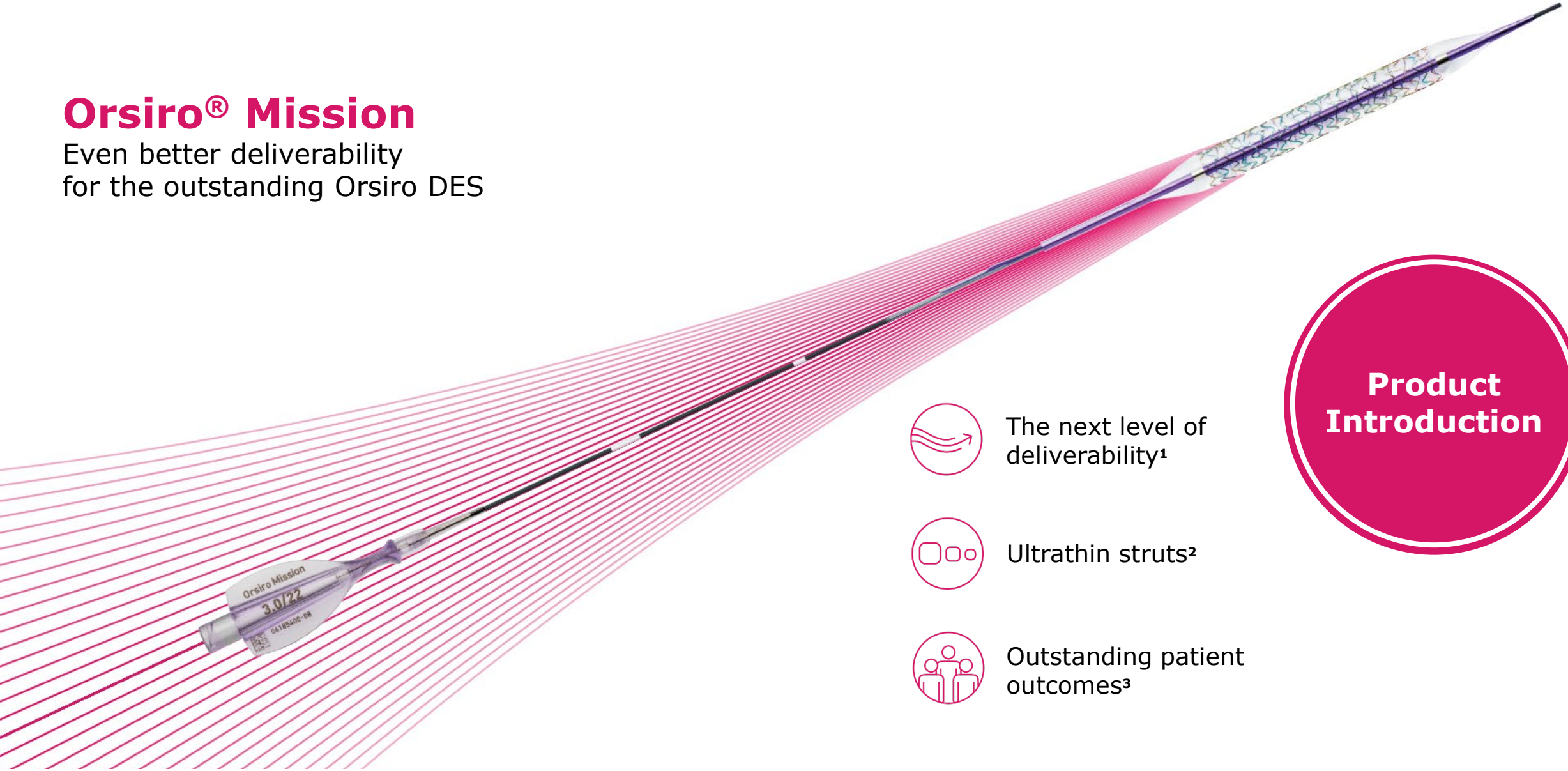
Orsiro® Mission

Even better deliverability
for the outstanding Orsiro DES



Product Introduction

- The next level of deliverability[1]
- Ultrathin struts[2]
- Outstanding patient outcomes[3]

1. In comparison to Xience Sierra, Resolute Onyx and Synergy for bench tests on pushability, trackability and crossability, BIOTRONIK data on file; 2. As characterized with respect to strut thickness in Bangalore et al. Meta-analysis; 3. Based on investigator's interpretation of BIOFLOW-V primary endpoint result. Orsiro and Orsiro Mission are trademarks or registered trademarks of the BIOTRONIK Group of Companies. Clinical data conducted with Orsiro, Orsiro Mission's predecessor device can be used to illustrate Orsiro Mission clinical outcomes.

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- The next level of deliverability
- Ultrathin strut platform
- Outstanding patient outcomes
- Indications
- Specifications (device technology)
- Ordering information
- Disclaimer + Trademarks

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Orsiro® Mission

Even better deliverability for the outstanding Orsiro DES

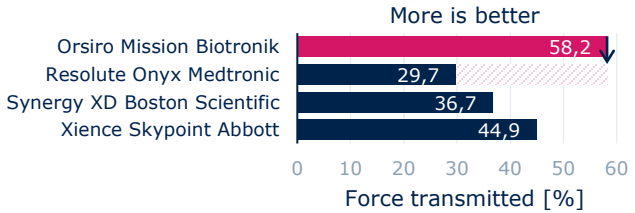
The next level of deliverability

Ultrathin strut platform

Outstanding patient outcomes

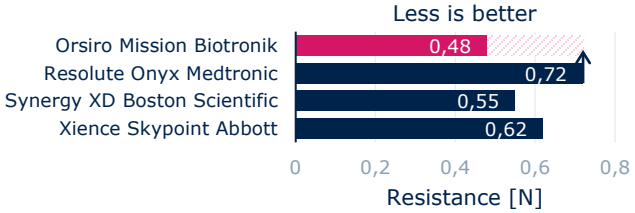
First in Push, Track and Cross[1]

