# CardioEgypt 2018

## Update in DES Technology

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Cairo, 26th Feb 2018

## Disclosures

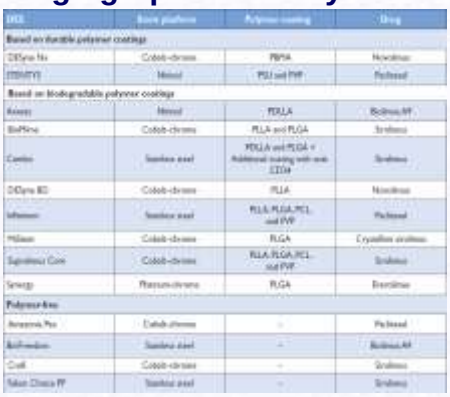
- Presenter: Adam Witkowski
- I have nothing to disclose

# Design of 2nd generation DES

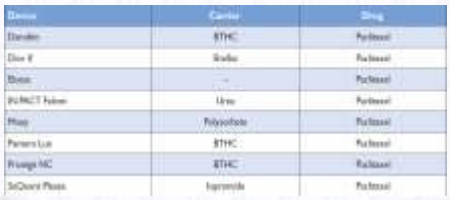
- Alloy: cobalt-chromium, platinium-chromium, thin struts (<80 mc)
- Polymer: durable or bioabsorbable vs non-polymeric, drug-coated stents, drug-filled stents
- Drug: ~~paclitaxel~~, sirolimus or sirolimus derivatives (EES, ZES, BES)
- Fully bioresorbable DES (3d generation DES or 1st generation BRS?)

## CE-approved DES with primary clinical endpoint

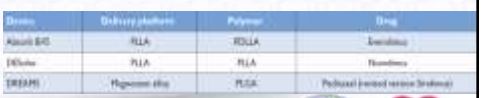
## CE-approved DES with angiographic efficacy data



## CE-approved DCB



## Bioresorbable stents



www.escardio.org/guidelines

European Heart Journal
doi:10.1093/eurheartj/ehu278

# DES: an update 2018

- Biodegradable polymer DES
- Drug-Filled Stents
- Bioresorbable DES

Thorax Centrum Twente

MST

# BIO-RESORT (TWENTE III):

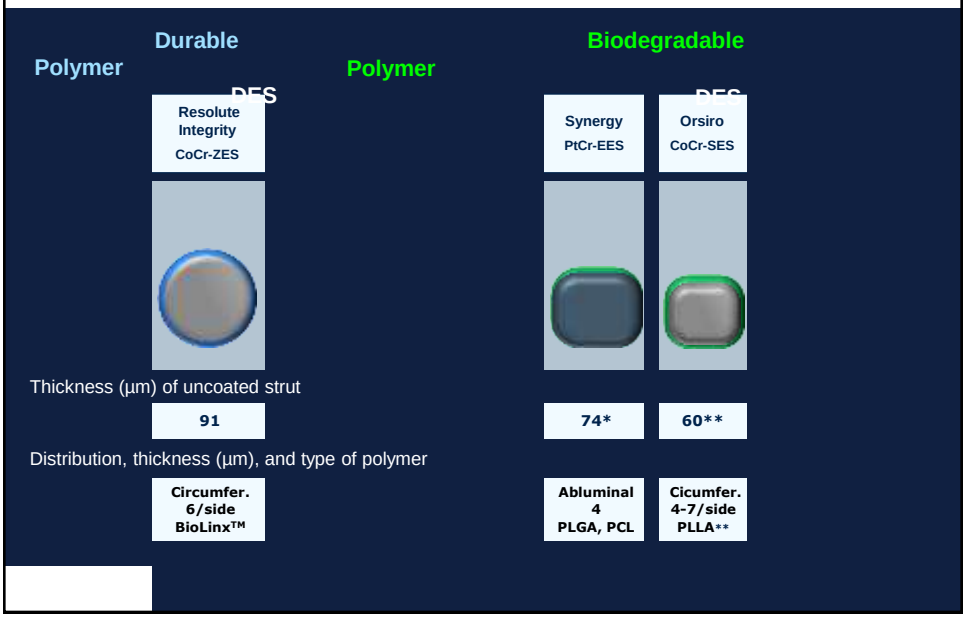
**A prospective, randomized, three-arm trial comparing two different biodegradable polymer-based drug-eluting stents and a durable polymer-based drug-eluting stent in all-comers with coronary artery disease**


