MedStar Heart Institute | Cleveland Clinic Heart and Vascular Institute

CARDIOVASCULAR SUMMIT TCTAP 2015

What Can We Look Forward From the Magnesium Scaffold?

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Boston Scientific • Biotronik • Biosensors • Astra Zeneca
• Consulting Fees/Honoraria	• Medtronic Vascular • Abbott Vascular

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Rationale for Bioabsorbable Magnesium Scaffold

- Bioabsorbable Mg is a metallic scaffold that temporarily support the vessel, and additionally can release a drug similar to a permanent DES.
- Absorption rate can be manipulated by modifications of the alloy, allowing to resume the vessel natural physiology faster then PLLA.
- Magnesium alloy has a similar radial force to stainless still and cobalt chromium stent.
- Profile of metallic scaffolds is superior to PLLA and they are more deliverable.
- Metallic bioresorbable scaffolds feels like metallic stent and bioabsorbed within 6-12 for Mg.

Key characteristics of absorbable scaffold materials

Material	Stainless Steel (316L)[3]	PLLA[1]	Iron[4]	Magnesium Alloy[2]
Tensile Strength (MPa)	500	~30-45	300	280
Tensile Modulus (GPa)	193	1.2 – 3.0	200	45
Elongation (%)	48	2 – 6	25	23
Total Degradation Time	N/A	2-3 Years	> 4 years	~ 12 months

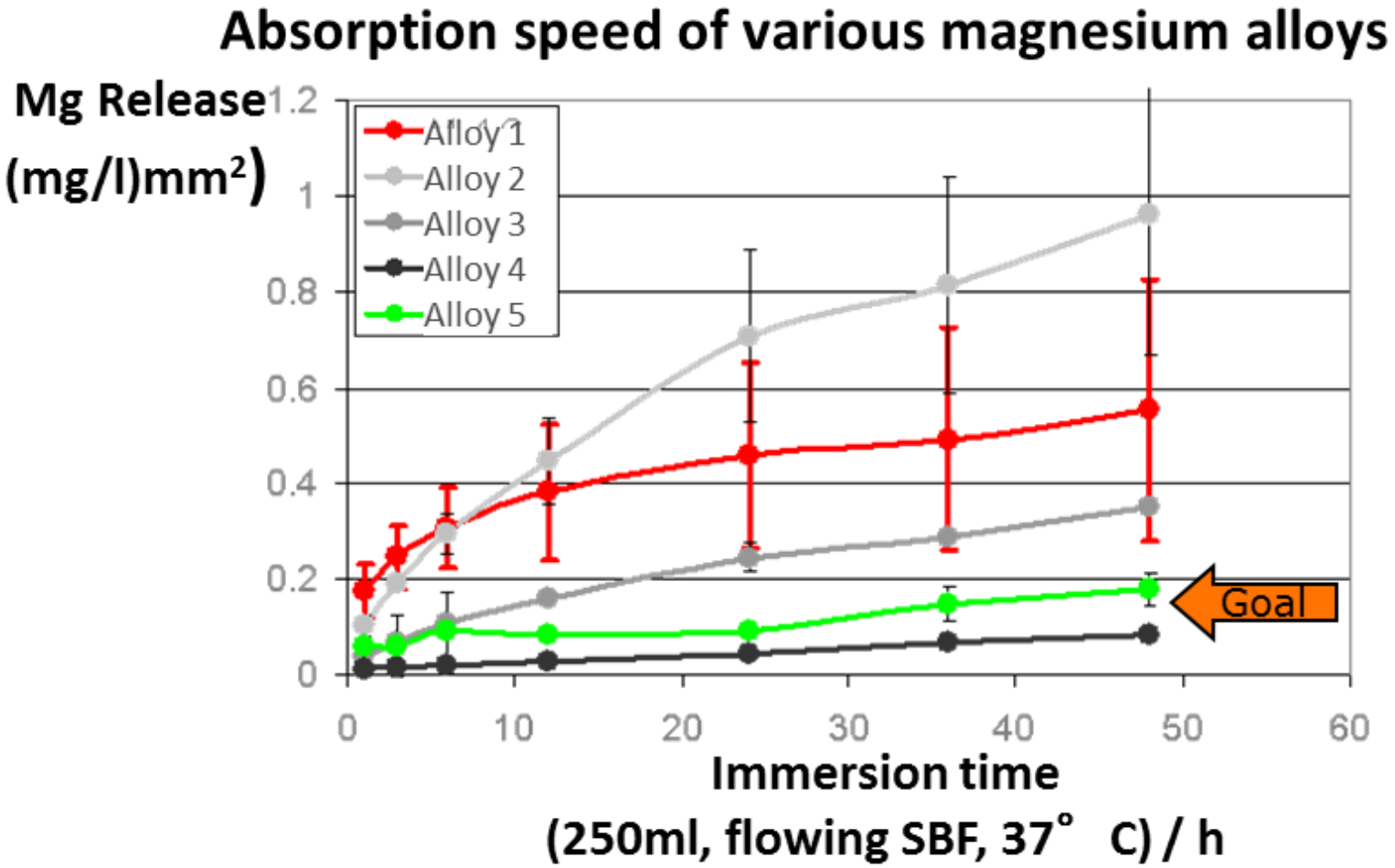
Advantages of magnesium:

- **Well-suited mechanical properties**
- **No time-dependant mechanical performance**
- **No material aging**
- **Deployment capabilities of >+2.0mm beyond nominal**
- **Very good biocompatibility**
  - Magnesium is an essential element in the human body
  - Total magnesium in body: 30 g
  - daily need: ~ 350 mg
  - Total Mg mass of scaffold: 8.5 mg

[1] Ratner BD, *et al*., editors, *Biomaterials Science, An Introduction to Materials in Medicine*, 2nd Edition (2004).
[3] Poncin P, *et al*., Stent Tubing: Understanding the Desired Attributes, *Materials & Processes for Medical Devices Conference* (2003).
[2/4] H. Hermawan et al. / Acta Biomaterialia 6 (2010) 1693–1697

