	5.2%
Current smoking	23.6%	22.7%
Clinical presentation		
Stable angina	48.4%	47.4%
Acute coronary syndrome	51.4%	49.6%

Angiographic Characteristics	BP SES (N=1,051 lesions)	DP EES (N=561 lesions)
Target lesion vessel		
Left anterior descending	41.0%	41.2%
Left circumflex	26.6%	26.0%
Right coronary artery	32.4%	32.8%
Thrombus	1.0%	0.9%
Bifurcation lesion	14.8%	15.0%
Moderate/severe calcification	24.0%	26.7%
Moderate/severe tortuosity	58.8%	61.5%
ACC/AHA lesion class B2/C	72.6%	75.9%

Angiographic/Procedural Results	BP SES (N=1,051 lesions)	DP EES (N=561 lesions)
Lesion length	13.3 ± 7.6	13.2 ± 7.7
Reference vessel diameter	2.6 ± 0.5	2.6 ± 0.6
No. target lesions/pt*	1.2 ± 0.4	1.3 ± 0.5
% diameter stenosis, pre	55.4 ± 13.3	55.9 ± 13.5
% diameter stenosis, post	7.1 ± 9.8	7.4 ± 9.8
Post-dilation performed	47.7%	46.2%
No. stents/lesion*	1.07 ± 0.3	1.13 ± 0.4
Stent length/lesion	20.8 ± 9.1	21.8 ± 10.5
Overlapping stents*	9.4%	15.0%

*$P<0.05$ for comparison

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Procedural Outcomes

	BP SES	DP EES	*P* value
Lesion success*	1102/1107 (99.5%)	579/583 (99.3%)	0.505
Device success†	1082/1107 (97.7%)	566/583 (97.1%)	0.415
Procedure success‡	827/881 (93.9%)	401/445 (90.1%)	0.019

***Lesion success** defined as attainment of < 30% residual stenosis of the target lesion using any percutaneous method.

†**Device success** defined as attainment of < 30% residual stenosis of the target lesion using the assigned study stent only.

‡**Procedure success** defined as attainment of < 30% residual stenosis of the target lesion using the assigned study stent only without occurrence of in-hospital major adverse cardiac events (MACE; composite of all-cause death, Q-wave or non-Q-wave MI, and any clinical-driven TLR).

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30 Day Outcomes

	BP SES (N=884)	DP EES (N=450)	*P* value
All-cause death	0.1%	0.2%	1.000
Myocardial Infarction	4.3%	6.9%	0.050
In-Hospital MI	3.9%	6.7%	0.029
TLR	0.5%	0.7%	0.694
Stent Thrombosis	0.3%	0.2%	1.000
TLF	4.2%	7.1%	0.026
TVF	4.3%	7.1%	0.037

All data represented as intention to treat

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Primary Endpoint: 12 Month Target Lesion Failure

	Orsiro BP SES (n=884)	Xience DP EES (n=450)	*P* value
Target lesion failure	6.2%	9.6%	0.040
Cardiac death	0.1%	0.7%	0.115
Target-vessel MI	4.7%	8.3%	0.016
Clinically-driven TLR	2.0%	2.4%	0.686

All data represented as intention to treat

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Pooled Bayesian Analysis: BIOFLOW V, II and IV Trials

	Orsiro BP SES (n=1466)	Xience DP EES (n=742)	Rate difference	Posterior probability	
Target-lesion failure (Bayesian analysis)				Non-inferiority margin 3.85%	Superiority (post-hoc)
12-Month Rate, posterior mean ± estimate of SD (%), 95% Credible Interval	6.3 ± 0.8 (4.9, 7.9)	8.9 ± 1.2 (6.7, 11.4)	-2.6 (-5.5, 0.1)	100.0%	96.9%