1st in Push[1]



Transmitting up to **96% more force** from hub to tip[2]

1st in Track[1]



Up to **33% less force** needed to follow the path to the lesion[2]

1st in Cross[1]

Up to **64% less force** needed to successfully cross demanding anatomies[3]

Proven deliverability on the bench and in a **real-world** user evaluation of over 1,000 implantations[4]

98%
Proven very good/ good pushability

97%
Proven very good/ good trackability

97%
Proven very good/ good crossability

1. BIOTRONIK data on file. IIB 24-2018; 2. Stefanini GG et al. Coronary stents: novel developments. Heart. 2014 Jul 1;100(13):1051-61; 3. Low AF. Stent platform for procedural success: Introducing the Continuous Sinusoidal & Core Wire Technologies. Presented at: AsiaPCR; 22-24 January, 2015; Singapore, Singapore; 4. Evaluation of Market Acceptance, BIOTRONIK data on file.

EMA results

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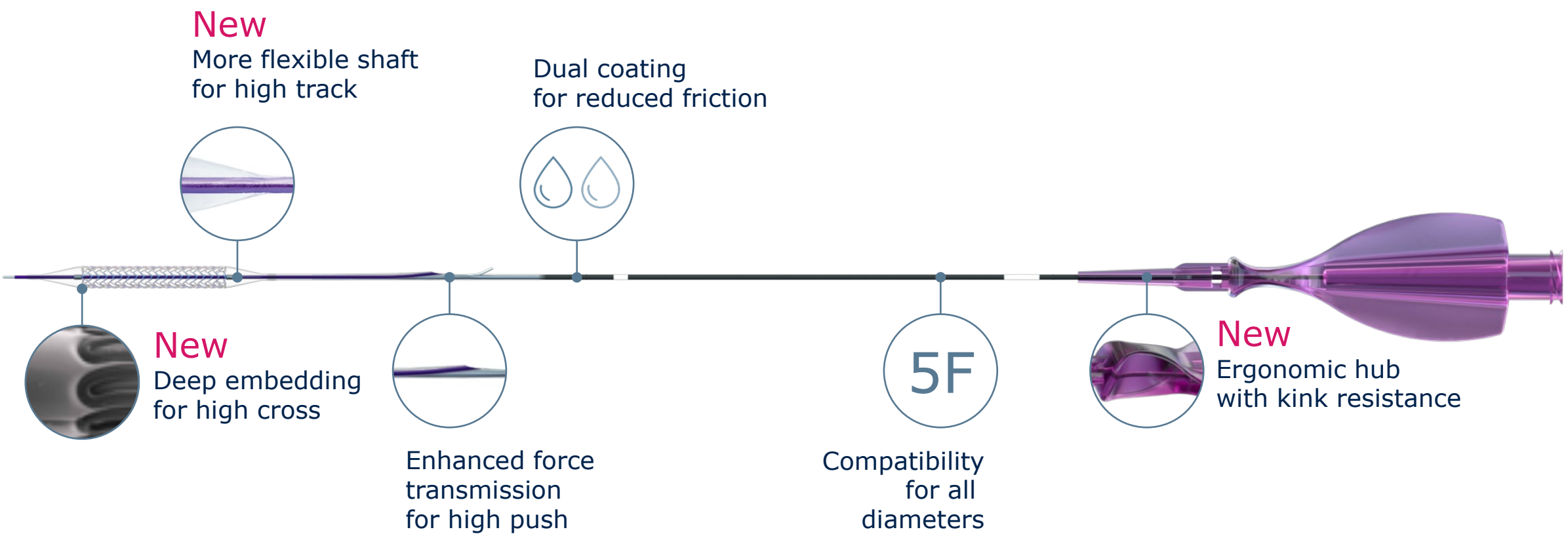
Delivery system features



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Even better deliverability for the outstanding Orsiro DES

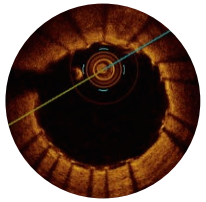
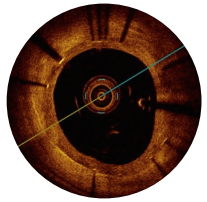
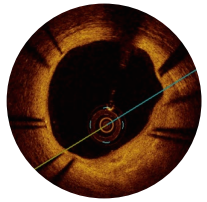
The next level of deliverability

Ultrathin strut platform

Outstanding patient outcomes

Early and Effective Endothelialization

Time after implantation

1 month[1]	3 months[1]	6 months[1]
		
>80%	>97%	>98%
Immature tissue coverage		Tissue maturation and full coverage

Healing progress

Strut thickness in perspective[2]

Biosensors **BioMatrix** 316L-BES	Boston **Promus** PtCr-EES	Abbott **Xience Family** CoCr-EES	Medtronic **Resolute Onyx** CoNi-ZES[3,4]	Terumo **Ultimaster** CoCr-SES	Boston **Synergy XD** PtCr-EES	Biotronik **Orsiro Mission** CoCr-SES
120µm	81µm	81µm	81µm	80µm	74µm	60µm*

*Ø2.25-3.0mm. 1. Secco, Gioel Gabrio, et al. "Time-related changes in neointimal tissue coverage of a novel Sirolimus eluting stent: Serial observations with optical coherence tomography." Cardiovascular Revascularization Medicine 17.1 (2016): 38-43; 2. Stefanini GG et al. Coronary stents: novel developments. Heart. 2014 Jul 1;100(13):1051-61; 3. Low AF. Stent platform for procedural success: Introducing the Continuous Sinusoidal & Core Wire Technologies. Presented at: AsiaPCR; 22-24 January, 2015; Singapore, Singapore; 4. Tolentino A. Evolving DES Strategy: Biodegradable Polymer vs. Bioabsorbable Scaffold. Presented at: Cardiovascular Nurse/Technologist Symposium; June 17, 2016; New York, USA.