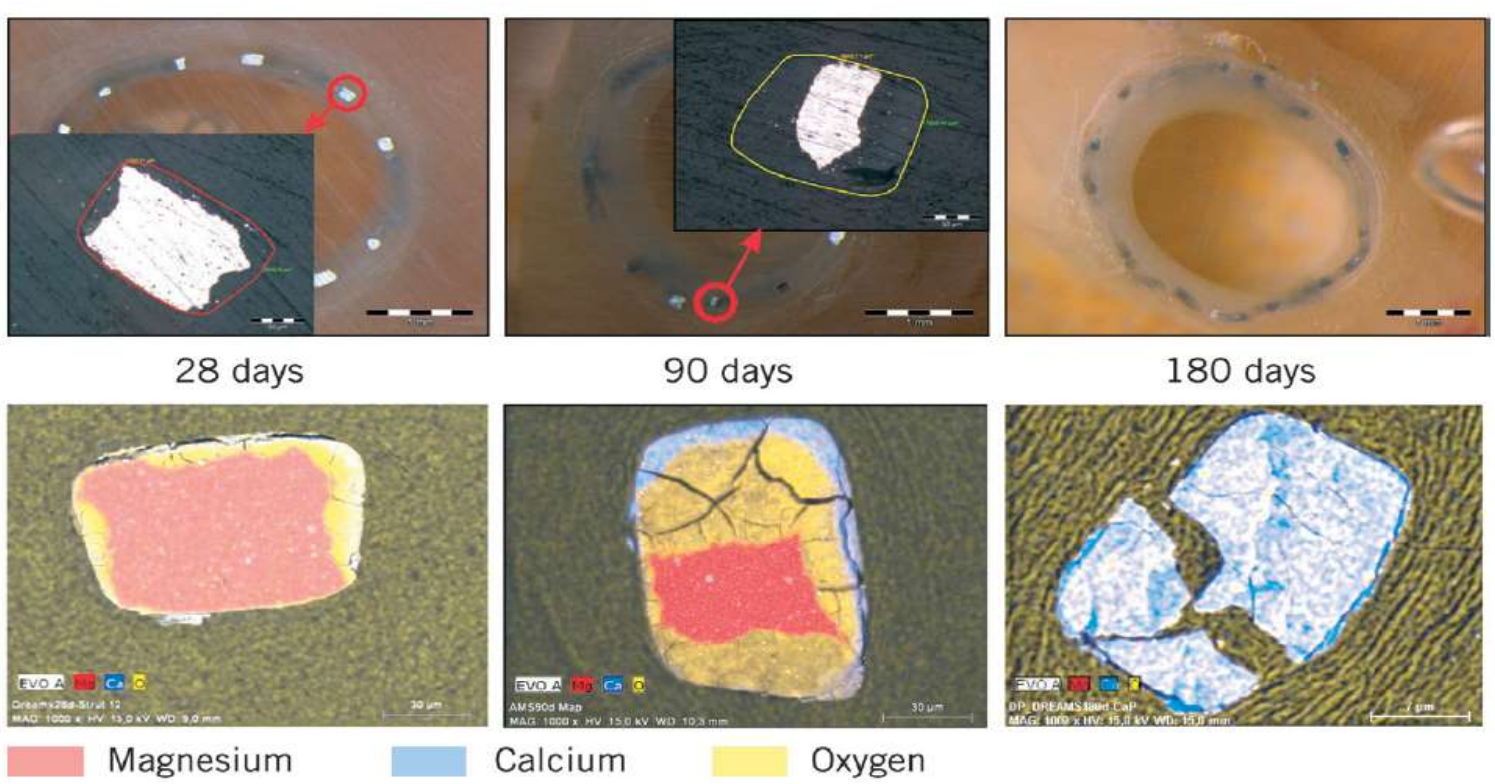
Not all magnesium alloys are created equally

- **Adding <u>alloying elements</u> to magnesium can significantly alter the absorption speed**



In-vivo magnesium absorption

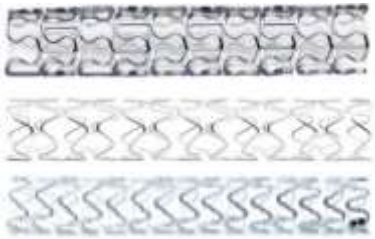
Animal histopathology demonstrates the process of bioabsorption: Magnesium is converted (by the body) into a soft amorphous calcium phosphate it can later absorb

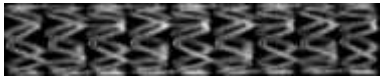


* Energy-dispersive X-ray spectroscopy was used to make can make elemental characterizations

Source: Wittchow E, et al. EuroIntervention 2013;8:1441-1450.

Absorbable Mg Scaffold Programs





Scaffold	
Biotronik AMS	Mg-Alloy
Biotronik DREAMS I	Mg-Alloy + Paclitaxel
Biotronik DREAMS II	Mg-Alloy + Sirolimus
Medtronic	Mg-Alloy + Sirolimus
BSCI	Mg-Alloy
QualiMed UNITY	Mg-Alloy + Polymer (Hybrid)

Biotronik Mg Scaffold Program: 1. Generation Bare AMS

PROGRESS-AMS	4 mo n = 63	12 mo n = 60
Late loss (mm)	**1.08 ± 0.49**	**-**
Cardiac death	**0**	**0**
MI	**0**	**0**
Scaffold thrombosis	**0**	**0**
TLR (clinically driven)	**23.8%**	**26.7%**

Bare absorbable magnesium scaffold (AMS)

- WE43 magnesium alloy
- Strut thickness of 165 µm
- 4-crown design
- Uncoated. no drug
- Used in PROGRESS-AMS study

Learnings from bare AMS

- Device was safe/feasible
- Effectiveness required optimization
- IVUS findings showed lumen loss was due to loss of scaffolding area and NIH
- 7 year FUP: No additional safety concerns between 1 to 7 years

DREAMS: 1st generation DRug-Eluting Absorbable Metal Scaffold
- Design Overview -

Scaffold Backbone

- Proprietary Mg-alloy
- 120µm strut thickness

Drug carrier

- 1 µm bioabsorbable PLGA Polymer

Delivery system

- Modified PRO-Kinetic Energy
- 6F compatible

Drug

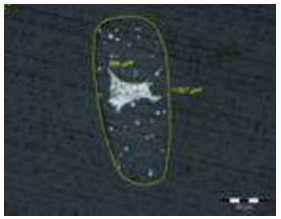
- Paclitaxel
- Proven elution behaviour

Biotronik Mg Scaffold Program: Paclitaxel Eluting AMS (DREAMS 1. Gen.)

AMS

No coating

No drug



28-day histology

- Refined Mg alloy with Slower absorption rate
- Reduced strut thickness
- 6-crown design
- PLGA polymer carrier
- Paclitaxel drug elution