**Clemens von Birgelen, MD PhD**

***Thoraxcentrum Twente, MST, Enschede, the Netherlands***
***on behalf of the BIO-RESORT Investigators***

TCT 2016

# BIO-RESORT: Study Devices




# Primary Endpoint and Sample Size

- **Primary endpoint is Target Vessel Failure (TVF) at 1-year, a composite of cardiac death, target-vessel MI, and clinically driven target-vessel revascularization.**
- **Sample size was calculated, assuming a TVF rate of 8.5% at 1-year (based on previous trials[1,2] and further assumptions), with the non-inferiority margin set at 3.5%.**

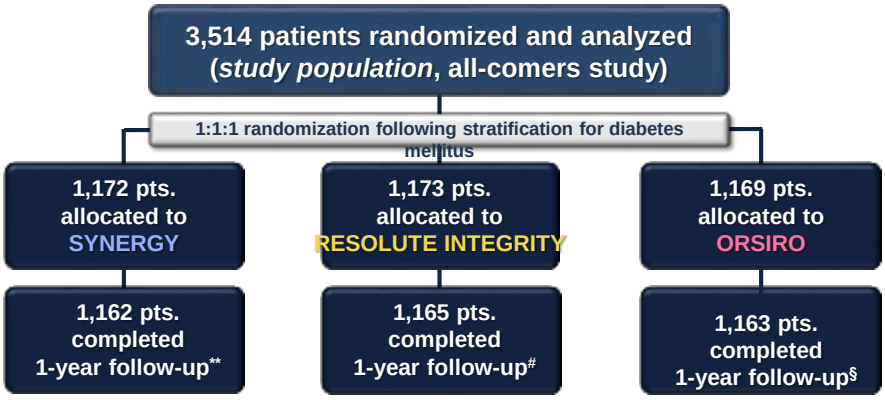
**A sample size of 3,540 randomized subjects would yield a power of at least 85% to detect non-inferiority with a one-sided alpha level of 0.025 (from 0.05 adjusted for multiple testing to 0.025), allowing for 3% loss to follow-up.**

**Sample size calculation was performed with PASS software (NCSS, Kaysville, UT, USA).**

Clemens von Birgelen @ TCT 2016

1. von Birgelen et al. J Am Coll Cardiol. 2012: TWENTE trial
2. Serruys et al. N Engl J Med. 2010: RESOLUTE All-comers trial

# Study Flow Diagram

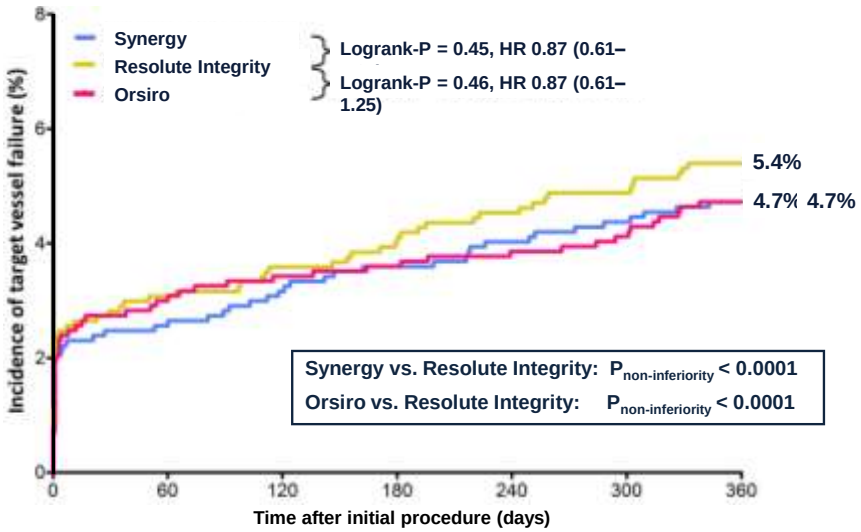



- 1-year follow-up data were obtained from 99.3% of the study population, which represents 99.9% of the patients who still participated in the trial or had died.
- During the first year of follow-up, 21 patients (0.6%) withdrew consent, while only
  3 / 3,514 patients (< 1 ‰) were actually "lost" (i.e., could not be contacted).