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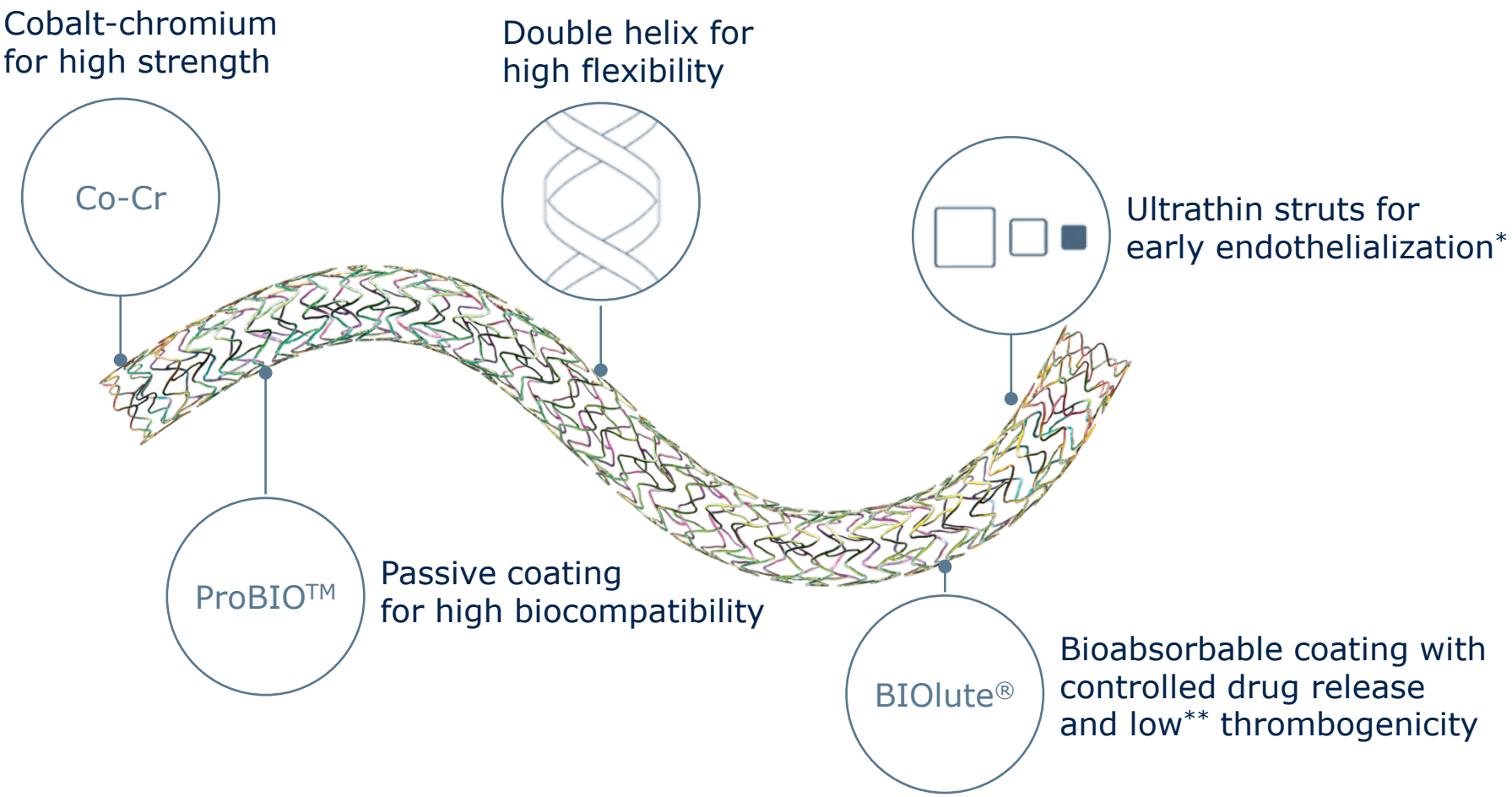
Stent features



* Per investigators' interpretation in Secco et al. Cardiovascular Revascularization Medicine. 2016; 17(1): 38-43. ** Per investigators' interpretation of preclinical studies with Orsiro as mentioned in Cassese et al. J Thorac Dis 2018;10(2):688-692.