DREAMS

1st generation

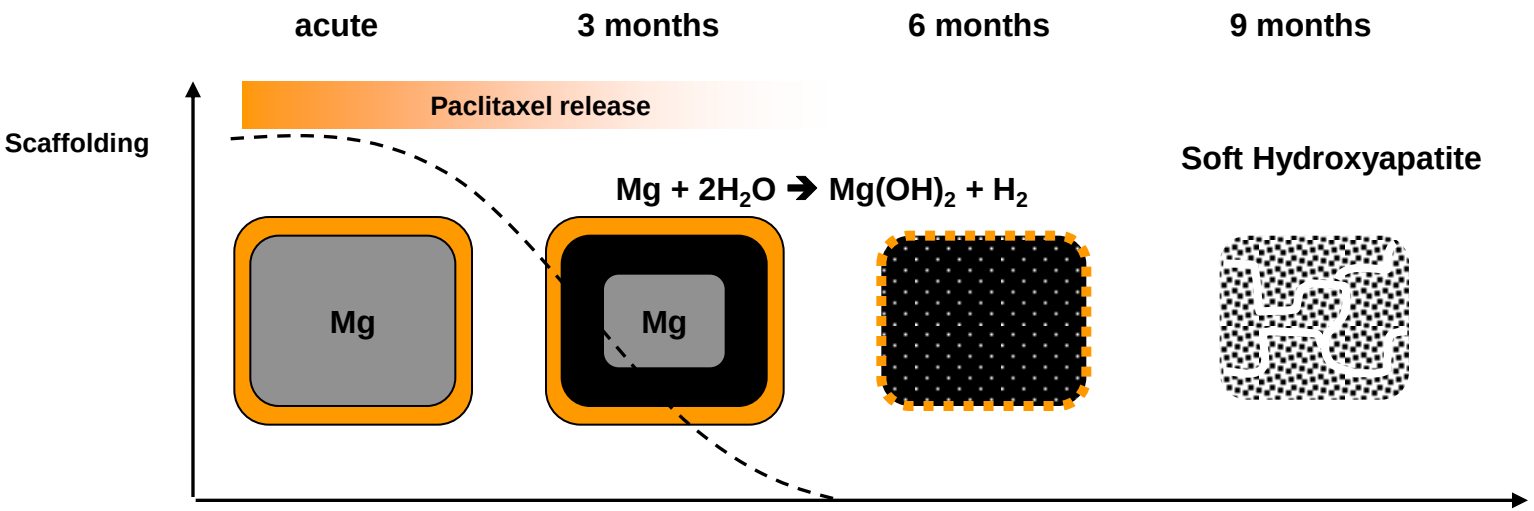
BIOSOLVE-I

PLGA Polymer

+Paclitaxel

90 day faxitron

DREAMS provides scaffolding and paclitaxel release up to 3 months



- Stable Mg backbone
- Stable drug carrier layer
- Controlled drug release

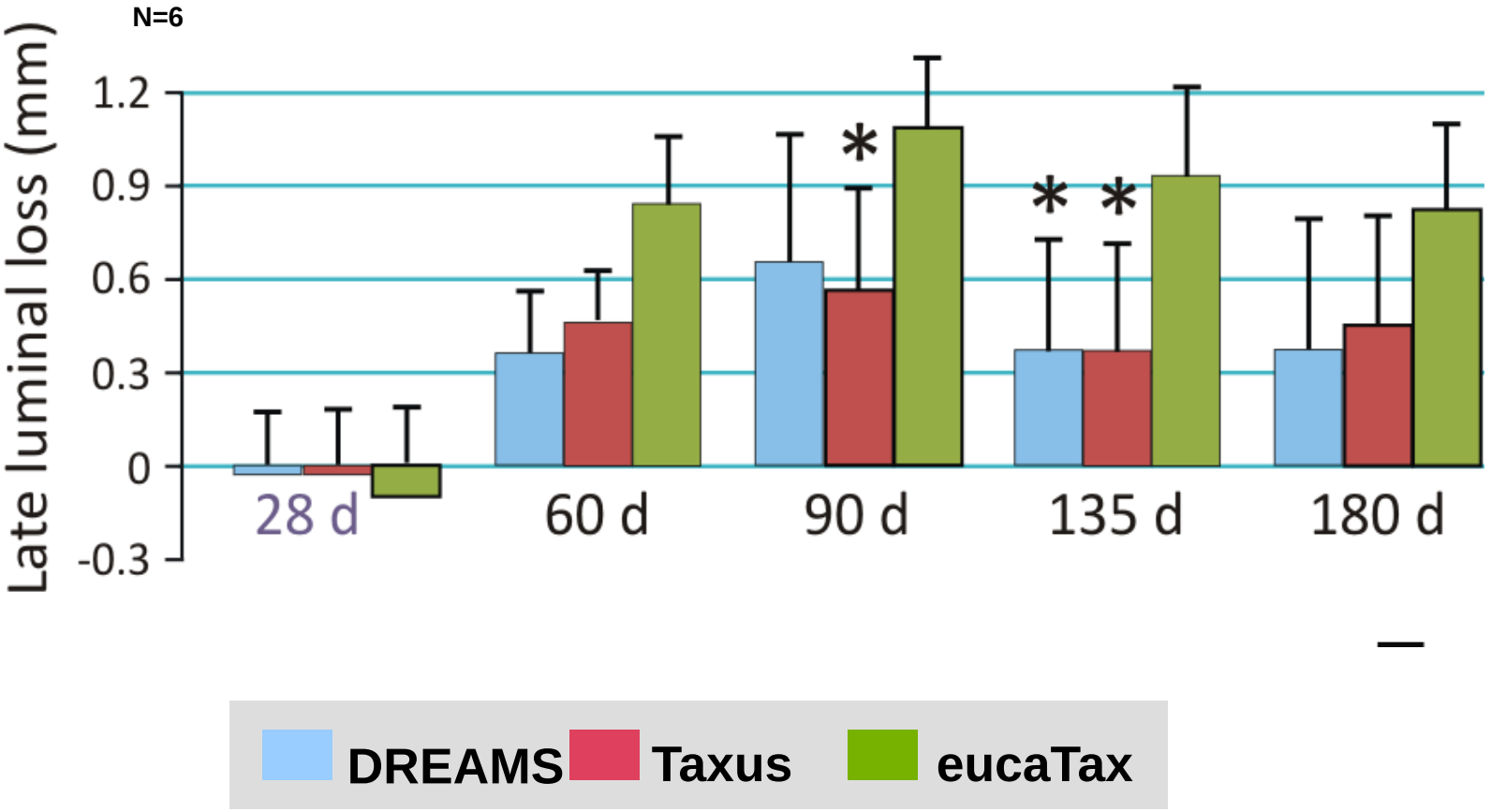
- Mg degradation completed
- Drug release completed
- Degradation of polymer ongoing

- Conversion of degradation product completed
- Drug carrier layer degradation completed
- Beginning of structural disintegration

Mg alloy
Mg degradation product
Polymer

Biotronik Mg Scaffold Program: Paclitaxel Eluting AMS (DREAMS 1. Gen.)

- **Preclinical animal data**



* *statistically significant*

Source: Wittchow E, et al. EuroIntervention 2013, 8: 1441-1450.

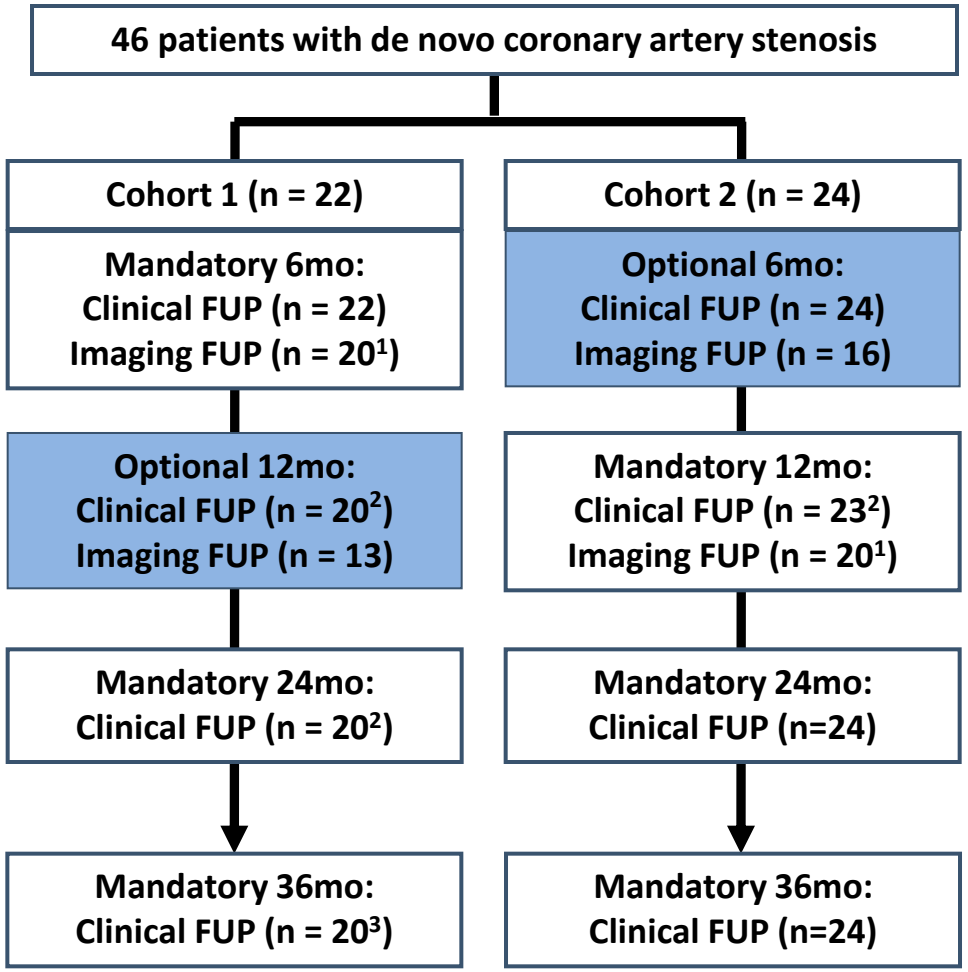
BIOSOLVE-I study design

- **DESIGN:**
  Prospective. multi-center. FIM. single *de novo* coronary artery lesions between 3.0-3.5 mm and ≤ 12 mm long

- **PRIMARY ENDPOINT:**
  Cohort 1: TLF at 6 months
  Cohort 2: TLF at 12 months

- **PRINCIPAL INVESTIGATOR:**
  J. Koolen. MD. Catharina Ziekenhuis. Eindhoven. Netherlands

[1] 5 pts withdrew consent for imaging FUP (2 at 6-month and 4 at 12-month FUP)
[2] 1 pt died a non-cardiac death (Cohort 1). 2 pts withdrew consent (1 Cohort 1 and 1 Cohort 2)
[3] 1 pt died a non-cardiac death 1 pt withdrew consent



BIOSOLVE-I

M Haude. et al. Lancet 2013; 381:836-44.