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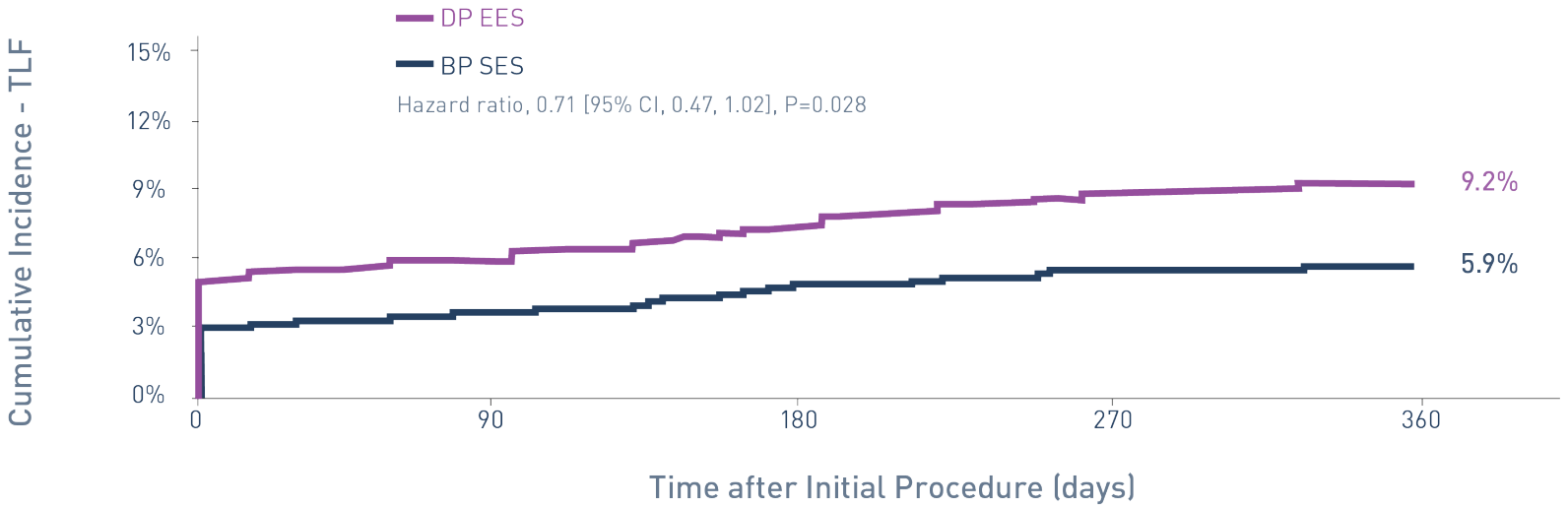
Primary Endpoint: 12 Month Target Lesion Failure



No. at Risk					
DP EES	450	421	411	400	392
BP SES	884	848	828	814	792

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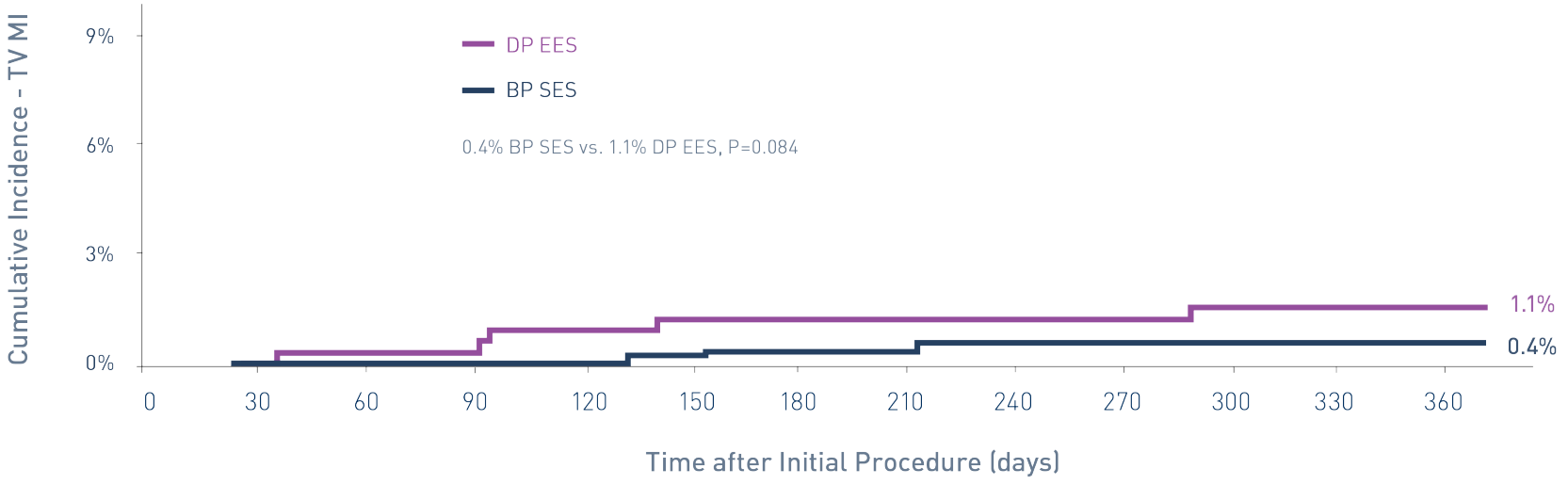
Landmark Analysis: Target Vessel MI, 30 Days to 12 Months



No. at Risk							
DP EES	445	444	441	431	425	417	345
BP SES	875	870	865	855	842	821	685