Orsiro® Mission

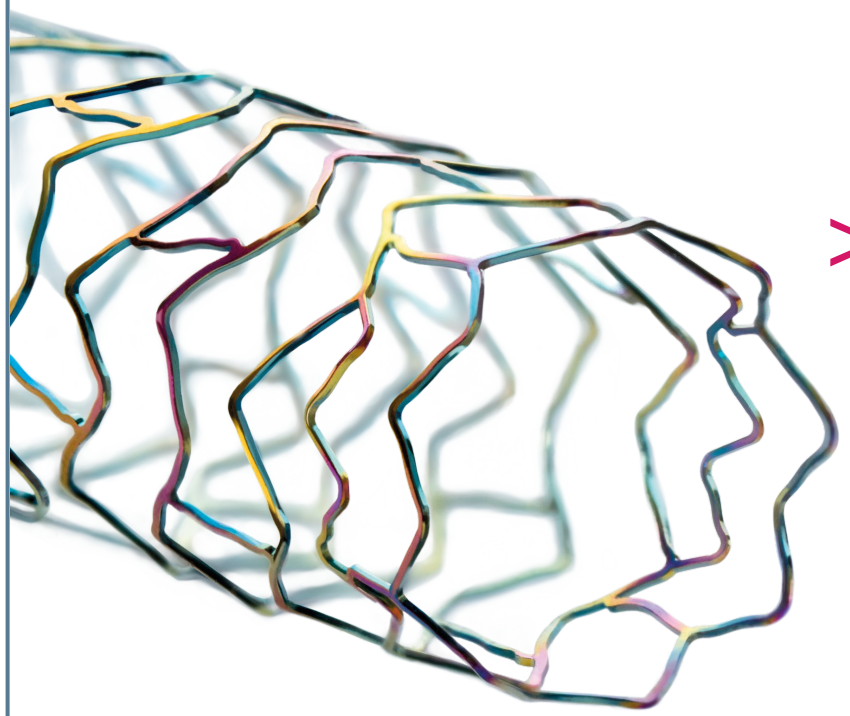
Even better deliverability for the outstanding Orsiro DES

The next level of deliverability

Ultrathin strut platform

Outstanding patient outcomes

One of the most studied DES[1]



>55,000
Patients enrolled[2]

>71,500
Patients planned in total[2]

>68
Studies started[2]

>70
Studies started or planned in total[2]

1. In large RCTs, based on Taglieri et al. Meta-analysis, against currently used DES; 2. BIOTRONIK data on file, status January 2020.

Key Trials
Clinical data

BIOSTEMI [1]	1,300	10 sites 1 country	1:1 RCT Orsiro vs. Xience	TLF at 12 months	24 months FU available	**NCT02579031**
BIOFLOW-V [2]	1,334	91 sites 13 countries	2:1 RCT Orsiro vs. Xience	TLF at 12 months	Completed 60 months FU available	**NCT02389946**
BIO-RESORT [3]	3,514	4 sites 1 country	1:1:1 RCT Orsiro vs. Resolute Integrity vs. Synergy	TVF at 12 months	Completed 60 months FU available	**NCT01674803**
BIOSCIENCE [4]	2,119	9 sites 1 country	1:1 RCT Orsiro vs. Xience Prime	TLF at 12 months	Completed 60 months FU available	**NCT01443104**

1. Pilgrim T et al. JACC, March, 2021; 2. Kandzari D et al. J Am Coll Cardiol. Cardiovasc Interven. 2022; 3. Buiten R et al. JACC Cardiovascular Interventions, 2019; 4. Pilgrim T et al. Lancet, August, 2018.

SCAAR

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BIOSTEMI Trial

2 years follow-up

BIOSTEMI

BIOSTEMI

n = 1,300, 1:1 Randomized, Superiority Trial

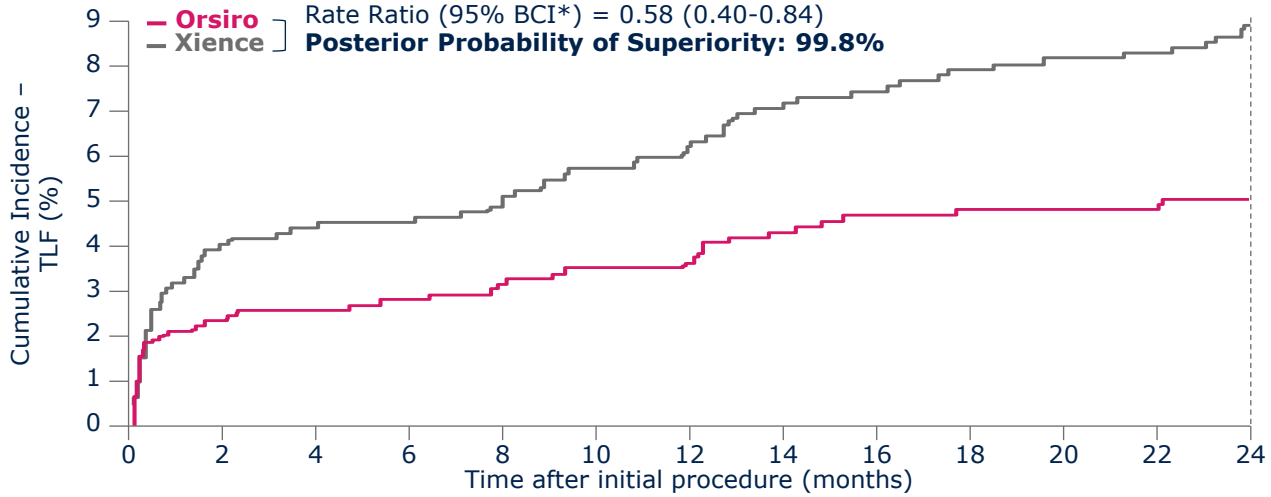
- At 24 months, Orsiro is superior to Xience in STEMI patients with respect to the primary endpoint of Target Lesion Failure (TLF) (5.1% vs. 8.1%, Rate Ratio (95% BCI*): 0.58 (0.40-0.84), **Posterior Probability of Superiority: 99.8%**).
- The difference in TLF rates remained statistically significant after the exclusion of historical information from the BIOSCIENCE trial (Rate Ratio (95% BCI*): 0.62 (0.40-0.96), **Posterior Probability of Superiority: 98.5%**) and was driven by significantly lower rates of clinically-indicated Target Lesion Revascularization (TLR) rate (2.5% vs. 5.1%, Rate Ratio (95% BCI*): 0.52 (0.30-0.87), Posterior Probability of Superiority: 99.3%).