BIOSOLVE-I study results

Six to 36-month clinical follow-up

Device success	100% (47 / 47)
Procedure success	100% (46 / 46)

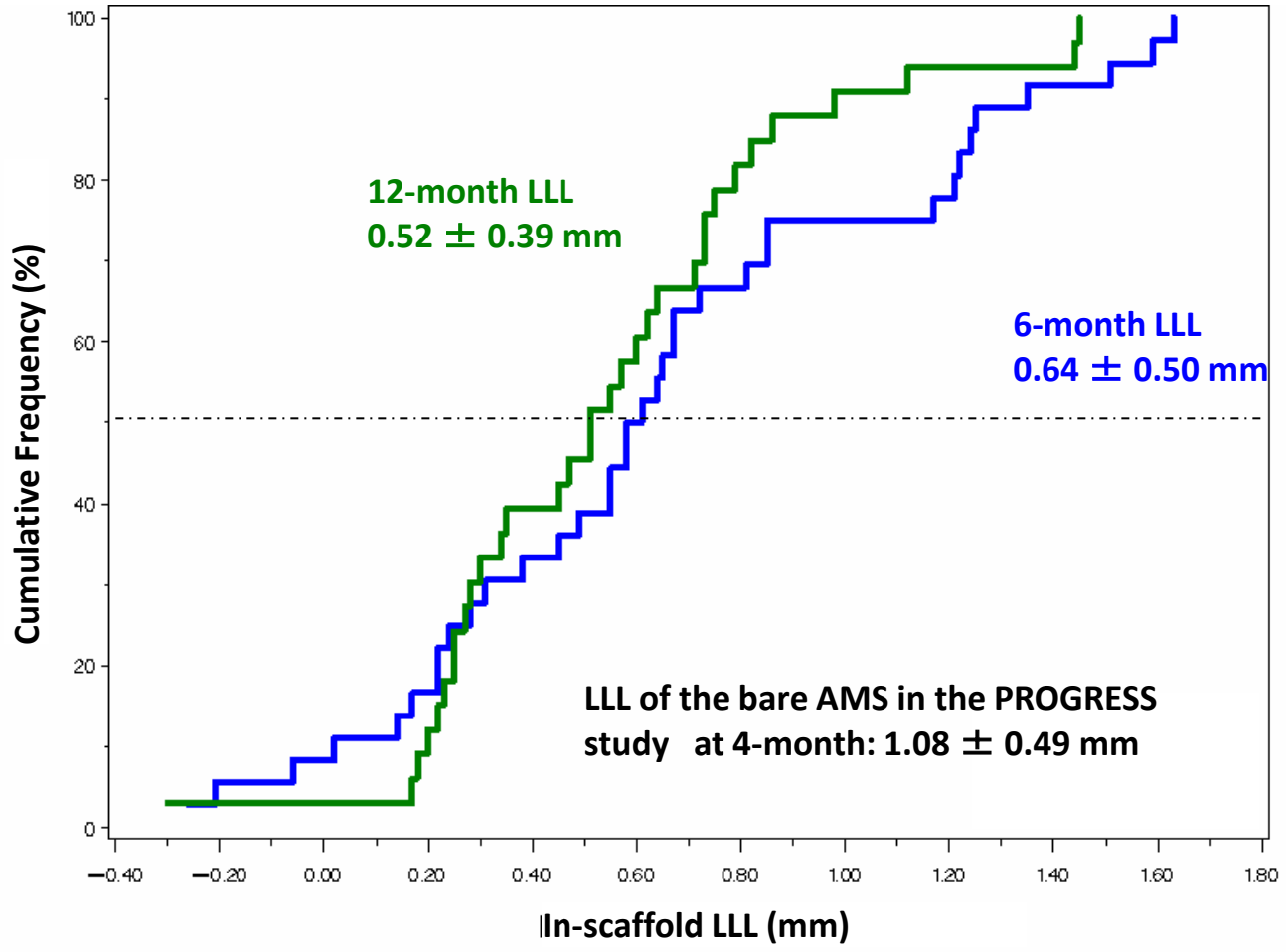
Clinical results	6-month[1]	12-month[1]	24-month	36-month
	Cohort 1&2	Cohort 1&2	Cohort 1&2	Cohort 1&2
TLF	4.3% (2/46)	6.8% (3/44)	6.8% (3/44)	6.8% (3/44)
Cardiac death	0.0%	0.0%	0.0%	0.0%
MI[2]	0.0%	2.3% (1/44)	2.3% (1/44)	2.3% (1/44)
Scaffold thrombosis	0.0%	0.0%	0.0%	0.0%
TLR (clinically driven)[3]	4.3% (2/46)	4.5% (2/44)	4.5% (2/44)	4.5% (2/44)

Device Success: successful delivery of the scaffold to the target lesion, appropriate deployment, successful removal of delivery system.
Procedure Success: device success plus attainment of a final residual stenosis of <50% of the target lesion. Absence of MACE during the hospital stay up to 7 days.
[1]M Haude. et al. Lancet 2013; 381:836-44. [2] Target vessel peri-procedural MI. [3] TLR occurred during 6M FUP, both subjects had angina. 1 subject received an additional DREAMS during the initial procedure due to a flow-limiting bailout.

BIOSOLVE-I

BIOSOLVE-I study results

6-and 12-month late lumen loss (LLL)