Clemens von Birgelen @ TCT 2016

# Primary Endpoint

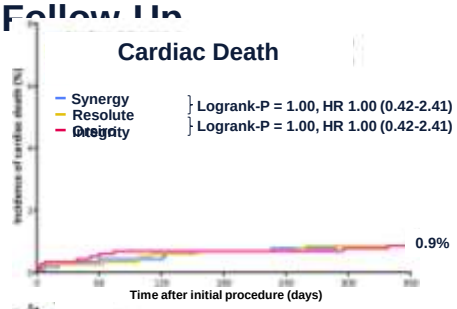
## Target Vessel Failure at 1-Year Follow-Up



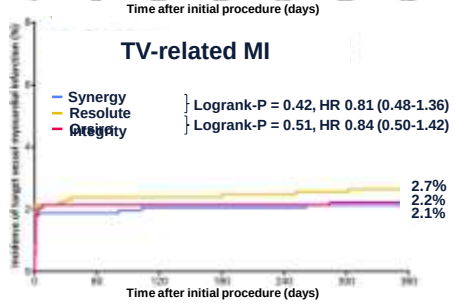

Clemens von Birgelen @ TCT 2016

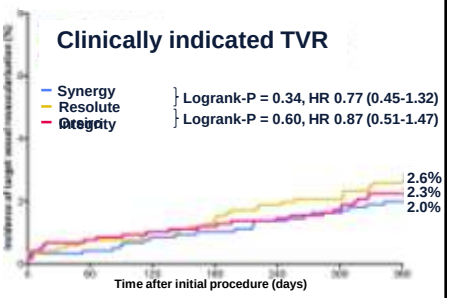
Vessel Failure is a composite of cardiac death, target vessel-related MI, or clinically driven target vessel revascularization.

# Components of TVF at 1-Year Follow Up




**At 1-year follow-up, there was no statistically significant difference between stent groups in the components of Target Vessel Failure (TVF).**




Clemens von Birgelen @ TCT 2016

TV-related MI was defined by the extended historical definition (Vranckx et al. (ARC), EuroIntervention 2010;5:871-4).

# Conclusion

- **Use of all three drug-eluting stents for the treatment of a complex all-comers population resulted in favorable clinical outcomes.**
- **Very thin strut everolimus-eluting Synergy and sirolimus-eluting Orsiro stents, which have dissimilar biodegradable polymer coatings, were non-inferior to the thin strut durable polymer zotarolimus-eluting Resolute Integrity stent.**
- **The absence of a loss of 1-year safety and efficacy with the use of the novel stents is a prerequisite before assessing potential benefits at longer term follow-up.**

Clemens von Birgelen @ TCT 2016

# Drug-Filled Stent

## Background

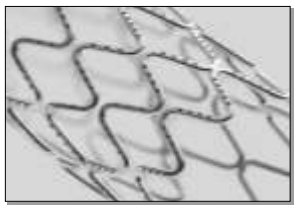
- Most drug-eluting stents (DES) use a polymer to control elution of an antiproliferative drug to reduce neointimal hyperplasia
- Alternatives to durable polymer DES also have shortcomings:
  - Bioabsorbable polymer technologies may increase inflammation during the polymer degradation phase
  - Polymer-free technologies have challenges controlling and sustaining drug elution
- The drug-filled stent (DFS, Medtronic, Santa Rosa, CA) is designed to achieve controlled and sustained drug elution without a polymer
  - Zero polymer exposure avoids adverse effects of polymer-induced inflammation and could potentially allow for a shorter DAPT duration



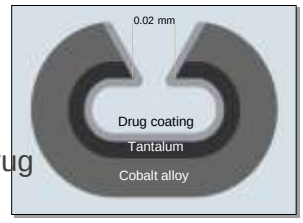
# Drug-Filled Stent

## Concept – I

- DFS is a novel polymer-free drug-eluting stent (81µm struts)