Target Lesion Failure (TLF)

at 24 months[1]

5.1% Orsiro | 8.1% Xience

Primary Endpoint – TLF at 24 months[1]



Continued Superiority in STEMI at 2 years**
Orsiro. Improving STEMI care[2]

*BCI: Bayesian Credible Interval. **In comparison to Xience, based on TLF, in the BIOSTEMI trial. 1. Pilgrim et al. Biodegradable – versus durable-polymer drug-eluting stents for STEMI. Final 2-year outcomes of the BIOSTEMI trial. J Am Coll Cardiol. Cardiovasc Interven. 2021, doi: 10.1016/j.jcin.2020.12.011; 2. In comparison to Xience, based on 12- and 24-months results of the BIOSTEMI trial For indications please see Instructions For Use.

BIOTRONIK excellence for life

BIOFLOW-V Trial

5 years follow-up

BIOFLOW-V

BIOFLOW-V (Pivotal FDA trial)

n = 1,334, 2:1 randomized, controlled IDE trial

Orsiro ultrathin struts DES outperformed Xience DP-EES at 1-year and sustained performance up to 5 years:

- 20% lower Target Lesion Failure
- 36% significantly lower Target Vessel Myocardial Infarction
- 23% lower Ischemia-Driven TLR
- 22% lower Cardiac Death/Myocardial Infarction

Additionally, Orsiro showed a 0.7% definite/probable stent thrombosis rate overall through 5 years: 64% lower vs. Xience.

20% Lower TLF rate* (p = 0.136)[4]

36% Significantly lower TV-MI rate* (p = **0.021**)[4]

83% Significantly lower late/verylate def/prob ST rates* (p = **0.021**)[4]

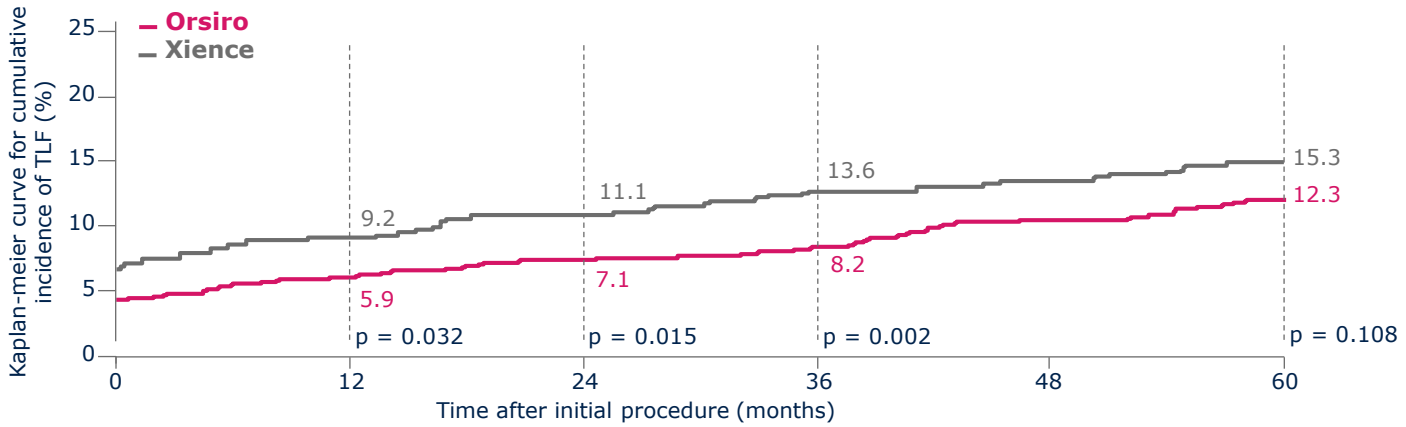
Target Lesion Failure (TLF)

at 60 months*[4]

Orsiro	Xience
13.2%	16.5%

p = 0.136

Strong start, continued performance◊. TLF out to 5 years [1-5]



Principal Investigator, BIOFLOW-V, Dr. D. Kandzari

"These long-term results confirm that the Orsiro DES sets a new clinical benchmark in PCI treatment options."

ACS Subgroup

TLF = Target Lesion Failure, TV-MI = Target Vessel Myocardial Infarction, TLR = Target Lesion Revascularization. *Vs. Xience based on 60-m frequentist analysis (see supplemental material). ◊ compared to Xience, based n BIOFLOW-V 5-year results. All figures from submitted manuscript are rounded by Biotronik after the BIOFLOW-V figures presented by D. Kandzari, at CRT 2022, Washington, USA. 1. Kandzari D, et al. BIOFLOW-V: A Prospective Randomized Multicenter Study to Assess the Safety and Effectiveness of the Orsiro SiroLimus Eluting Coronary Stent System in the Treatment Of Subjects With up to Three De Novo or Restenotic Coronary Artery Lesions Science. Presentation at ESC 2017; 2. Kandzari D et al. Ultrathin Bioresorbable Polymer Sirolimus-Eluting Stents versus Thin Durable Polymer Everolimus-Eluting Stents: Journal of American College of Cardiology (2018), doi: https//doi.org/10.1016/j.jacc.2018.09.019; 3. Kandzari D et al. J Am Coll Cardiol. Cardiovasc Interven. 2020, doi: 10.1016/j.jcin.2020.02.019; 4. Kandzari D et al. Ultrathin Bioresorbable Polymer Sirolimus-Eluting Stents versus Thin Durable Polymer Everolimus-Eluting Stents for Coronary Revascularization: Final 5-year Outcomes from the Randomized BIOFLOW V Trial, Submitted manuscript to JACC:2022 NCT02389946.