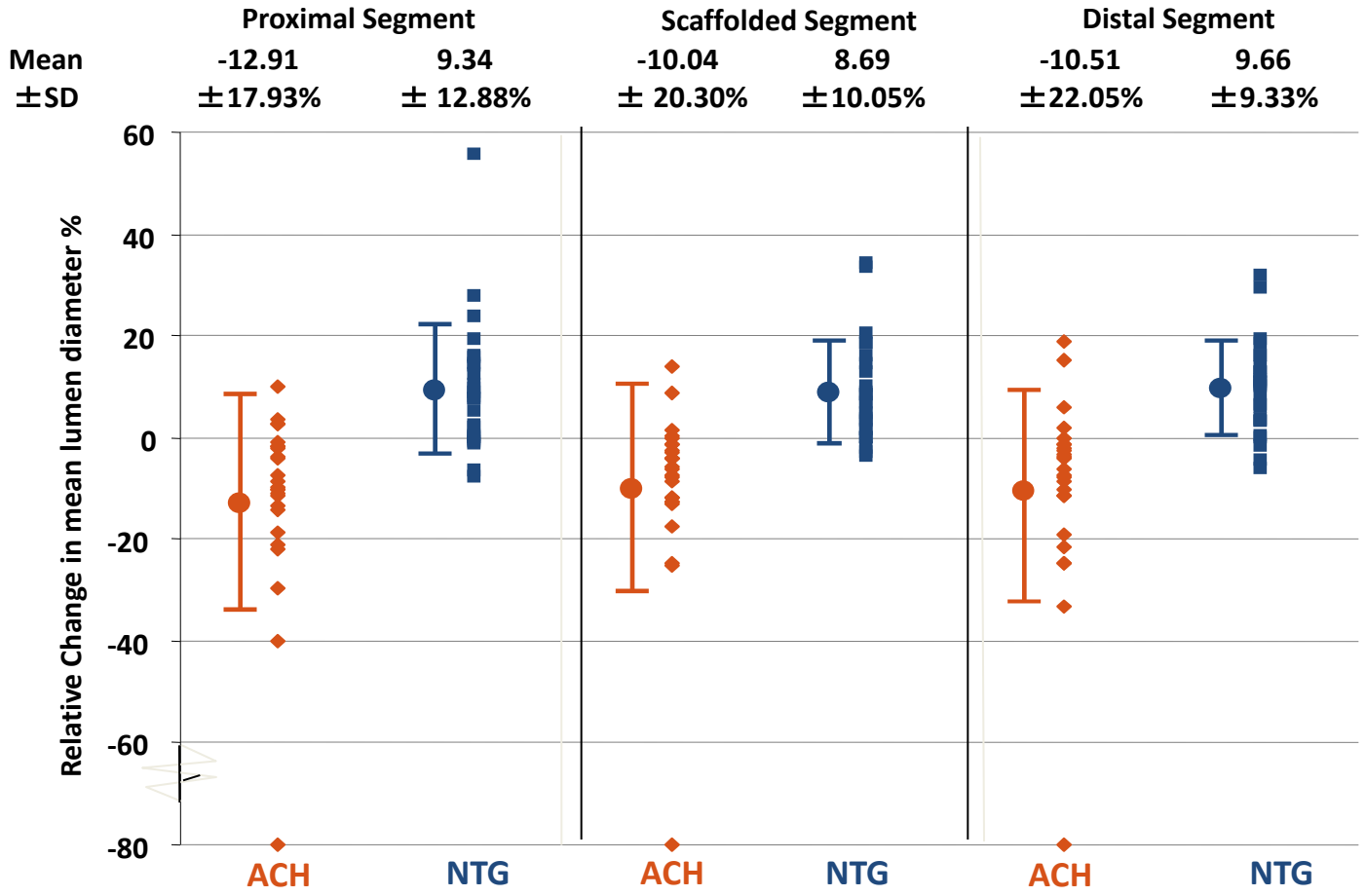


BIOSOLVE-I

M Haude. et al. Lancet 2013; 381:836-44.

BIOSOLVE-I study results

Vasomotion results at 6-month (N=26)



ACH concentration

- Low: 0.36 µg/mL
- Medium: 3.6 µg/mL
- High: 18 µg/mL

Nitro concentration

- 200 µg/mL

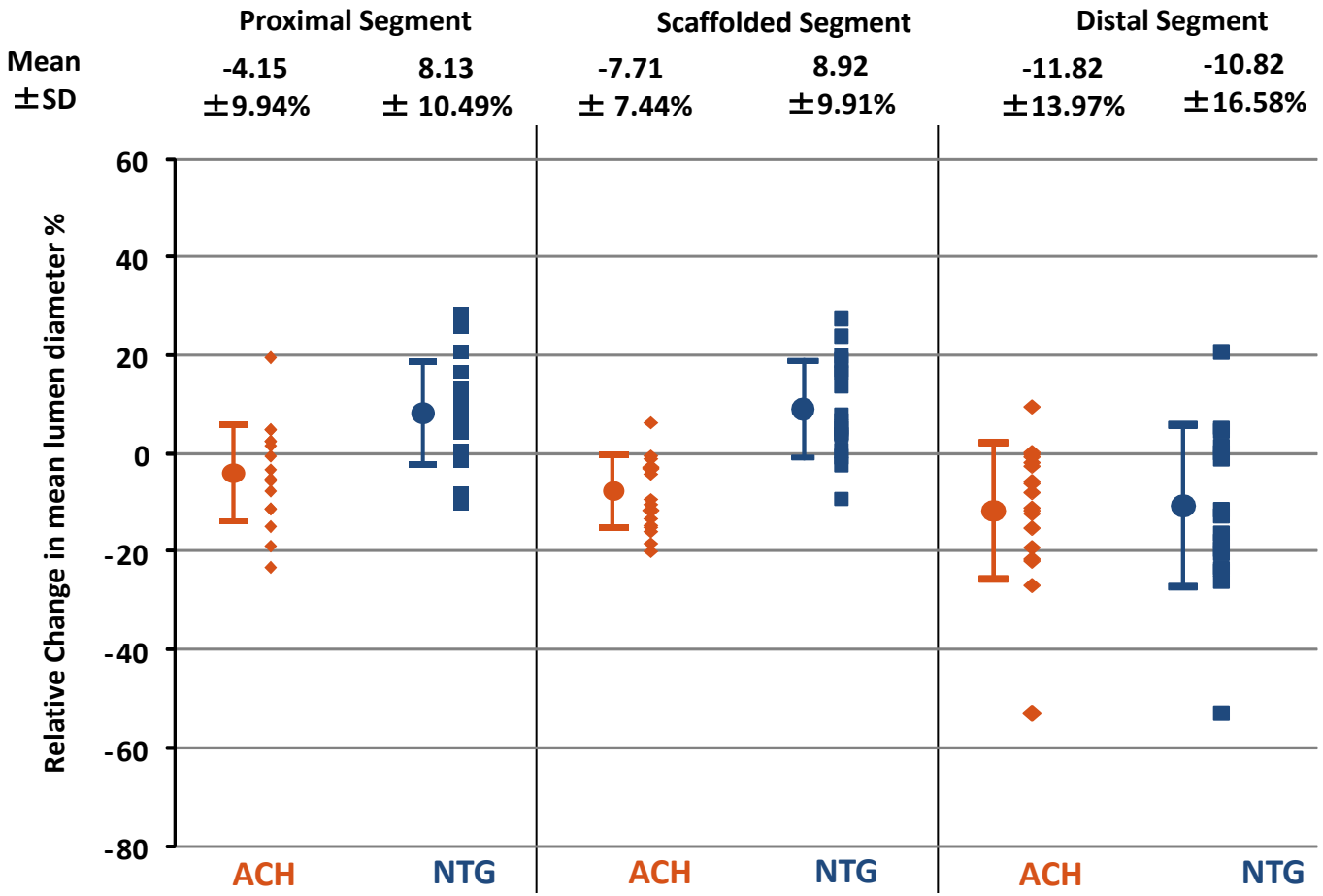
Acetylcholine (ACH): Presents the % change in mean lumen diameter between pre-and post-Acetylcholine (ACH) at the highest response

Nitroglycerine (NTG): Presents the % change in mean lumen diameter between post-ACH and Nitroglycerine

BIOSOLVE-I

BIOSOLVE-I study results

Vasomotion results at 12-month (N=18)



ACH concentration
Low: 0.36 µg/mL
Medium: 3.6 µg/mL
High: 18 µg/mL

Nitro concentration
200 µg/mL

Acetylcholine (ACH): Presents the % change in mean lumen diameter between pre-and post-Acetylcholine (ACH) at the highest response

Nitroglycerine (NTG): Presents the % change in mean lumen diameter between post-ACH and Nitroglycerine

BIOSOLVE-I

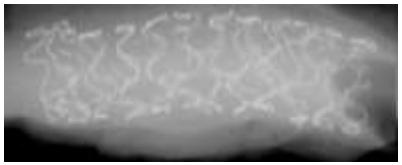
Biotronik Mg Scaffold Program: Sirolimus Eluting AMS (DREAMS 2. Gen.)

DREAMS
1st generation
BIOSOLVE-I

Magnesium

PLGA Polymer

+Paclitaxel



90 day faxitron

- 120-150µm strut thickness
- Addition of radiopaque markers at both ends
- Increased post-dilatation capabilities
- PLLA polymer carrier
- Sirolimus drug elution

DREAMS
2nd generation
BIOSOLVE-II

Magnesium

PLLA Polymer

+Sirolimus

90 day faxitron

Biotronik Mg Scaffold Program: Sirolimus Eluting AMS (DREAMS 2. Gen.)