- DFS is made from a tri-layer wire:
  - Outer cobalt alloy layer for strength
  - Middle tantalum layer for radiopacity
  - Inner lumen continuously coated with drug

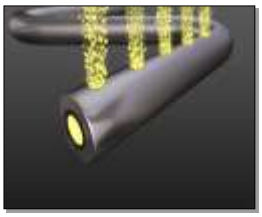


# Drug-Filled Stent

## Concept – II

- Drug (sirolimus) is protected and contained inside the stent
- Drug releases through abluminal laser-drilled holes
- Drug elution is controlled through natural diffusion via direct interaction with the vessel wall
- Elution profile is similar to durable polymer DES

Drug coats inner lumen



Drug elutes through abluminal holes

Uniform distribution in stented area

Stephen G. Worthley @ EuroPCR 2017

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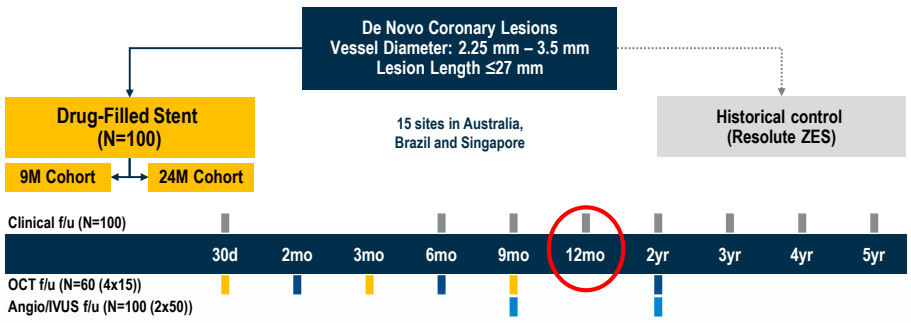
# RevElution Trial

## Study Design

PI: A. Abizaid, S. Worthley




| | |
|---|---|
| PRIMARY ENDPOINT: | In-stent late lumen loss at 9 months in 9M cohort (50 pts) |
| Key 2° Endpoints: | Major Adverse Cardiac Events (MACE), Target Lesion Failure (TLF) and components |
| QCA / IVUS Endpoints: | % diameter stenosis, in-segment late lumen loss, NIH volume and % volume obstruction |
| Key OCT Endpoints: | Stent strut tissue coverage, neointimal tissue thickness, stent (mal)apposition, % volume obstruction and NIH tissue characterization |
| Pharmacokinetic Analysis: | 12 PK timepoints up to 30 days will be assessed |
| DAPT Regimen: | ASA indefinitely and clopidogrel ≥ 6 months (12 months in pts not at high risk of bleeding) |

Study sponsor: Medtronic
NCT02480348

Worthley S, et al. *JACC Cardiovasc Interv*. 2017;10(2):147-156.

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# RevElution Trial

## Baseline Angiographic Characteristics

| % | 9 Month Cohort N=50 pts, 56 lesions |
|---|---|
| Target vessel location | |
| LAD | 52.0 |
| LCX | 32.0 |
| RCA | 26.0 |
| ACC/AHA lesion class – B2 | 50.0 |
| – C | 26.8 |
| TIMI 3 flow | 98.2 |
| RVD (mm) | 2.70 ± 0.43 |
| MLD (mm) | 0.97 ± 0.28 |
| % Diameter stenosis | 63.8 ± 9.5 |
| Lesion length (mm) | 12.85 ± 5.21 |
| Lesions treated per patient | 1.1 ± 0.3 |
| Radial approach | 86.0 |
| Lesion success[1] | 100.0 |
| Device success[2] | 100.0 |
| Procedure success[3] | 100.0 |