BIOTRONIK excellence for life

BIO-RESORT Trial

5 years follow-up

BIO-RESORT

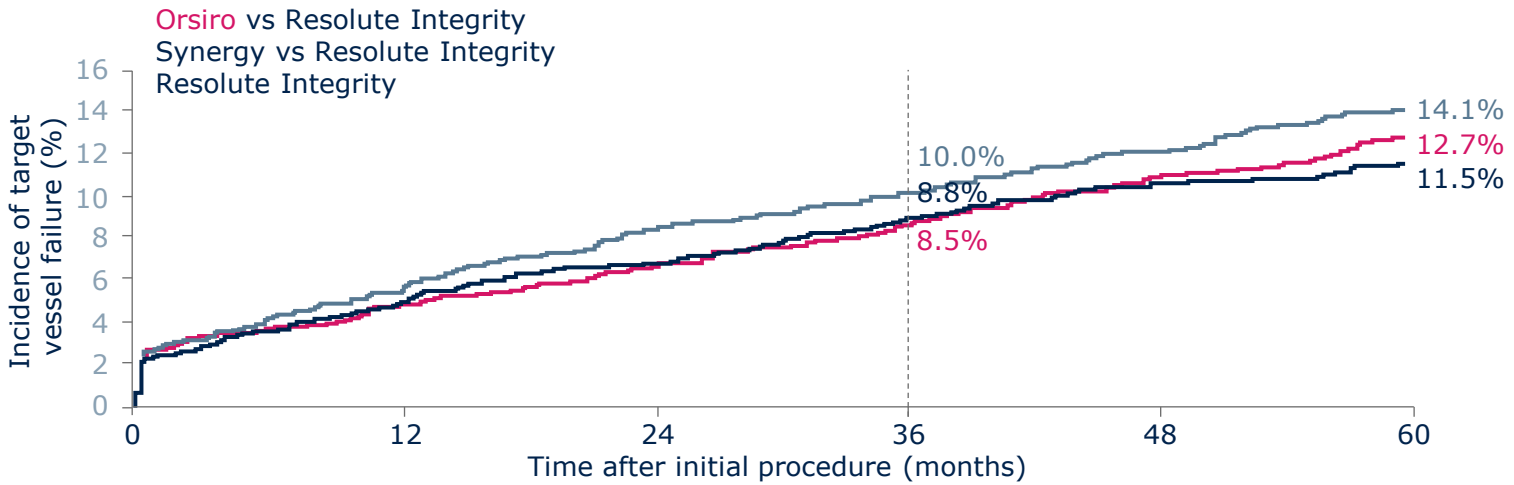
BIO-RESORT

n = 3,514 All-comers, 1:1:1 RCT

- BP-SES Orsiro demonstrated **non-inferiority** to Resolute Integrity while performing equally well as Synergy [TVF at 12 months: Orsiro 4.7%, Synergy 4.7%, Resolute Integrity 5.4%, $p_{non\text{-}inferiority}$ <0.0001].[1]
- At 36 months Orsiro shows favorable outcomes with **numerically lower event rates in TVF** compared to both Synergy and Resolute Integrity.[2]
- At 60 months, Orsiro **shows similar 5-year safety and efficacy to Synergy DES and Resolute Integrity DES**.[3]

At 60 months, Orsiro shows similar 5-year safety and efficacy to Synergy DES and Resolute Integrity DES.[3]

TVF at 60 months[2,3]



3Y
- Synergy
- Resolute Integrity
- Orsiro

p = 0.32
p = 0.22

5Y
- Synergy
- Resolute Integrity
- Orsiro

p = 0.08
p = 0.31

Small Vessel Subgroup

1. Von Birgelen C et al. The Lancet. 2016;388(10060):2607-17; 2. von Birgelen C et al. 3-Years BIO-RESORT: Results of the 3-Arm randomized study in all-comers, treated with contemporary biodegradable or durable polymer-coated drug-eluting stents. Presented at CRT 2019, March, 2019; Washington DC, USA; ClinicalTrials.gov: NCT01674803. 3. BIO-RESORT 5Y small-vessels subgroup, Presented by E.Ploumen at euroPCR 2022

BIOTRONIK excellence for life

BIOSCIENCE Trial

5 years follow-up

BIOSCIENCE

n = 2,119, All-comers, 1:1 RCT

- BP-SES Orsiro demonstrated non-inferiority to Xience Prime in regards to TLF at 12 months [Orsiro 6.7% vs. Xience 6.7% Rate ratio: 0.99 (95% CI 0.71 - 1.38), p-value = 0.95]
- Orsiro is associated with **numerically lower rates** of Target Vessel-Myocardial Infarction (TV-MI) and definite/probable ST at 5 years follow-up