ORSIRO DES Delivery System

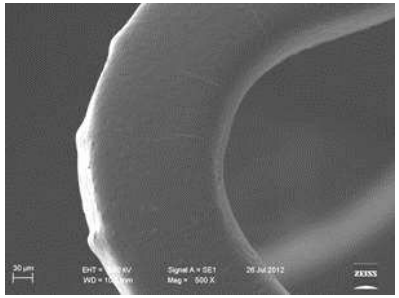
- RX, 0.014”
- 6F compatible
- Adapted from ORSIRO DES† delivery system

Bioabsorbable Scaffold

- Magnesium backbone
- 6-crown 2-link design
- 150µm strut thickness
- Fully absorbed*

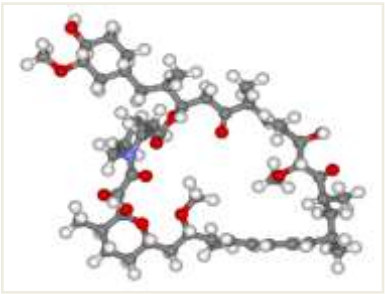
Bioabsorbable Coating

- Poly-L-lactide, PLLA
- Naturally absorbed
- Identical to ORSIRO DES



Sirolimus

- Proven clinical history
- Identical dose density and release rate to ORSIRO DES

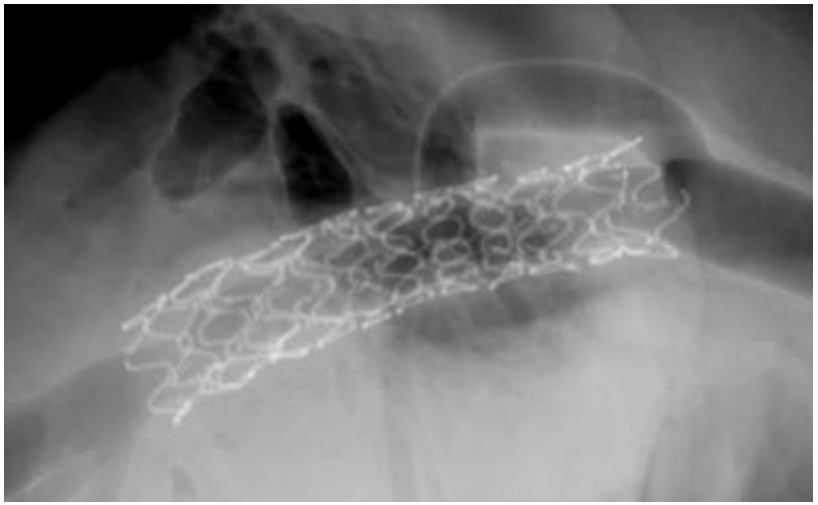


† CE marked Feb 2011
* Except for Ta/polymer markers

Biotronik Mg Scaffold Program: Sirolimus Eluting AMS (DREAMS 2. Gen.)

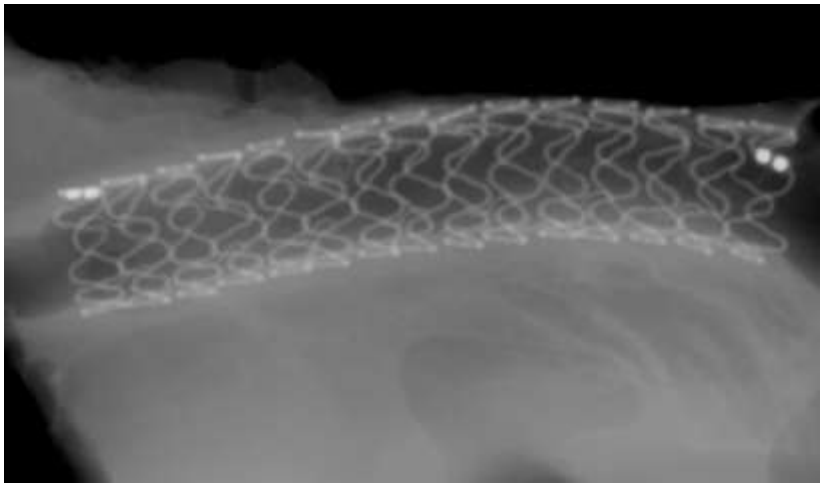
Prolonged scaffolding Faxitron imaging 90 days