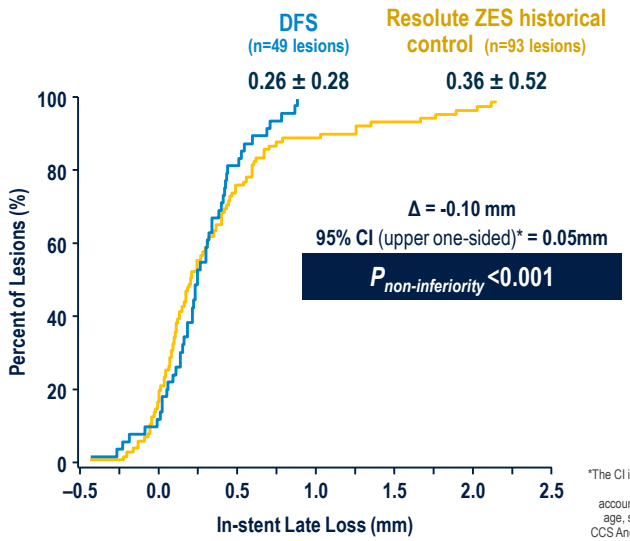
[1] The attainment of <50% residual stenosis of the target lesion using any percutaneous method.
[2] The attainment of <50% residual stenosis of the target lesion using only the DFS
[3] The attainment of <50% residual stenosis of the target lesion and no in-hospital MACE.

Worthley S, et al. *JACC Cardiovasc Interv*. 2017;10(2):147-156.



# RevElution Trial – Primary Endpoint

## Late Loss Cumulative Frequency Distribution at 9 Months



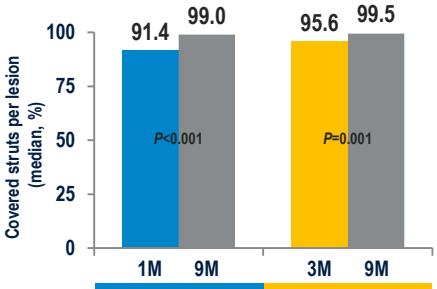

*The CI is based on a prespecified propensity score-based adjusted comparison, accounting for lesion-length, baseline RVD, age, sex, diabetes, history of MI and worst CCS Angina Class as independent variables.

Worthley S, et al. *JACC Cardiovasc Interv*. 2017;10(2):147-156.

# RevElution Trial

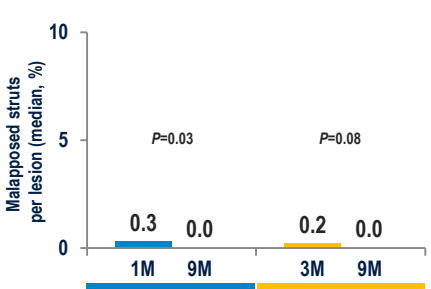
## OCT Results at 1, 3 and 9 Months

### Covered Struts




| | 1M OCT Cohort | | 3M OCT Cohort | |
|---|---|---|---|---|
| IQR | 84.8 to 93.2 | 97.9 to 99.8 | 90.3 to 97.2 | 98.3 to 100 |
| Mean | 89.3 ± 6.3 | 98.1 ± 2.7 | 92.9 ± 6.0 | 98.8 ± 2.0 |

### Malapposed Struts




| | 1M OCT Cohort | | 3M OCT Cohort | |
|---|---|---|---|---|
| IQR | 0 to 2.3 | 0 to 0 | 0 to 7.0 | 0 to 0 |
| Mean | 1.5 ± 2.3 | 0.1 ± 0.4 | 1.1 ± 2.2 | 0.3 ± 0.8 |

1M: n=14 patients, 17 lesions, 19 stents, 605 cross-sections and 7403 struts analyzed
3M: n=15 patients, 17 lesions, 19 stents, 651 cross-sections and 7451 struts analyzed
9M: n=25 patients, 29 lesions, 32 stents, 1102 cross-sections and 12819 struts analyzed

Worthley S, et al. *JACC Cardiovasc Interv*. 2017;10(2):147-156.