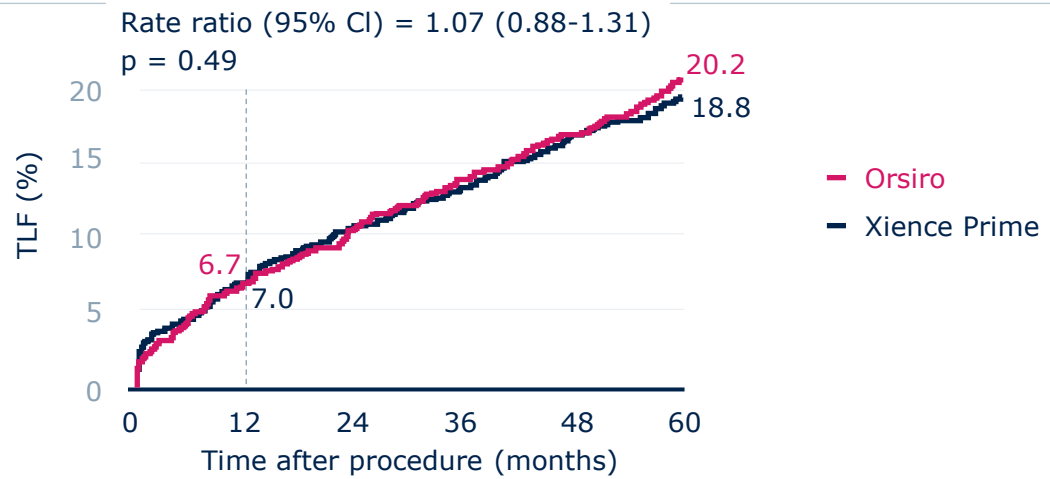
Definite Stent Thrombosis (ST)

at 60 months[1]

Orsiro	Xience
1.6%	1.6%

p = 0.95

TLF rates – all subjects out to 5 years[2,3]



Proven long-term safety with Orsiro in an all-comers population

1. Pilgrim T et al. Ultrathin-strut, biodegredable-polymer, sirolimus-eluting stents versus thin-strut, durable-polymer, everolimus-eluting stents for percutaneous coronary revascularization: 5-year outcomes of the BIOSCIENCE randomized trial. Lancet, August, 2018; 2. Pilgrim T, Piccolo R, Heg D, et al. Ultrathin-strut, biodegradable-polymer, sirolimus-eluting stents versus thin-strut, durable-polymer, everolimus-eluting stents for percutaneous coronary revascularisation: 5-year outcomes of the BIOSCIENCE randomised trial. The Lancet. 2018 Sep 1;392(10149):737-46; 3. Pilgrim T. et al. 5-year outcomes of the BIOSCIENCE randomised trial. Supplementary appendix; Lancet 2018; published online Aug 28. http://dx.doi.org/10.1016/S0140-6736(18)31715-X.

Orsiro® Mission

Indications*

Orsiro Mission is indicated for improving coronary luminal diameter in patients with symptomatic ischemic heart disease due to discrete de-novo stenotic lesions and in-stent restenotic lesions (length ≤ 40mm) in the native coronary arteries with a reference vessel diameter of 2.25 mm to 4.0 mm including the following patient and lesion subsets:

- Acute Coronary Syndrome (ACS)
- ST-Elevation Myocardial Infarction (STEMI)
- Diabetes Mellitus (DM)
- Complex Lesions (B2/C)
- High Bleeding Risk (HBR)
- Long Lesions (LL) (e.g. ≥ 20 mm)
- Small Vessels (SV) (e.g. ≤ 2.75 mm)
- Multi-Vessel Disease (MVD)
- Male/Female
- Old Patients (e.g. > 65 y)

*Indications as per IFU

Orsiro® Mission

Description

The Orsiro Mission Sirolimus Eluting Coronary Stent System (Orsiro Mission) is a drug-eluting balloon-expandable stent that is pre-mounted on a rapid-exchange PTCA catheter delivery system with a usable catheter length of 140 cm.

- There are two stent configurations: small and medium. The respective stent diameters and lengths are:

		Length [mm]								
Design	Diameter [mm]	9	13	15	18	22	26	30	35	40
SMALL	2.25	X	X	X	X	X	X	X	X	X
	2.5	X	X	X	X	X	X	X	X	X
	2.75	X	X	X	X	X	X	X	X	X
	3.0	X	X	X	X	X	X	X	X	X
MEDIUM	3.5	X	X	X	X	X	X	X	X	X
	4.0	X	X	X	X	X	X	X	X	X

- The stent is made from a cobalt chromium alloy (L-605) and is intended as a permanent implant. It is completely covered with a thin layer of amorphous silicon carbide (**proBIO** coating).

- The stent's abluminal, adluminal, and strut side-surfaces are coated with **BIOlute**, a bioabsorbable drug matrix consisting of a drug substance sirolimus and polymer poly-l-lactide (PLLA).

Orsiro® Mission

Specifications

Stent	
Stent Material	Cobalt chromium, L-605
Strut Thickness	Ø 2.25 – 3.0 mm: 60 µm (0.0024”); Ø 3.50 – 4.0 mm: 80 µm (0.0031”)
Passive coating	**proBIO** (Amorphous Silicon Carbide)
Active Coating	**BIOlute** bioabsorbable Poly-L-Lactide (PLLA) eluting a limus drug
Drug dose	1.4 µg/mm²
Delivery System	
Catheter type	Rapid exchange
Recommended guide catheter	5 F (min. I.D. 0.056”)
Guide wire diameter	0.014”
Usable catheter length	140 cm
Balloon material	Semi crystalline polymer material
Coating (Distal shaft)	Hydrophilic
Coating (Proximal shaft)	Hydrophobic
Marker Bands	Two swaged platinum-iridium markers
Lesion entry profile	0.017”
Distal shaft diameter	2.7 F: Ø 2.25 – 3.0 mm; 2.9 F: Ø 3.5 - 4.0 mm
Proximal shaft diameter	2.0 F
Nominal pressure (NP)	10 atm
Rated burst pressure (RBP)	16 atm

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Stent Implant – Expansion and Strut Opening

Geometry

Nominal Diameter	2.25	2.5	2.75	3.0	3.5	4.0
Design	SMALL (S)				MEDIUM (M)	
Strut thickness (µm)	60				80	
Strut width (µm)	75				85	
Amount of connectors	3					
Amount of crowns at end	8					