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Stent Thrombosis

12 Month DAPT Adherence: 92.1% BP SES, 91.2% DP EES

	BP SES (N=884)	DP EES (N=450)	*P* value
Stent Thrombosis			
Any Stent Thrombosis	0.5%	1.2%	0.175
Definite	0.5%	0.7%	0.694
Definite/Probable	0.5%	0.7%	0.694
Timing of Event (Definite/Probable ST)			
Acute (≤ 24 hours)	0.1%	0.0%	1.000
Sub-acute (> 24 hours and ≤ 30 days)	0.2%	0.2%	1.000
Late (> 30 days and ≤ 1 year)	0.1%	0.5%	0.264
Timing of Event (Any ST)			
Acute (≤ 24 hours)	0.1%	0.0%	1.000
Sub-acute (> 24 hours and ≤ 30 days)	0.2%	0.2%	1.000
Late (> 30 days and ≤ 1 year)	0.1%	0.9%	0.047

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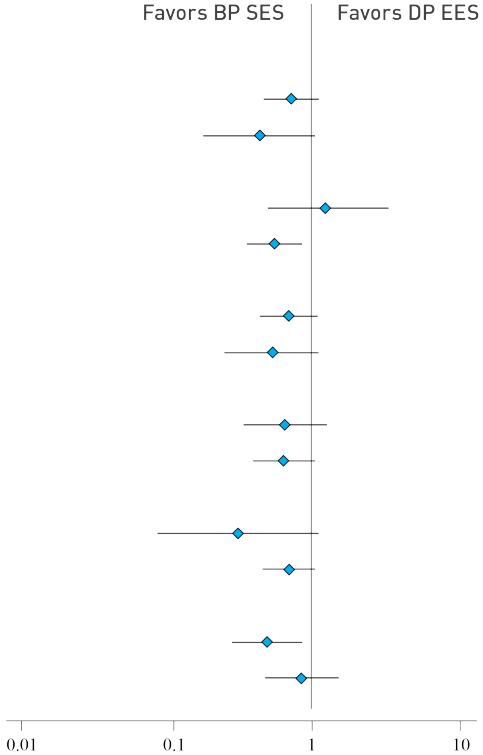
Target Lesion Failure at 12 Months by Subgroups

Subgroup	BP SES (N=884)	DP EES (N=450)	HR and 95% CI	P Value for Interaction
	no. of events / total no. (%)			
Vessel Size				0.37
Small Vessels*	43/554 (7.8)	31/290 (10.7)	0.71 (0.45, 1.13)	
Large Vessels	9/269 (3.3)	10/135 (7.4)	0.45 (0.18, 1.10)	
Age				0.16
>75	12/124 (9.7)	6/71 (8.4)	1.20 (0.45, 3.21)	
≤75	40/709 (5.6)	35/356 (9.8)	0.56 (0.35, 0.88)	
Gender				0.61
Male	39/628 (6.2)	28/312 (9.0)	0.69 (0.42, 1.11)	
Female	13/205 (6.3)	13/115 (11.3)	0.54 (0.25, 1.16)	
Diabetes				0.91
Diabetic	18/280 (6.4)	15/153 (9.8)	0.66 (0.33, 1.31)	
Non-diabetic	34/552 (6.2)	26/273 (9.5)	0.63 (0.38, 1.05)	
Lesion Length				0.25
>26 mm	4/78 (5.1)	6/36 (16.7)	0.31 (0.09, 1.11)	
≤ 26 mm	48/746 (6.4)	35/387 (9.0)	0.69 (0.45, 1.07)	
ACS†				0.24
ACS	24/426 (5.6)	23/209 (11.0)	0.50 (0.28, 0.89)	
Non-ACS	28/407 (6.9)	18/218 (8.3)	0.82 (0.45, 1.48)	



*Small vessels defined as ≤ 2.75mm.
†ACS defined as: subjects with unstable angina or any elevated cardiac enzymes at baseline (any pre procedure CK, CK MB or Troponin out of normal range).

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Conclusions

- In an international, randomised trial, treatment with the ultra-thin strut Orsiro BP SES was superior to the Xience DP EES regarding 12 month TLF and MI
  - Differences in MI observed early but persisted in landmark analysis
- Revascularization with Orsiro BP SES was associated with favorably low TLR and stent thrombosis
- Bayesian pooled analysis including patient level outcomes from BIOFLOW II and IV trials demonstrated unequivocal non-inferiority with mean TLF treatment difference of -2.6 % favoring Orsiro and posterior probability of superiority 96.9%
- These results endorse the safety and efficacy of the ultrathin Orsiro BP SES in patients representative of those treated in clinical practice and advance a new standard for DES comparison

THE LANCET

Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a randomised trial

David E Kandzari, Laura Mauri, Jacques J Koolen, Joseph J Massaro, Gheorghe Doros, Hector M Garcia-Garcia, Johan Bennett, Ariel Roguin, Elie G Gharib, Donald E Cutlip, Ron Waksman, for the BIOFLOW V Investigators

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