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# RevElution Trial

## Clinical Results at 12 Months (DFS first 50 pts)

| % (n) | 30 Days (n=50 pts) | 12 Months (n=50 pts) |
|---|---|---|
| **Death (all)** | 0 | 0 |
| **Cardiac** | 0 | 0 |
| **Target vessel MI** | 0 | 4.0 (2) |
| **Q-wave** | 0 | 0 |
| **Non-Q-wave** | 0 | 4.0 (2) |
| **Cardiac death or target vessel MI** | 0 | 4.0 (2) |
| **ARC definite/probable ST** | 0 | 0 |
| **Early** (0-30 days) | 0 | 0 |
| **Late** (31-360 days) | 0 | 0 |
| **Clinically-driven TLR** | 0 | 2.0 (1) |
| **Clinically-driven TVR** | 0 | 2.0 (1) |
| **TLF** (cardiac death, TV-MI, TLR) | 0 | 4.0 (2) |
| **TVF** (cardiac death, TV-MI, TVR) | 0 | 4.0 (2) |
| **MACE** (death, MI, TLR, emCABG) | 0 | 4.0 (2) |



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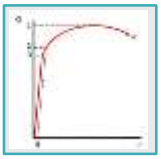
Not CE marked – not yet available

## Which material selection criteria are important for a BRS?


**Biocompatibility profile**[1]:
Material should not produce any negative local or systemic side effects

**Resorption parameters:**
Need to be carefully controlled to ensure material resorption in a timely manner without causing tissue damage or inflammation. At the same time it also ensures vascular support during healing process.
Ideally, resorption should occur within 1 year[2]



**Mechanical characteristics**[1]:
Material & Design have to be adapted (e.g. yield strength, tensile strength, elongation) to achieve optimal scaffold performance
(e.g. prevent for strut breakage with high flexibility while expansion)

1. Heiden et al. *J Biotechnol Biomater* 2015
2. Garg et al. Biodegradable and non-biodegr. Stents. *Minerva Cardioangiol* 2009;

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Not CE marked – not yet available

## Which materials can be used for BRS?

Current BRS technologies are

**Polymeric materials**

**Natural metallic elements**

Garg et al. Biodegradable and non-biodegr. Stents, Minerva Cardioangiol 2009

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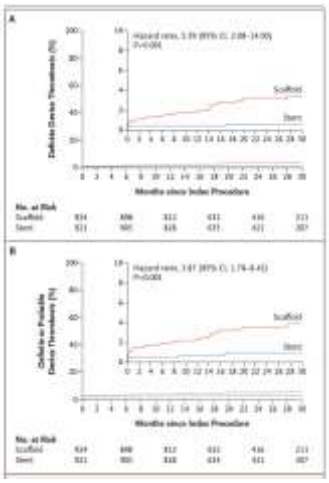
# AIDA: Bioresorbable Scaffolds versus Metallic Stents in Routine PCI

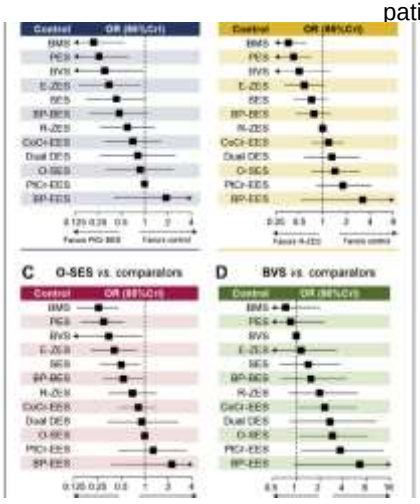


- Randomised: EES vs BVS
- 924 vs 921 pts
- no significant difference in the rate of TVF between the patients who received a bioresorbable scaffold and the patients who received a metallic stent
- The bioresorbable scaffold was associated with a higher incidence of device thrombosis than the metallic stent through 2 years of follow-up

JJ Wyrzykowska et al. NEJM 2017

# Stent Thrombosis With Drug-Eluting Stents and Bioresorbable Scaffolds

Evidence From a Network Meta-Analysis of 147 Trials (n=126,526 patients)




- Contemporary DES, including biocompatible DP-DES, BP-DES, and polymer-free DES, showed a low risk of definite or probable stent thrombosis at 1 year
- BVS had an increased risk of device thrombosis compared with CoCr-EES, PtCr-EES, and H-SES
- Data from extended follow-up are warranted to confirm the long-term safety of contemporary coronary devices.