DREAMS
1st Generation



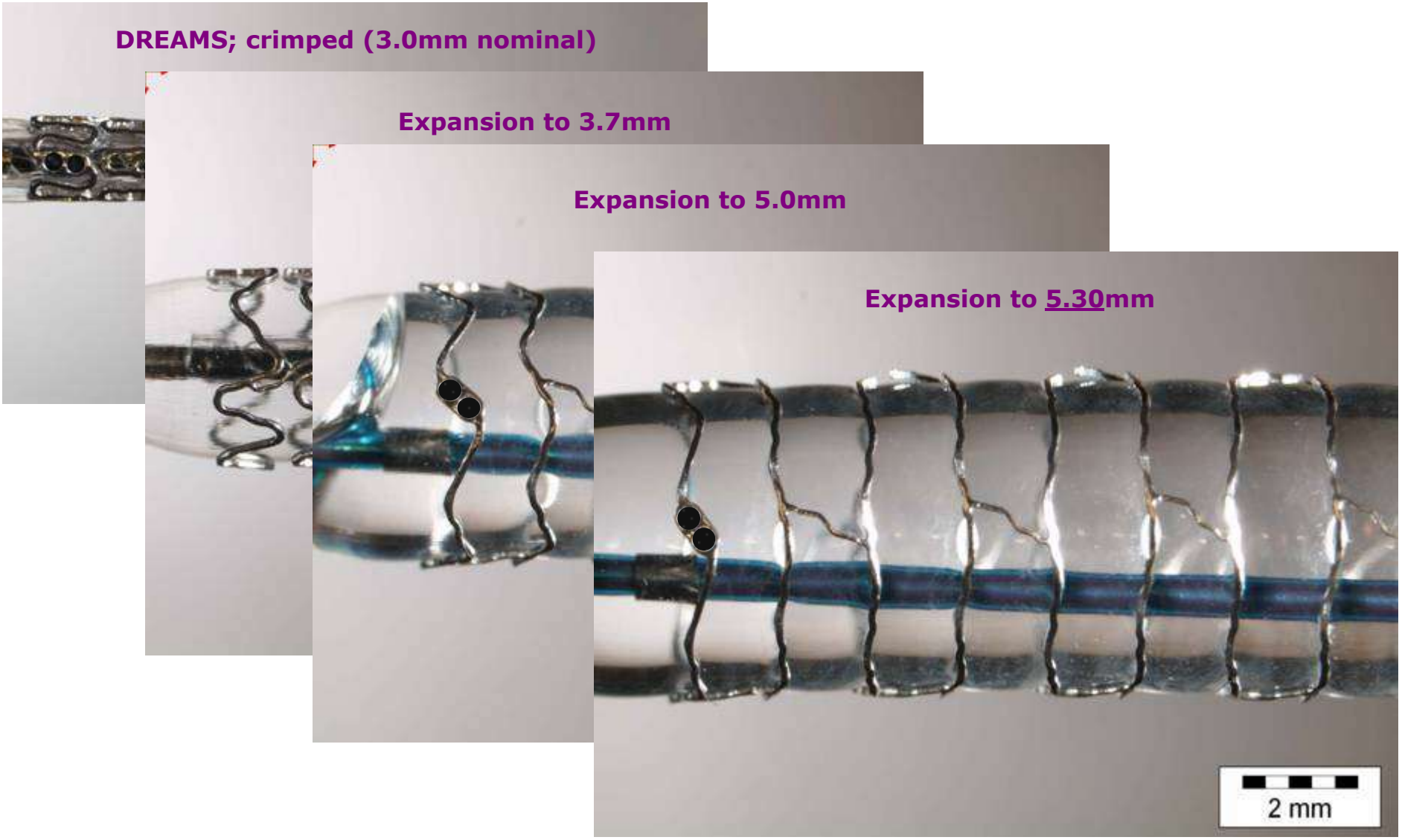
90d

DREAMS
2nd Generation



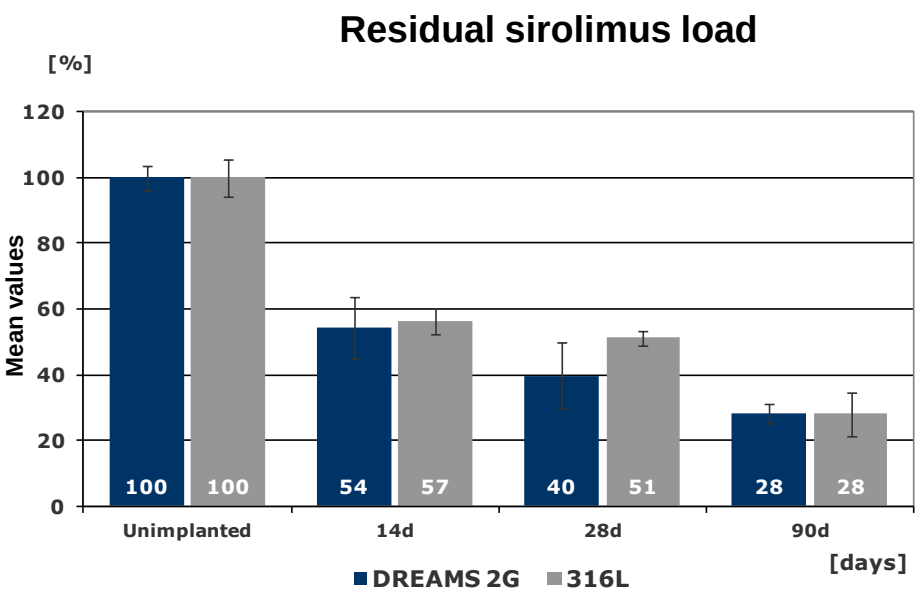
AccelLAB preclinical studies

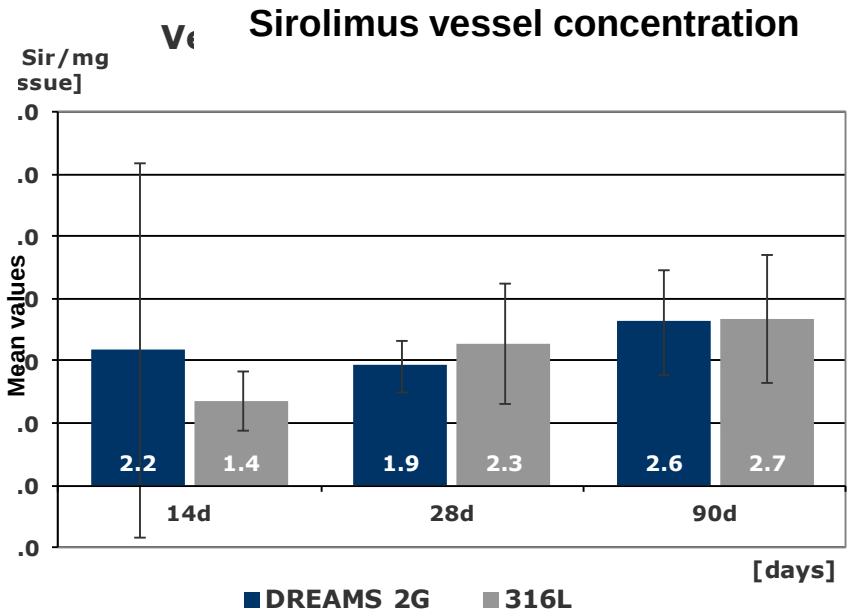
Post-dilation capability of a 3.0mm scaffold



Does magnesium degradation affect sirolimus?

Pharmacokinetic study shows no significant difference between scaffold and control device made from 316L





- Magnesium scaffolds coated with a matrix of PLLA and Sirolimus were compared to an identical device made from 316L of identical geometry and coating/drug
- Implantation in coronary arteries of hybrid farm pigs for up to 90 days
- Blood, scaffold and tissue surrounding scaffold were analyzed by HPLC

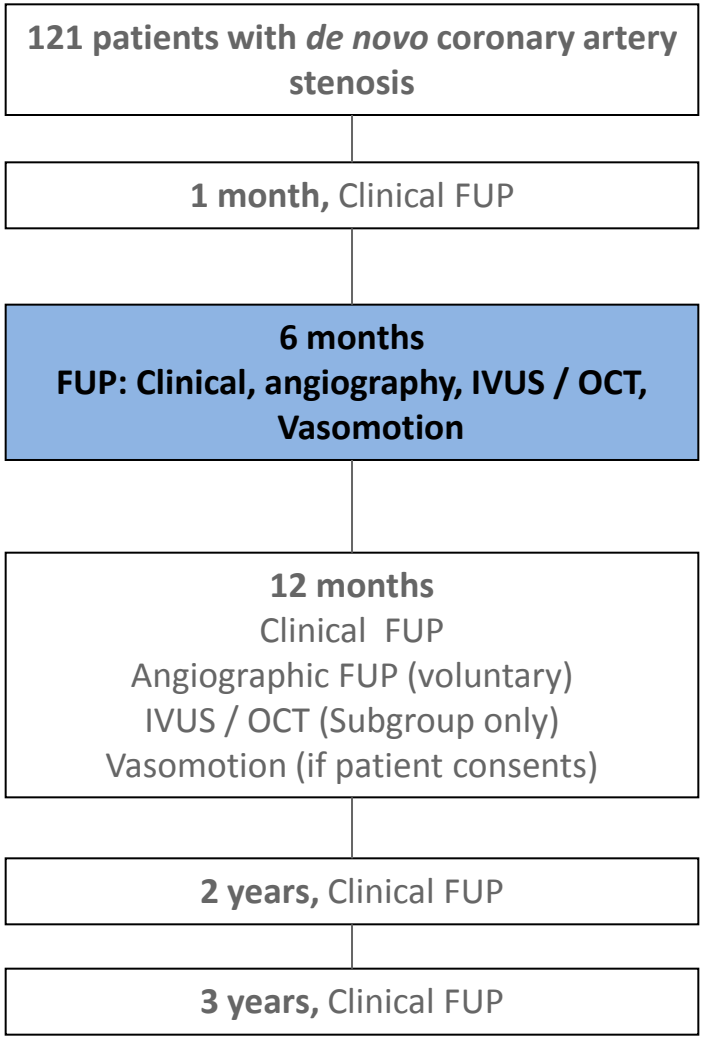
Data on file at BIOTRONIK

BIOSOLVE-II study design

- **DESIGN:**
  Prospective, multi-center FIM
  Single *de novo* coronary artery lesions in up to two coronary arteries