Maximal Expansion and Stent Strut Opening

Nominal Diameter	2.25	2.5	2.75	3.0	3.5	4.0
Maximal expansion diameter (mm)	3.5				4.5	
Maximal diameter of expanded stent cell (mm)	3.59				4.42	
Stent strut opening diameter at NP* (mm)	0.79	0.92			1.06	1.25
Nominal outer diameter of the stent at NP (mm)	2.37	2.62	2.87	3.12	3.66	4.16

* Mean of the largest possible opening diameter within a stent cell at NP

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Compliance chart

Inflation Pressure			Stent Inner Diameter (mm)					
			SMALL				MEDIUM	
	atm	(kPa)	**2.25**	**2.5**	**2.75**	**3.0**	**3.5**	**4.0**
NP	**10**	**(1013)**	**2.27**	**2.56**	**2.82**	**3.08**	**3.56**	**4.08**
	11	(1115)	2.32	2.61	2.87	3.14	3.61	4.45
	12	(1216)	2.37	2.66	2.93	3.19	3.66	4.20
	13	(1317)	2.41	2.70	2.97	3.23	3.71	4.25
	14	(1419)	2.44	2.73	3.01	3.27	3.75	4.30
	15	(1520)	2.47	2.76	3.04	3.31	3.78	4.33
RBP	**16**	**(1621)**	**2.50**	**2.79**	**3.08**	**3.34**	**3.82**	**4.37**
Maximum Diameter for Post-dilation (Ø max) (mm)			**3.5**				**4.5**	

NP	In vitro tests* have shown that the balloons will reach their indicated diameter at the given nominal pressure.
RBP	In vitro tests* have shown that with 95% confidence, 99.9% of the balloons will not burst at or below the rated burst pressure (RBP). DO NOT exceed the RBP
Note	if post-dilation is required, DO NOT post-dilate more that the Maximum Diameter for Post-dilation.

* BIOTRONIK data on file

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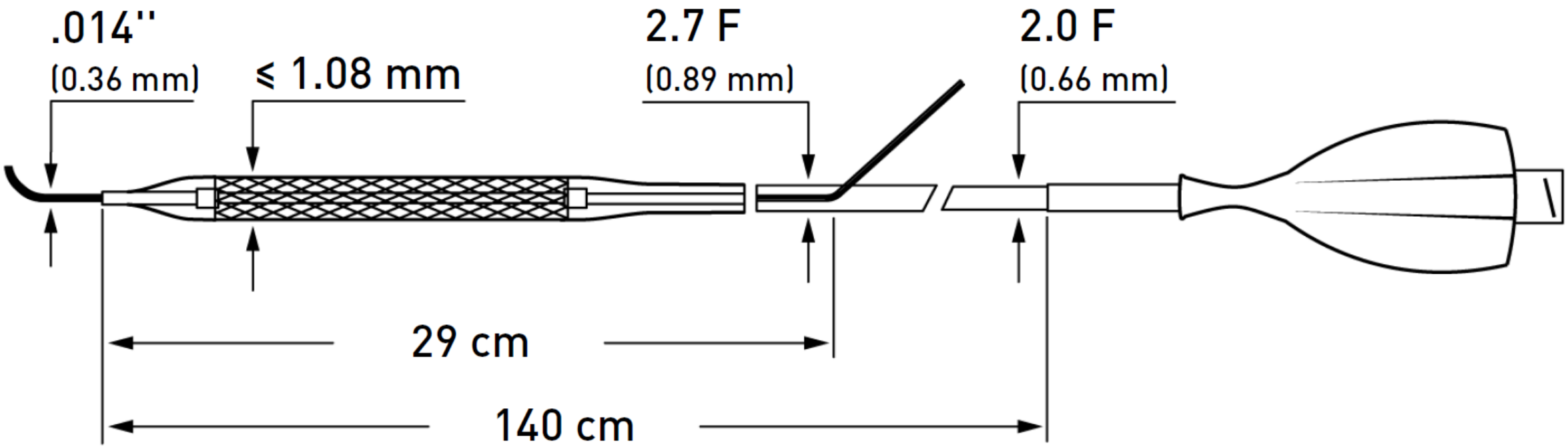
Product schematic representation (Ø 3.0/9 mm)



Orsiro® Mission

Ordering information

Diameter[mm]	Length [mm]								
	9	**13**	**15**	**18**	**22**	**26**	**30**	**35**	**40**
2.25	419101	419107	419113	419119	419125	419131	419137	419143	419149
2.5	419102	419108	419114	419120	419126	419132	419138	419144	419150
2.75	419103	419109	419115	419121	419127	419133	419139	419145	419151
3.0	419104	419110	419116	419122	419128	419134	419140	419146	419152
3.5	419105	419111	419117	419123	419129	419135	419141	419147	419153
4.0	419106	419112	419118	419124	419130	419136	419142	419148	419154

Disclaimer & Trademarks

Disclaimer

- Clinical data conducted with Orsiro, Orsiro Mission's predecessor device can be used to illustrate Orsiro Mission clinical outcomes.

Trademarks

- Orsiro, Orsiro Mission, **proBIO** and **BIOlute** are trademarks or registered trademarks of the BIOTRONIK Group of Companies
- Synergy, Synergy XD and Promus are trademarks or registered trademarks of the Boston Scientific Group of Companies
- Resolute and Resolute Onyx are trademarks or registered trademarks of the Medtronic Group of Companies
- Xience, Xience Prime, Xience Sierra and Xience Skypoint are trademarks or registered trademarks of the Abbott Group of Companies