Si-Hyuck Kang et al, J Am Coll Cardiol Intv 2016

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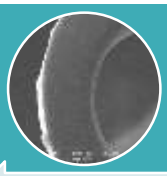
## Magmaris components

**A combination of proven Orsiro elements and the benefits of a resorbable Magnesium Scaffold**

**Backbone**
Mg alloy
Tantalum markers

6-crown & 2-link design

150µm strut thickness

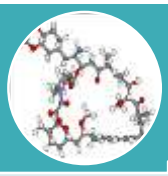


**Coating**
PLLA

Proven resorption profile

Proven technology identical to Orsiro coating

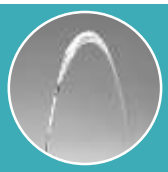
**BIOlute**



**Drug**
Limus

1.4 µg/mm² same as for Orsiro

Release kinetics comparable to Orsiro



**Delivery system**
RX, 0.014"

6F compatible

Adapted from Orsiro system

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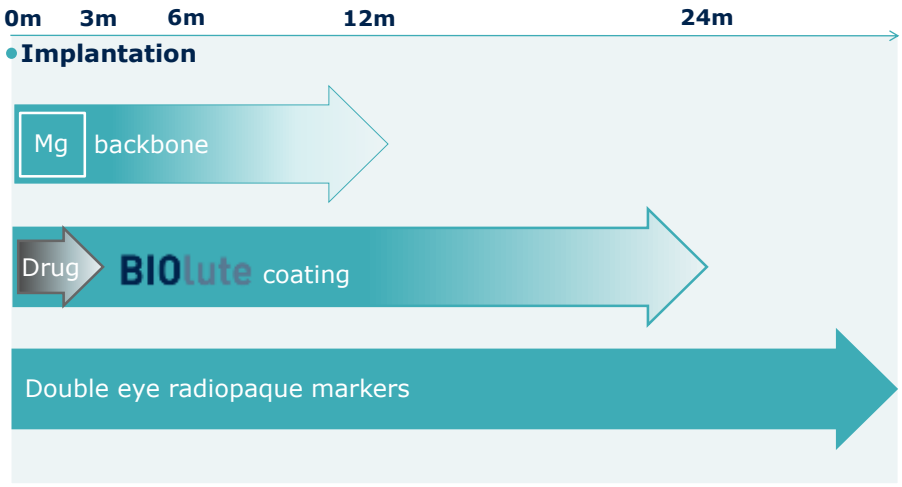
## Magmaris resorption process over time

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## Magmaris resorption in OCT imaging

BIOSOLVE-II

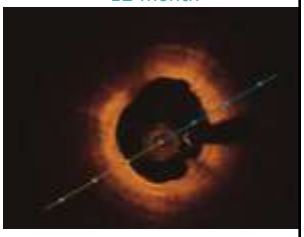
Post-Implantation

Immediately after implantation, struts are well apposed to the vessel wall.

6 month

While the Magnesium resorption process continues, endothelialization progresses.

12 month



At 12 months after implantation, the Magnesium resorption is almost completed.

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BIOSOLVE-II case, GER443-001. Courtesy of M. Haude, Lukaskrankenhaus Neuss, Germany 2015.

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## Clinical Results TLF rate at 6-month

BIOSOLVE-II

| | n=120 | % | 95% CI |
|---|---|---|---|
| **TLF[1]** | 4 | 3.3 | 1.3-8.3 |
| Cardiac Death | 1[2] | 0.8 | 0.0-4.6 |
| Target Vessel MI | 1 | 0.8 | 0.0-4.6 |
| Clinically driven TLR | 2 | 1.7 | 0.2-5.9 |
| CABG | 0 | 0.0 | 0.0-3.1 |
| **Scaffold Thrombosis Definite or probable** | 0 | 0.0 | 0.0-3.1 |

1. Composite of cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization and CABG
2. 58 old smoker, CV RF: hypertension and hyperlipidemia, stable angina CCS Class II, treated with a DREAMS 2G 3.0x20mm in the distal RCA. Patient experienced an unwitnessed death 134 days post procedure. Since a cardiac cause could not be ruled out, patient was adjudicated as cardiac death by the Clinical Event Committee

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Prof. Haude, First Report Investigations of BIOSOLVE-II, TCT 2015