- **PRIMARY ENDPOINT:**
  In-segment late lumen loss @ 6-month

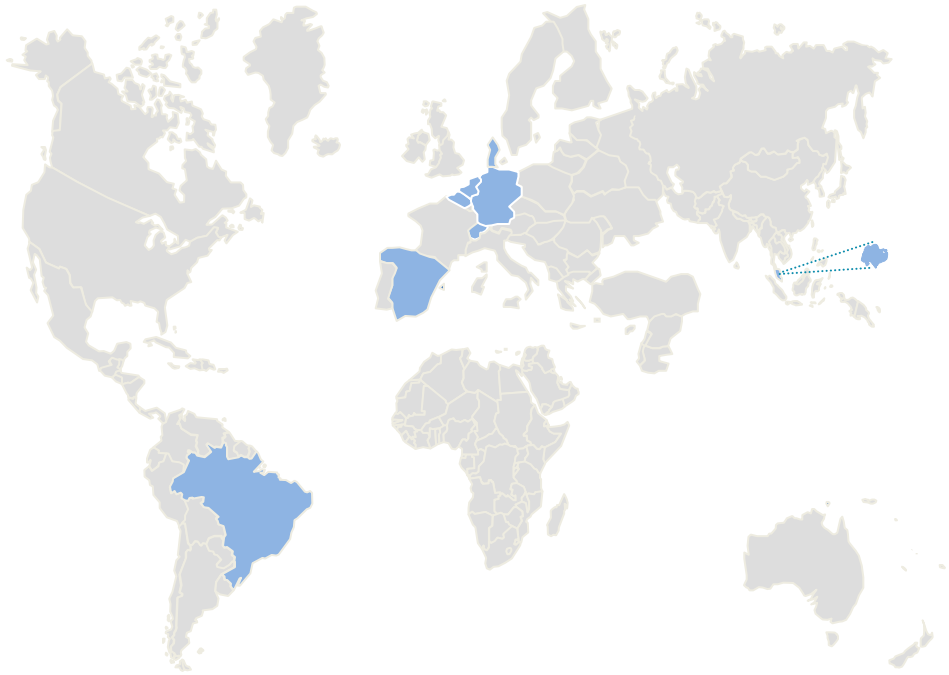
- **COORDINATING CLINICAL INVESTIGATOR**
  M.Haude, Lukaskrankenhaus GmbH, Neuss, Germany



BIOSOLVE-II

BIOSOLVE-II Investigational Sites

Investigator	Country
M. Haude, MD (CCI)	Germany
R. Tölg, MD	Germany
F.J. Neumann, MD	Germany
W. Wijns, MD	Belgium
C. Kaiser, MD	Switzerland
E. Eeckhout, MD	Switzerland
C. von Birgelen, MD	The Netherlands
E. Christiansen, MD	Denmark
N. Gonzalo, MD	Spain
A. Abizaid, MD	Brazil
P. Lemos, MD	Brazil
S.T. Lim, MD	Singapore

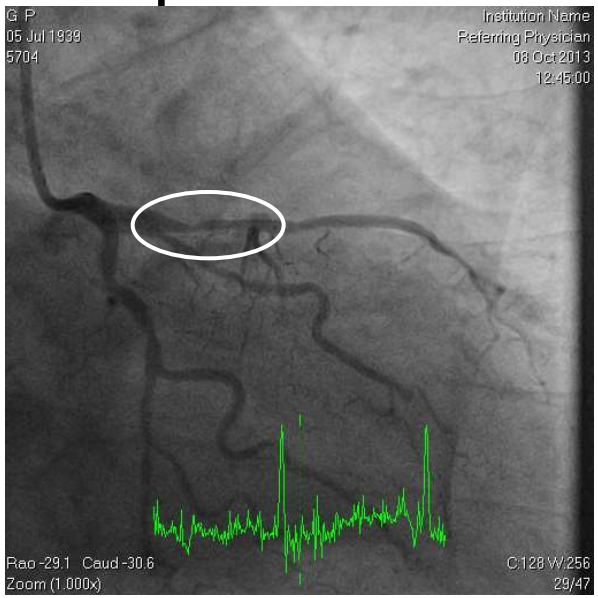


- First patient implanted on October 8 by Prof. Haude

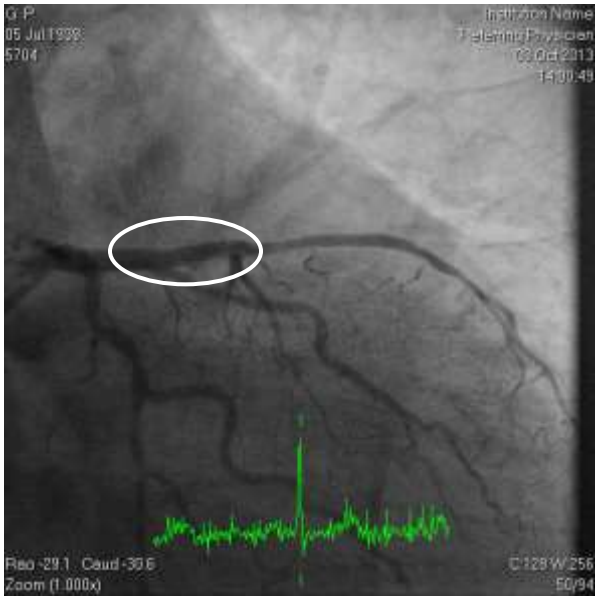
BIOSOLVE-II

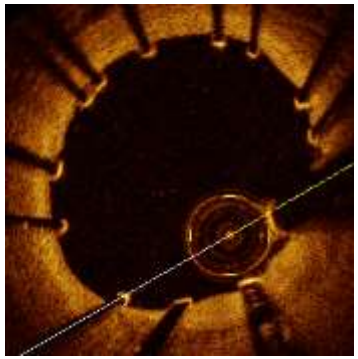
6month follow-up case presentation

Pre-procedure

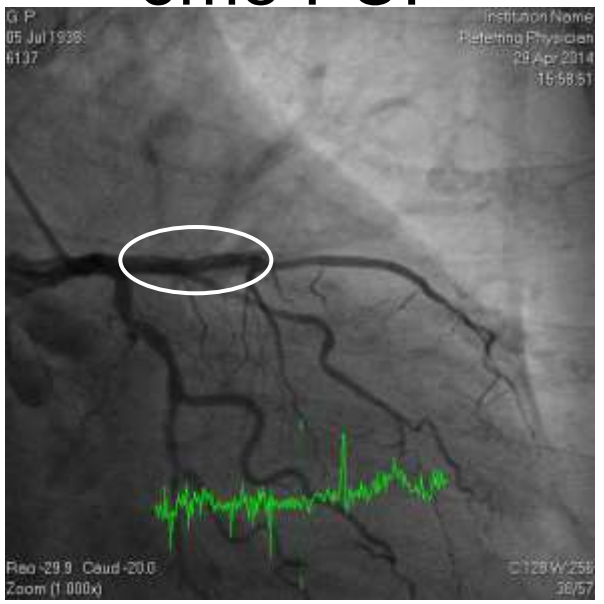


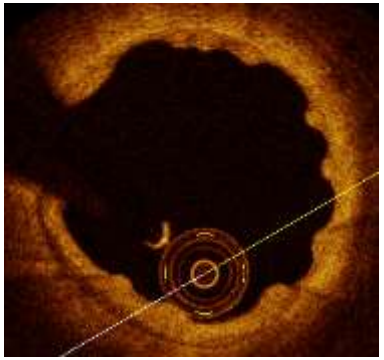
Post-





6mo FUP





(GER443-001, Prof. Haude, Lukaskrankenhaus Neuss, Germany)

BIOSOLVE-II

Summary

- Magnesium offers an ideal balance between biocompatibility, mechanical performances and absorption, feels like a metal deliver like a metallic stent.
- Does not require vessel preparation like with PLLA
- Does not require imaging

- Not all Magnesium alloys are the same

- The Biotronik absorbable Mg program is most advanced:
  - BIOSOLVE-I has proven safety of DREAMS 1. generation with Paclitaxel elution and improved efficacy compared to the bare AMS version
  - BIOSOLVE-II is currently testing safety and efficacy of DREAMS 2. generation with Sirolimus elution

Other companies are also working on absorbable Mg scaffold programs, but none of them are in clinical phase

Metal Versus PLLA Consumer Report

	PLLA	Mg
Degradation Time	24-48 MONTHS	6-12 MONTHS
Radial strength	++	+++
Deliverability	++	+++
Vasoreactivity	12 months	6 months
Malapposition	Frequent	Rare
Clinical data	Modest	Minimal
Angio late lumen Loss 12 months	0.20	0.52
Ischemic driven TLR at 24 months	7%	6.8%

THANK YOU