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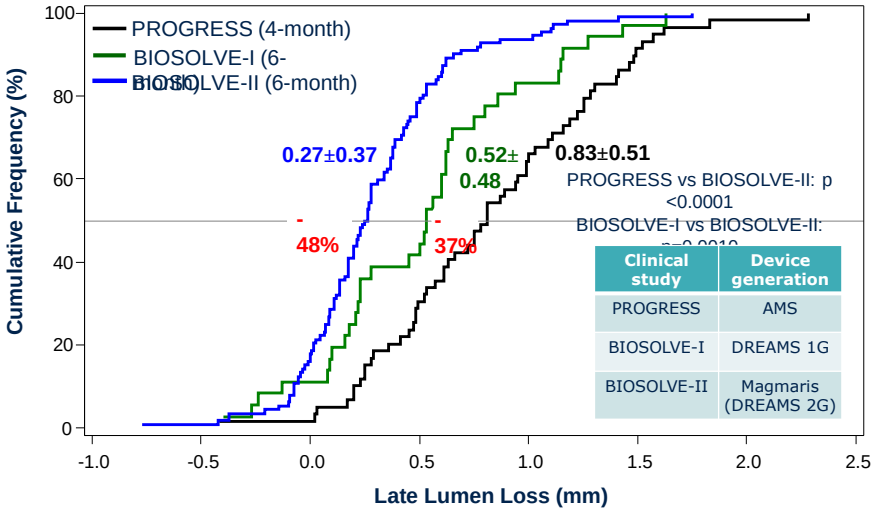
Not CE marked – not yet available

## Comparison of in-segment LLL in PROGRESS, BIOSOLVE-I and BIOSOLVE-II

BIOSOLVE-II




| Clinical study | Device generation |
|---|---|
| PROGRESS | AMS |
| BIOSOLVE-I | DREAMS 1G |
| BIOSOLVE-II | Magmaris (DREAMS 2G) |

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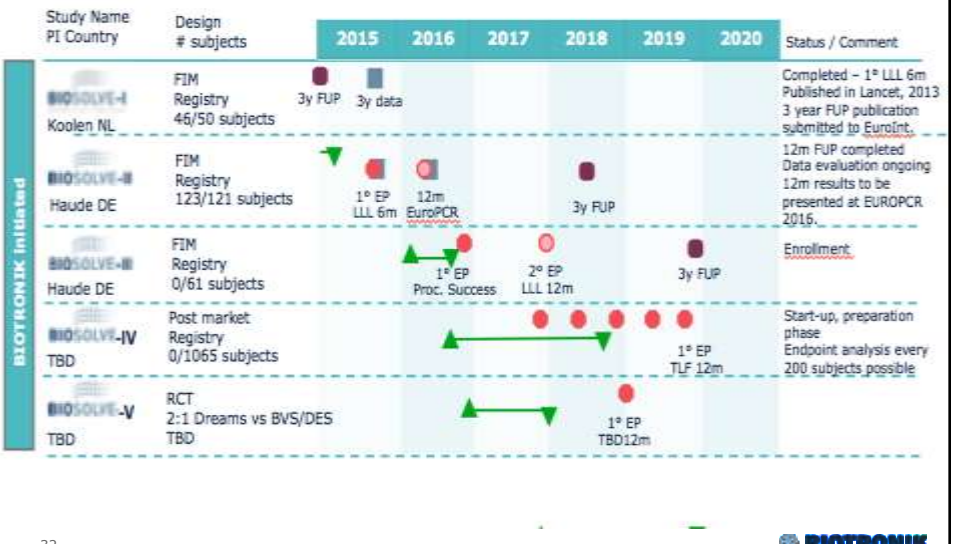
R Erbel et al, Lancet 2007; 369:1869-75, M Haude. et al. Lancet 2013; 381:836-44

Not CE marked – not yet available

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# CONCLUSIONS

- Biodegradable polymer DES and drug-filled stents shows similar efficacy and safety as second generation durable biocompatible polymer DES
- DAPT with 2nd generation DES may be shorter (1 month) in patients with high risk of bleeding
- Bioabsorbable DES – promising, but currently still under investigation. More randomised trials vs 2nd generation DES are needed.